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Modern Approaches to Chemical Science: Concepts and Techniques

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Preface

The field of chemical science is undergoing a profound transformation, driven by the convergence of new technologies, interdisciplinary research, and a growing commitment to sustainable development. In response to these evolving demands, "Modern Approaches to Chemical Science: Concepts and Techniques" presents a curated collection of recent advancements, innovative methodologies, and emerging applications that are reshaping the landscape of modern chemistry.

This volume brings together a diverse range of topics, each reflecting the spirit of contemporary chemical research. The journey begins with an exploration of Computational Chemistry, highlighting its pivotal role as a modern tool to simulate, predict, and understand complex chemical phenomena with unprecedented accuracy. Computational methods have become indispensable for accelerating discovery and optimizing experimental design in today's laboratories.

Advancements in catalysis are addressed through the study of Micellar Media, emphasizing how micelles enhance reaction efficiency and sustainability by providing environmentally benign alternatives to conventional solvents. In the realm of green chemistry, the chapter on the Green Synthesis of Silver and Copper Nanoparticles Using Pithecellobium dulce showcases nature-inspired routes for producing functional nanomaterials with significant biomedical and environmental applications.

The search for novel therapeutics is represented by research on Benzimidazole Derivatives as promising anticancer agents, offering deep structural insights and uncovering their therapeutic potential. This chapter bridges chemical synthesis and medicinal chemistry, underlining the importance of targeted drug design.

Environmental sustainability and energy conversion are at the forefront in the discussion of Fe_2O_3/g-C_3N_4 Nanocomposites, demonstrating a synergistic

approach for enhancing photocatalytic activity in applications such as pollutant degradation and clean energy production.

Broader perspectives on contemporary chemical science are reflected in the chapters on Modern Approaches to Chemical Sciences—Concept and Technology and Modern Synthetic Methods, which together provide a comprehensive overview of how novel strategies, tools, and conceptual frameworks are redefining chemical research and education.

Finally, the book addresses biomedical innovation with a focus on Polymeric Nanoparticles-Based Topical Delivery Systems for dermatological diseases, offering a glimpse into how polymer science and nanotechnology are converging to revolutionize drug delivery and skin therapy.

Each contribution in this volume is designed to not only inform but also inspire researchers, educators, and students by presenting clear concepts, current techniques, and the future possibilities of chemical science. We are grateful to all the authors for their outstanding contributions, and to the editorial and review teams for their dedication in bringing this work to fruition.

It is our hope that Modern Approaches to Chemical Science: Concepts and Techniques will serve as a valuable reference, spark curiosity, and encourage innovation in the ever-expanding field of chemistry.

Date: *12 March, 2025*

Editors

Modern Approaches to Chemical Science: Concepts and Techniques

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Computational Chemistry: A Modern Approach to Chemical Science

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Abstract

Computational chemistry has emerged as a pivotal discipline in modern chemical science, integrating principles from chemistry, physics, and computer science to address complex chemical problems through computational methods. This field leverages mathematical models, algorithms, and simulations to study molecular structures, properties, and behaviours, enabling accurate predictions of molecular interactions, reaction mechanisms, and thermodynamic properties. Key techniques include quantum mechanical calculations, molecular dynamics simulations, and Monte Carlo methods, each tailored to specific chemical inquiries. The advent of high-performance computing (HPC) and machine learning (ML) has further expanded its scope, allowing researchers to tackle large and complex systems. Computational chemistry finds applications in drug design, material science, environmental chemistry, and reaction mechanism studies, significantly reducing experimental costs and time. Despite challenges such as balancing accuracy with computational cost and scalability issues, advancements in hybrid methods, machine learning, and quantum computing promise to revolutionize the field. This chapter provides an overview of computational chemistry's historical development,

key concepts, methodologies, applications, and future directions, highlighting its indispensable role in scientific and technological innovation.

Keywords: Computational Chemistry, Quantum Mechanics, Molecular Drug Design, Material Science, Machine Learning, Quantum Computing etc.

Introduction to Computational Chemistry:

Definition and Scope

Computational chemistry is a multidisciplinary area that trusts principles from chemistry, physics, and computer science to resolve complex chemical difficulties using computational methods. It comprises the use of mathematical models, algorithms, and computer simulations to study the structure, properties, and behavior of molecules and materials. By leveraging computational power, researchers can predict molecular interactions, reaction mechanisms, and thermodynamic properties with high accuracy. This field incorporates a wide range of techniques, including quantum mechanical calculations, molecular subtleties simulations, and Monte Carlo methods, each tailored to address specific chemical questions. The integration of high-performance computing (HPC) and machine learning (ML) has further expanded the scope of computational chemistry, empowering the study of large and complex systems that were formerly intractable [1]. As a consequence, computational chemistry has become an essential tool in both theoretical and applied chemical research, bridging the gap between experimental observations and theoretical predictions.

Historical Development

The origins of computational chemistry can be drawn back to the early 20th century, with the progress of quantum mechanics providing the theoretical foundation for understanding atomic and molecular behavior. The formulation of the Schrödinger equation in 1926 was a pivotal moment, as it allowed scientists to describe the electronic structure of atoms and molecules mathematically. Early pioneers like Linus Pauling and John Pople made significant contributions to the field, with Pople's development of computational approaches for quantum chemistry earning him the Nobel Prize in Chemistry in 1998 [2]. The introduction of density functional theory (DFT) by Walter Kohn in the 1960s revolutionized the field by so long as a more efficient and accurate approach to solving the electronic structure of complex systems [3]. Over the decades, computational chemistry has evolved from simple calculations on trivial molecules to sophisticated simulations of large biomolecular systems and materials. The initiation of high-performance computing and advanced algorithms has further accelerated progress, permitting researchers to tackle problems of unprecedented complexity and scale [4].

Importance and Relevance

Computational chemistry plays a critical role in modern chemical science by providing a virtual laboratory where hypotheses can be tested and new ideas can be explored without the need for extensive experimental work. In drug design, computational methods such as

virtual screening and molecular docking are used to predict potential drug candidates and optimize their relation with biological targets, significantly reducing the time and cost of drug development [5]. In material science, computational chemistry aids in the project of novel entity with new properties, such as high-performance catalysts, energy storage systems, and nanomaterials [6]. Environmental chemistry also benefits from computational modeling, which is used to study atmospheric reactions, pollutant degradation, and the impact of human activities on the environment [7]. As computational power continues to grow and algorithms become more sophisticated, the applications of computational chemistry are expected to expand even further, making it an indispensable tool in the pursuit of scientific and technological innovation.

Key Concepts in Computational Chemistry

Quantum Chemistry

Quantum chemistry forms the theoretical backbone of computational chemistry, providing a framework for understanding the electronic structure and behavior of molecules. At its core is the Schrödinger equation, a fundamental equation in quantum mechanics that describes how the quantum state phase physical system changes over time. Solving the Schrödinger equation for molecular systems suggests researchers to determine the wave functions and energy levels of electrons, which are vital for predicting molecular properties and reactivity [8]. Past decades, numerous computational methods have been developed to approximate solutions to the Schrödinger equation. The Hartree-Fock method, one of the latest and most commonly used approaches, provides a mean-field approximation for electron-electron interactions but often requires post-Hartree-Fock corrections (e.g., MP2, CCSD) to contribute for electron correlation effects [9]. Density functional theory (DFT), introduced by Walter Kohn, has become a foundation of modern quantum chemistry use of this balance between accuracy and computational efficiency. DFT relies on the electron density rather than the wave function, making it suitable for studying larger and more complex systems [10]. These chemical methods are indispensable for exploring chemical reactions, spectroscopy, and electronic properties of molecules.

Molecular Mechanics

Molecular mechanics (MM) is a classical approach to modeling molecular systems, relying on empirical force fields to describe the interactions between atoms. Unlike quantum chemistry, which focuses on electrons, molecular mechanics treats atoms as spheres and bonds as springs, using potential energy functions to represent bond stretching, bending, torsional strains, and non-bonded interactions (e.g., van der Waals and electrostatic forces) [11]. These force fields are parameterized using experimental data or high-level quantum chemical calculations, making them computationally efficient for studying large molecular systems such as proteins, polymers, and materials. Molecular mechanics is particularly useful for simulating the structural activities of biomolecules, enabling researchers to study protein collapsible, ligand capacity of bonding, and

conformational changes [12]. While MM lacks the electronic detail of quantum chemistry, its simplicity and scalability make it an authoritative tool for discovering systems with thousands to millions of atoms.

Statistical Mechanics and Thermodynamics

Statistical mechanics bridges the microscopic world of atoms and molecules with the macroscopic properties of matter, providing a theoretical foundation for understanding thermodynamics. It describes how the behavior of individual particles (microstates) gives rise to observable properties (macrostates) such as temperature, pressure, and energy. By employing statistical ensembles (e.g., canonical, microcanonical, and grand canonical), computational chemists can analyze physical properties like enthalpy, entropy, and free energy, which are important for forecasting the stability and spontaneity of chemical processes [13]. Molecular dynamics (MD) and Monte Carlo (MC) simulations are commonly used to sample microstates and compute ensemble averages. For example, free energy determination using system like umbrella sampling or thermodynamic integration provide insights into binding affinities, phase transitions, and reaction pathways [14]. These methods are mostly applied in drug design, material science, and biophysics, where understanding thermodynamic behavior is essential for optimizing molecular interactions and designing new materials.

Computational Methods and Techniques

Quantum Mechanical Methods

QMM are important for considerate the electronic structure and properties of molecules and materials. These methods are devided into ab initio, semi-empirical, and density functional theory (DFT). Ab initio methods, such as Hartree-Fock and post-Hartree-Fock techniques (e.g., MP2, CCSD), solve the Schrödinger equation from first principles, providing high accuracy but at a significant computational economy, especially for big systems [1]. Semi-empirical methods, such as AM1 and PM3, simplify calculations by incorporating experimental data, making them computationally well-organized but less precise [16]. DFT, on the other hand, uses electron density as the central variable, offering a balance between relevant and computational efficiency, and is widely used for studying large systems, including solids and surfaces [17]. Favourite computational tools that use these methods include Gaussian (for molecular modelling and spectroscopy), ORCA (for high-performance quantum chemistry calculations), and VASP (for solid-state physics and materials science) [18].

Molecular Dynamics Simulations

MD simulations are a cornerstone of computational chemistry and biophysics, enabling the analysis of how molecular systems evolve over time by solving Newton's equations of motion. These simulations give detailed insights into molecular interactions, conformational changes, and thermodynamic properties over time [19]. MD is handy for investigating processes like protein folding, ligand binding, and the properties of materials under varying conditions. The accuracy of MD

simulations depends on the force fields used to describe interatomic interactions, with extensively used force fields including AMBER, CHARMM, and GROMOS [21]. MD simulations are computationally rigorous, mainly for large systems or extended timescales, and often demand high-performance computing resources [22]

Monte Carlo Simulations

Monte Carlo (MC) simulations are a class of computational techniques that rely on statistical sampling to explore the behavior of complex systems. Unlike MD, which follows deterministic trajectories, MC methods use random sampling to generate equilibrium properties and optimize system configurations [23]. These simulations are important for analyzing systems with many degrees of freedom, including polymers, fluids, and reaction dynamics. [24]. MC methods are also employed in optimization problems, such as finding the lowest energy configuration of a molecule or material [25]. However, their dependence on random sampling can make it less efficient for studying dynamic processes compared to MD. [26].

Hybrid Methods

Hybrid methods, such as quantum mechanics/molecular mechanics (QM/MM), combine the strengths of quantum mechanical and classical mechanical approaches to study complex systems. In QM/MM, the region of interest (e.g., an active site in an enzyme) is worked with quantum mechanical methods for high accuracy, while the surrounding environment is modeled using molecular mechanics for computational efficiency [27]. This approach is particularly useful for studying biochemical reactions, catalysis, and materials with localized electronic effects [28]. Nevertheless, hybrid methods encounter challenges, such as achieving seamless coupling between the QM and MM sections and managing the computational costs of the QM calculations [29]. QM/MM is a influential tool that addresses the balance between accuracy and efficiency in computational studies, despite inherent challenges. [30].

Applications of Computational Chemistry

Drug Synthesis Design and Biochemistry

Computational chemistry plays an essential role in drug design and biochemistry, enabling researchers to understand molecular interactions and accelerate the discovery of new therapeutics. Molecular docking and virtual screening are widely used to analyse how small molecules (ligands) bind to target proteins, helping identify potential drug reagents [31]. For example, docking studies have been crucial for understanding molecular interactions. in the development of HIV protease inhibitors and kinase inhibitors for cancer therapy [32]. Computational methods also provide insights into protein-ligand interactions and enzyme mechanisms, such as the catalytic activity of enzymes like cytochrome P450 [33]. Case studies in drug discovery, such as the design of the antiviral drug oseltamivir (Tamiflu), highlight the power of computational tools in optimizing drug efficacy and reducing experimental costs [34]. These approaches are complemented by molecular dynamics (MD) simulations,

which reveal the dynamic behavior of biomolecules over time [35].

Materials Science and Nanotechnology

In materials science and nanotechnology, computational chemistry is used to design novel materials and predict their properties before synthesis. For instance, density functional theory (DFT) and Molecular dynamics simulations are used to investigate the electronic, mechanical, and thermal properties of materials such as graphene, carbon nanotubes, and metal-organic frameworks (MOFs). [36]. These methods are useful to design nanomaterials for specific applications, such as photovoltaics, where computational studies optimize the efficiency of solar cells by predicting the bandgap and charge transport properties of materials [37]. Simulations in polymer science enhance our understanding of polymer chain behavior and permit the design of materials with specific properties, such as flexibility and conductivity [38]. Additionally, computational chemistry aids in the development of catalysts by identifying active sites and reaction mechanisms, as seen in the design of zeolite catalysts for industrial processes [39].

Chemical Reaction Mechanisms

Computational chemistry is crucial for studying chemical reaction mechanisms, contribution valuable insights into reaction pathways and transition states. By analyzing potential energy surfaces, researchers can identify intermediates and transition states that are often difficult to observe experimentally [40]. Computational chemistry has elucidated the mechanisms of organic reactions like the Diels-Alder reaction and enzymatic processes like the hydrolysis of peptides [41]. These perceptions are crucial for reaction rate calculations and process optimization in industrial chemistry, to developed of more efficient catalysts or the optimization of reaction conditions [42]. Transition state theory, combined with quantum mechanical methods, allows for accurate prediction of reaction rates and activation energies, controlling the development of new synthetic routes [43].

Environmental Chemistry

In environmental chemistry, computational modelling is informative to study the behavior and transport of pollutants, as well as atmospheric processes that influence climate. For example, molecular dynamics simulations and quantum chemical calculations help predict the fate of contaminants in water and soil, such as the degradation of pesticides or the adsorption of heavy metals on mineral surfaces [44]. Computational models are utilized to investigate atmospheric chemistry, including the formation of ozone, smog, and aerosols. These factors are essential for understanding air quality and climate change. [45]. Climate models, which incorporate chemical reactions and transport processes, rely on computational chemistry to predict the impact of greenhouse gases and pollutants on global warming [46]. These applications demonstrate the importance of computational tools in addressing environmental challenges and informing policy decisions.

Computational Tools and Software

Overview of Computational Chemistry Software

Computational chemistry relies on a diversity of software tools, each item is designed for specific applications. and methodologies. Key software includes Gaussian, VASP, ORCA, NWChem, and GROMACS. Gaussian is extensively used for quantum chemistry calculations, with ab initio, DFT, and semi-empirical methods, and is particularly popular for studying molecular properties, spectroscopy, and reaction mechanisms [47]. VASP (Vienna Ab initio Simulation Package) specializes in solid-state physics and materials science, offering advanced DFT capabilities for periodic systems [48]. ORCA is a high-performance quantum chemistry program that supports a wide range of methods, including post-Hartree-Fock and multireference approaches, making it suitable for both molecular and solid-state systems [49]. NWChem is an open-source software that supports large-scale simulations, with molecular dynamics, quantum chemistry, and biomolecular modeling [50]. GROMACS, from another way, is a leading tool for dynamics simulations, mainly for biomolecular systems, offering high efficiency and scalability [51]. Each software has unique strengths, and the choice depends on the precise necessities of the study, such as system size, accuracy, and computational resources.

User Guides and Interfaces

Selecting the right computational chemistry software be contingent on the task at hand, such as electronic structural analysis, molecular dynamics, or materials modeling. For beginners, Gaussian and ORCA provide user-friendly interfaces and extensive documentation, making them accessible for molecular modeling and spectroscopy [52]. VASP and NWChem, while more complex, are ideal for advanced users focusing on solid-state systems or large-scale simulations [1]. Common input formats include Z-matrix, XYZ, and PDB files, which define molecular geometries, while output formats often include log files, trajectory files, and energy profiles. Understanding these formats is crucial for analyzing results and integrating data across different software platforms [54]. Many programs also offer graphical user interfaces (GUIs) and visualization tools, such as Gauss view and VMD, to simplify setup and analysis [55].

Computational Resources and High-Performance Computing

The complexity and scale of computational chemistry problems often require significant computational power, making high-performance computing (HPC) essential. HPC systems, including clusters and supercomputers, enable parallelization, where calculations are distributed across multiple processors to reduce computation time [56]. For example, GROMACS and NWChem are optimized for parallel computing, allowing efficient simulations of large biomolecular systems or periodic materials [57]. Cloud computing has also emerged as a flexible and scalable alternative, providing access to computational properties without the need for local infrastructure [58]. Tools like Amazon Web Services (AWS) and Google Cloud Platform (GCP) offer pre-configured environments for running computational chemistry software. Efficient use of these resources requires understanding parallelization techniques, such as MPI (Message Passing Interface) and OpenMP, which are mostly used in

HPC environments [59]. As computational demands grow, leveraging these resources will remain critical for advancing research in chemistry and materials science.

Challenges in Computational Chemistry

Accuracy vs. Computational Cost

One of the most essential and important challenges in computational chemistry is balancing accuracy with computational cost. High-accuracy methods, such as ab initio quantum mechanical approaches (e.g., coupled cluster theory) or high-level density functional theory (DFT), provide precise results but are computationally expensive, especially for large systems [60]. For example, post-Hartree-Fock methods like CCSD(T) are considered the "gold standard" for small molecules but become impractical for structures with hundreds of atoms due to their rapid increase concerning system size. [61]. Another way, lower-cost methods, like semi-empirical approaches or force field-based molecular mechanics, are computationally efficient but may lack the accuracy essential for positive applications, such as studying reaction mechanisms or electronic properties [62]. Researchers must carefully select methods that provide an acceptable trade-off between accuracy and computational feasibility, often using hybrid approaches like QM/MM for large systems [63].

Scalability and System Size

Simulating large molecular systems, such as biomolecules, nanostructures, or materials, presents significant scalability challenges. For instance, molecular dynamics (MD) simulations of proteins or DNA require modeling thousands to millions of atoms over long timescales, which demands substantial computational resources [64]. Similarly, simulating periodic systems like crystals or surfaces using DFT can become prohibitively expensive as the system size increases [65]. Techniques such as coarse-graining, which simplifies the representation of molecules, and linear-scaling algorithms, which decrease the computational economy of quantum mechanical methods, solutions have been created to tackle these challenges. [66]. These methods often involve trade-offs in accuracy and resolution, limiting their applicability to specific problems. Advances in high-performance computing (HPC) and parallelization have alleviated some of these issues, but scalability remains a critical concern in computational chemistry [67].

Validation of Computational Results

Validating computational results against experimental data. data is essential to ensure the reliability and accuracy of simulations. This process involves comparing calculated properties, such as bond lengths, reaction energies, or spectroscopic data, with experimentally measured values [68]. Benchmarking studies, which estimate the performance of computational methods against standardized datasets, play a vital role in assessing the accurate and limitations of different approaches [69]. For example, databases like the Minnesota Database for Chemical Accuracy provide reference data for benchmarking quantum chemical methods [70]. Additionally, error estimation techniques, such as statistical analysis and uncertainty quantification, help identify possible sources of error in

computational models [71]. Validation is particularly important in fields like drug design and materials science, where computational predictions guide experimental work and decision-making [72]. Without rigorous validation, computational results may lack credibility and practical utility.

The Future of Computational Chemistry

Machine Learning and Artificial Intelligence

Machine learning (ML) and artificial intelligence (AI) are revolutionizing computational chemistry by empowering faster and more precise predictions of molecular properties, reaction pathways, and material behaviors. ML models, such as neural networks and Gaussian processes, are being trained on large datasets of molecular structures and properties to predict outcomes without the need for classy quantum mechanical calculations [73]. For example, ML has been effectively applied to materials discovery, where it accelerates the identification of novel materials that exhibit specific desired properties, such as high conductivity or catalytic activity [74]. Additionally, AI-driven tools are being utilized for. reaction forecasting, enabling chemists to predict reaction outcomes and optimize synthetic routes with minimal experimental effort [75]. Despite these advancements, challenges persist, such as the necessity for high-quality training data and the interpretability of machine learning models, which are crucial for their adoption in chemical research. [76].

Quantum Computing

Quantum computing grips immense promise for computational chemistry by potentially addressing issues that are difficult to resolve. classical computers. Quantum algorithms, such as the variational quantum eigensolver (VQE) and quantum phase estimation (QPE), are being developed to simulate molecular systems with unprecedented accuracy [77]. These algorithms leverage the principles of quantum mechanics to model electron correlation and molecular dynamics more efficiently, offering advantages for simulating large, complex systems like catalysts or biomolecules [78]. While quantum computers are still in their infancy, recent advancements in hardware and error correction techniques are bringing them closer to practical applications in chemistry [79]. However, challenges such as qubit coherence, error rates, and scalability must be addressed before quantum computing can fully realize its potential in computational chemistry [80].

Interdisciplinary Approaches

The future of computational chemistry lies in interdisciplinary collaboration, where computational chemists work alongside biologists, material scientists, engineers, and data scientists to tackle complex problems. For instance, the integration of computational chemistry with genomics is enabling the design of targeted drugs and the understanding of biological pathways at the molecular level [81]. Similarly, collaborations with material scientists are driving innovations in nanotechnology, such as the development of advanced materials for energy storage and conversion [82]. The convergence of computational chemistry with AI and big data analytics is also opening new avenues for research, such as the use of predictive models to guide experiments and

optimize processes [83]. These interdisciplinary approaches are fostering a more holistic understanding of chemical systems and accelerating the translation of computational insights into real-world applications [84].

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MODERN APPROACHES TO CHEMICAL SCIENCE: CONCEPTS AND TECHNIQUES

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The Role of Micellar Media in Catalysis: Advancing Reaction Efficiency and Sustainability

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Abstract

This chapter examines the latest developments in catalytic reactions conducted within aqueous micellar systems, which utilize surfactants. Special attention is given to how these environmentally benign and economical reaction media affect key factors like catalyst recyclability, reaction rates, and the specificity of both reactants and products. Surfactants are crucial tools in organic synthesis, as their micelle formation above the critical micelle concentration allows for the emulsification and solubilization of otherwise immiscible organic compounds, thereby enabling diverse chemical transformations.

This section specifically highlights biosurfactants, environmentally friendly amphiphilic molecules produced by living organisms. These "green" surfactants, originating from renewable sources and often waste byproducts, are gaining prominence as sustainable replacements for harmful organic solvents and synthetic surfactants. Their inherent advantages, such as minimal toxicity, robust performance in harsh environments, and biodegradability, are fueling their growing use. Through an examination of recent developments and illustrative examples, this chapter demonstrates the significant potential of micellar systems in catalysis, providing novel approaches to tackle current challenges in sustainable chemistry.

Keywords: Surfactant, catalysts, organic synthesis, colloidal particles

Introduction

Catalytic processes are fundamental to contemporary chemical practices, underpinning a wide array of industrial, environmental, and pharmaceutical applications. However, the traditional reliance on organic solvents in these processes poses considerable environmental and safety challenges. As a response, micellar systems have been

recognized as a promising pathway towards more sustainable and efficient catalytic methodologies. These systems, formed by the self-assembly of surfactant molecules in water, generally adopt a spherical architecture, featuring a hydrophobic core and a hydrophilic shell. This unique structural organization provides a tailored reaction space that can significantly influence the kinetics and selectivity of catalytic events. This section intends to clarify the ways in which micellar media enhance catalytic reactions and to demonstrate their broad applicability across the spectrum of chemical disciplines.

Structural Characteristics of Micellar Media

Formation and Stability

Micelles form when surfactant molecules exceed the critical micelle concentration (CMC). In this process, the hydrophobic tails of the surfactants cluster together within the core, while the hydrophilic heads remain in contact with the surrounding aqueous environment. This configuration minimizes the systems overall free energy, resulting in a stable yet dynamic structure.

Surfactants Different categories

Surfactants have the inherent ability to reduce interfacial tension between two immiscible liquids, facilitating the formation of emulsions. (Sorhie et al., 2022) However, surfactants differ in their origins, allowing them to be categorized into two distinct groups (Table 1).

Table 1: Different categories of surfactants

Synthetic surfactant	Anionic surfactants	➢ The hydrophobic tail typically consists of an alkyl chain of different lengths and may appear in structures like alkyl phenyl ether or alkyl benzene.(Sorhie et al., 2022) ➢ The hydrophilic portion contains a negatively charged head group, often including functional groups like carboxyl, sulfonate, sulfate, or phosphate. e.g. Lignosulfonates, lauryl sulphate, dialkyl-sulfosuccinate.
	Cationic surfactants	➢ Composed of one or more long alkyl chains, often derived from natural fatty acids. ➢ Nitrogen-containing compounds, including amide linkages with fatty acids and quaternary ammonium compounds. ➢ Exhibited antibacterial activity against bacteria e.g. Sodium dodecyl sulfate, p-dodecylbenzenesulphonic acid, Cetyltrimethylammonium bromide

	Nonionic surfactants	➢ Compounds containing active hydrogen atoms, such as ethylene oxide and/or propylene oxide derivatives with an alcohol functional group. ➢ Additionally, alkyl phenols, sugar esters, alkanolamides, amine oxides, fatty amines, fatty acids, and polyols find extensive applications across multiple industries. E.g. Triton X-100 and Tween 80 (Sorhie et al., 2022)
	Zwitterionic surfactants	➢ Amphiphiles that bearing both positive and negative charges, separated by a spacer segment. ➢ This spacer is typically a methylene group, $–(CH_2)_n–$, which generates a high dipole moment that does not increase directly with n. ➢ The structures consist of a positively charged ammonium or imidazolium group and a negatively charged sulfonate, sulfate, carboxylate, or phosphate group.(Sorhie et al., 2022)
Designer surfactants		➢ - Designer surfactants are specially formulated using sources like vitamin E, proline, tocopherol, or β-sitosterol. These innovative and cost-efficient surfactants improve reaction efficiency and yield, with their performance influenced by the amphiphile's structure and the nature of the reaction they support. e.g. PTS, Sito-350-M, TPG-lite, SPGS-550-M
Green surfactant	Green surfactants from microorganisms	➢ - Microbial biosurfactants are secondary metabolites generated by microorganisms, which can either be secreted into the environment or remain bound to the cell surface. ➢ The most well-known bacterial species that effectively produce biosurfactants include *Pseudomonas sp.*, *Bacillus sp.*, *Arthrobacter sp.*, *Nocardia sp.*, and *Mycobacterium tuberculosis*.(Sorhie et al., 2022) ➢ Microbial biosurfactants are classified into low molecular weight types like glycolipids and lipopeptides, and high molecular weight types such as proteins, polysaccharides, lipoproteins, and lipopolysaccharides. Examples include rhamnolipids, sophorolipids, and surfactin, which are widely utilized across industries due to their distinctive properties.

	Green surfactant derived from plants	➢ Plant-based surfactants are natural surface-active compounds present in different plant parts, including stems, roots, leaves, flowers, legumes, and fruits.(Sorhie et al., 2022) ➢ Common plant-derived surfactants, such as phospholipids, saponins, and protein hydrolysates, are abundantly found in nature. ➢ Saponins are widely distributed in the plant kingdom, and biosurfactants extracted from plants hold great potential as cosmetic additives, contributing to surface tension reduction and emulsion stabilization in formulations.
	Green surfactant-derived from animals	➢ Various surfactant compounds, including synthetic and animal-derived types, have been developed and clinically evaluated. ➢ Studies indicate that infants with respiratory distress syndrome treated with surfactants from animal sources experienced a lower risk of pneumothorax, mortality, pulmonary interstitial emphysema, and bronchopulmonary dysplasia.(Sorhie et al., 2022)

Types of Micelles

1. Spherical Micelles

These are the most commonly observed micelles in aqueous environments. They consist of amphiphilic molecules arranged in a way that forms a hydrophobic core and a hydrophilic outer shell. The hydrophobic interior serves as a microenvironment for the solubilization of nonpolar compounds, making them useful in various applications such as drug delivery, detergency, and catalytic reactions. Spherical micelles play a significant role in enhancing the solubility of hydrophobic molecules in water-based systems, facilitating their transport and controlled release.

2. Reverse Micelles

Unlike traditional micelles, reverse micelles are formed in nonpolar solvents such as oils or organic media. Their structure is characterized by a hydrophilic core surrounded by a hydrophobic outer region. This unique arrangement enables the encapsulation of polar molecules, including catalysts, enzymes, and water-soluble reactants. Reverse micelles function as nanoreactors, offering a confined space where chemical transformations can take place efficiently. These systems are particularly useful in enzymatic catalysis, nanoparticle synthesis, and nonpolar solvent-based reactions, where they enhance reactivity by concentrating reactants in their confined water pockets.

3. Bicontinuous Structures

Bicontinuous micellar systems arise when the interactions between hydrophilic and hydrophobic components are finely balanced. Unlike spherical or reverse micelles, these structures do not have a distinct core but rather consist of an interconnected network of hydrophilic and hydrophobic domains. This intricate organization creates dynamic environments that facilitate molecular transport and catalytic activity. Such structures are particularly valuable in advanced materials science, nanotechnology, and heterogeneous catalysis, where their complex morphology allows for improved mass transfer, stability, and efficiency in chemical transformations. Bicontinuous micelles have been explored for applications in controlled drug release, self-assembled nanostructures, and sustainable catalytic processes.

Mechanisms of Catalysis in Micellar Media

Enhanced Reactivity

Micelles increase reactivity by concentrating reactants within their cores, effectively increasing local concentrations and facilitating interactions. The hydrophobic core also stabilizes transition states and intermediates, lowering activation energies and accelerating reaction rates.

Selectivity and Control

Micellar environments enhance regioselectivity and stereoselectivity by restricting the spatial orientation of reactants. Moreover, the headgroup of the surfactant can form hydrogen bonds or ionic interactions, actively playing a key role in guiding reaction pathways.

Environmental Benefits

Micellar catalysis often occurs in water, an environmentally benign solvent, reducing the need for hazardous organic solvents. Additionally, the ability to perform reactions under mild conditions enhances the sustainability of these processes. (Siddiqui & Khan, 2014)

Applications in Inorganic Chemistry

Nanoparticle Synthesis

Micellar systems serve as effective templates for the synthesis of metal nanoparticles. By modifying the micelle structure, it is possible to control the size and shape of the nanoparticles, resulting in catalysts with customized properties. (Taware, A.S., Rathod, P.B., Katariya, 2024)

Environmental Catalysis

Micelles have been used to catalyse the degradation of pollutants. By encapsulating and concentrating contaminants, they improve the efficiency of degradation reactions, supporting efforts to achieve cleaner water and air.

Applications in Organic Synthesis

Hydroformylation

Micellar media have demonstrated potential in hydroformylation reactions by improving the rate and selectivity of aldehyde from alkenes. The micellar environment helps stabilize the catalyst and intermediates, resulting in increased yields and reduced formation of side products.

Oxidation Reactions

Micellar systems have been shown to significantly enhance the efficiency of oxidation reactions. For instance, the oxidation of alcohols to aldehydes and ketones can occur under milder conditions with improved selectivity compared to conventional approaches.

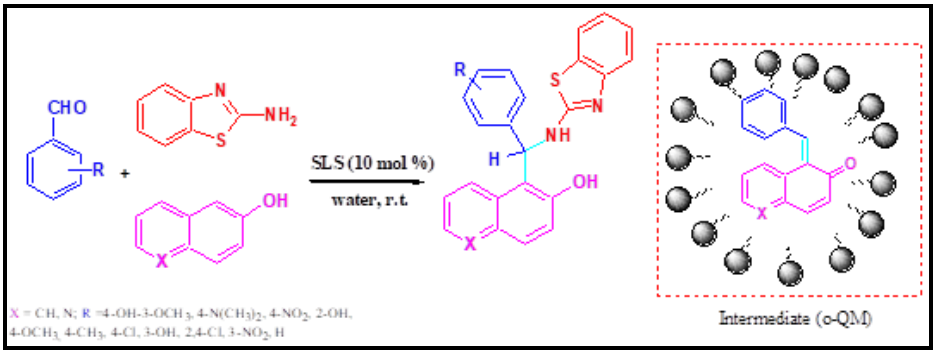
C-C Bond Formation

Micellar media support a range of carbon-carbon bond-forming reactions, such as Suzuki and Heck couplings. The hydrophobic core within micelles aids in solubilizing organometallic catalysts and substrates, thereby improving reaction efficiency. (Manabe, Mori, Wakabayashi, Nagayama, & Kobayashi, 2000)

Significance of surfactants in organic synthesis

Sahu et. al. explored the synthesis of synthesis of 2-aminobenzothiazolomethyl naphthols and 5-(2-aminobenzothiazolomethyl)-6-hydroxyquinolines. (Shaabani, Rahmati, & Farhangi, 2007) Among the various catalysts screened SLS (Sodium Lauryl Sulphate) found to be optimal for the best outcome of the product in water as a solvent. The generality of protocol was tested with various aromatic aldehydes, 2-naphthol/ 6-hydroxyquinoline and 2-aminobenzothiazole to afford the substituted 2-aminobenzothiazolomethyl naphthol and 5-(2-aminobenzothiazolomethyl)-6-hydroxyquinoline at room temp. (Scheme 1) The study found that the ortho and meta (75-89 %) substituted aldehydes produced a comparatively lower yield than para (86-96%) substituted aldehydes. (Sahu, Sahu, & Agarwal, 2014)

The in-situ experiment investigating the intermediate (o-QM) generated from the reaction of aldehyde and naphthol, followed by the addition of 2-aminobenzothiazole and 2-naphthol, revealed that the imine intermediate did not lead to product formation. These findings suggest that the product forms through the o-QM intermediate rather than the imine pathway. (Kumar, Rao, & Rao, 2010) The role of micelles likely involves concentrating and organizing chemical species, with the outer layer of SDS micelles exhibiting strong binding to reactants, intermediates, and the final product due to structural properties and electrostatic interactions. Reusability studies showed that the catalyst does not show any substantial loss upto fourth cycle.

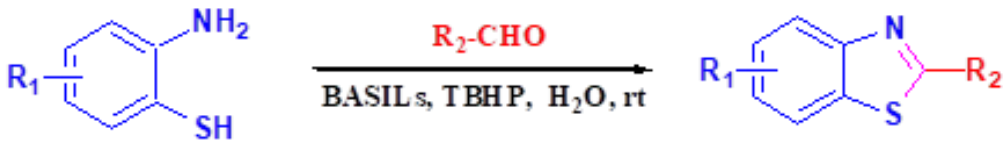


X = CH, N; R =4-OH-3-OCH_3, 4-$N(CH_3)_2$, 4-NO_2, 2-OH, 4-OCH_3, 4-CH_3, 4-Cl, 3-OH, 2,4-Cl, 3-NO_2, H

Scheme 1: Synthesis of substituted 2-aminobenzothiazolomethyl naphthol and

5-(2-aminobenzothiazolomethyl)-6-hydroxyquinoline using SLS.

Senapak et al. discussed the synthesis of 2-alkyl and 2-arylbenzothiazoles using Brönsted acid-surfactant-combined ionic liquid (BASILs) (Amarasekara, 2016; Manabe, Mori, Wakabayashi, Nagayama, & Kobayashi, 2000) in water. (Scheme 2) The series of Brönsted acidic ionic liquids (BAILs) and BASILs based imidazolium cation showed promising results for the synthesis of benzothiazoles. Form the tested catalysts 10 mol % of [bsdodecim][OTf] (figure 1) found to be best for the reaction of 2-aminothiopheno and aldehyde. (Senapak, Saeeng, Jaratjaroonphong, & Sirion, 2018)



R_1= H, 6-Cl; R_2 = ph, 4-Cl-ph, 4-F-ph, 2,4-Cl-ph,3-NO_2-ph, 4-NO_2-ph, 4-COOH-ph, 4-CO_2Me-ph, 4-OH-ph, 4-OMe-ph, 3,4-OMe-ph, 3-OMe-ph, 4-NO_2-ph, 4-OH-ph, 2-Pyridyl, 2-Furyl, 3-Indolyl, 2-Pyrrolyl-N-Boc, 2-Pyrrolyl, Isobutyl, Propyl, H, Cyclohexyl

Scheme 2: Synthesis of 2-sunstituted benzothiazoles using BASILs

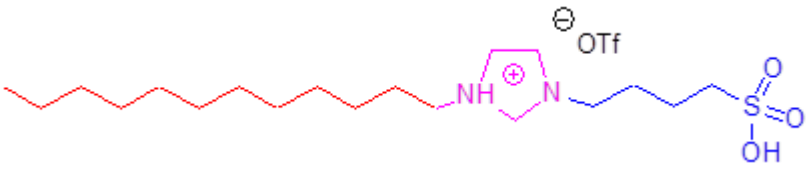


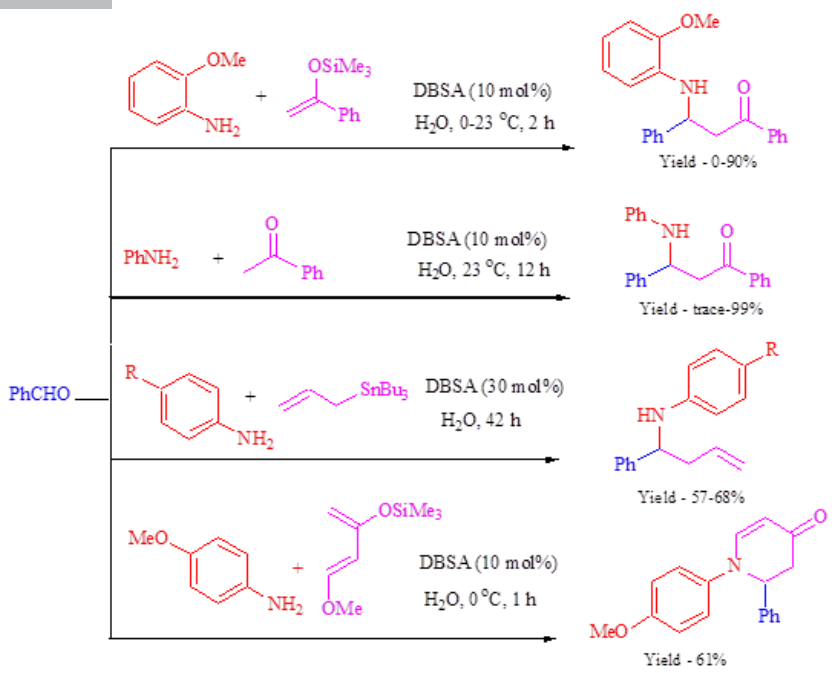
Figure 1: Brönsted acid-surfactant-combined ionic liquid in water

The [bsdodecim][OTf] catalyst has been effectively utilized for this transformation in water, either at room temperature or at 80 °C. The protocol demonstrated its versatility with a wide range of substrates, including aliphatic, aromatic, and heteroaromatic aldehydes, providing the desired products in 7-98% when 1 equivalent of TBHP was used at room temperature. When the reaction was conducted at 80 °C, several substrates produced moderate to excellent yields ranging from 69-98%. The catalyst facilitated the formation of micelles or colloidal dispersions in water, and light microscopy confirmed the presence of stable spherical colloidal particles in the reaction mixture. Importantly, reusability studies revealed no significant decline in catalytic efficiency even after four cycles. (Senapak, Saeeng, Jaratjaroonphong, & Sirion, 2018)

A long-chain alkyl acidic ionic liquid functions as both a Brønsted acid and a surfactant in aqueous media, leading to micelle formation. The catalyst's hydrophobic core concentrates hydrophobic substrates, while its hydrophilic Brønsted acidic component activates the oxygen in the aldehyde substrate. This activation facilitates the reaction, promoting dehydration and cyclization to generate an intermediate. Finally, TBHP oxidizes the intermediate, yielding 2-substituted benzothiazoles. (Senapak et al., 2018)

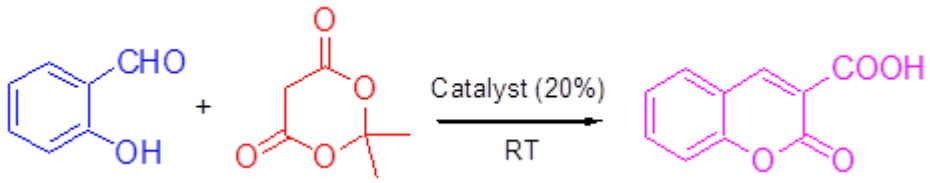
Multicomponent reactions are highly significant in organic synthesis, enabling the direct transformation of multiple reactants into the desired product in a single step. (Dömling, 2006; Kale, Kahandal, Disale, & Jayaram, 2012) Among these, Mannich (Lin, Junhua, Huangshu, Xiaomei, & Mingxiao, 1991) and related reactions are crucial for producing β-amino carbonyl compounds, which are key intermediates in the synthesis of numerous industrially valuable compounds. Typically, β-amino carbonyl compounds are synthesized using aldehydes, amines, and silyl enolates. The use of p-dodecylbenzenesulfonic acid (DBSA) as a Brønsted acid-surfactant-combined catalyst (BASC) has been reported to facilitate reactions involving aldehydes, amines, and various nucleophiles, such as silyl enolates, ketones, Danishefsky's diene, or allyltributyltin, (Manabe, Iimura, Sun, & Kobayashi, 2002) in an aqueous medium. (Scheme 3)

Among the catalysts evaluated, DBSA demonstrated exceptional efficiency in promoting the conversion of structurally diverse reactants in both Mannich-type and allylation reactions. (Manabe, Mori, & Kobayashi, 2001b) Notably, p-toluenesulfonic acid (TsOH), which has a shorter alkyl chain than DBSA, produced only trace amounts of the desired product. This highlights the critical role of DBSA's longer alkyl chain in catalysis, as it facilitates the formation of hydrophobic colloidal particles in water, significantly enhancing its catalytic performance. In contrast, lauric acid, a long-chain carboxylic acid with weaker acidity, exhibited much lower efficiency. Microscopic analysis of the colloidal dispersion revealed that the substrates and catalyst molecules are concentrated within spherical particles, which act as hydrophobic reaction sites, enabling rapid reactions in an aqueous medium. (Manabe, Mori, & Kobayashi, 2001)



Scheme 3: Mannich-type and allylation reactions in the presence of DBSA catalyst in water

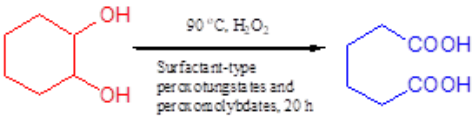
The aqueous extract of Acacia concinna pods has been explored as a potential natural surfactant-based catalyst. This extract effectively promotes the condensation of Meldrum's acid with salicylaldehyde and various aromatic aldehydes, enabling the efficient synthesis of 3-carboxycoumarins and cinnamic acids under mild conditions with high yields. (Scheme 4) For instance, the reaction between benzaldehyde and Meldrum's acid at room temperature produces the condensation product, while heating the reaction to 60 °C results in the formation of cinnamic acid with excellent yield. (Chavan & Bandgar, 2013)



Scheme 4: Synthesis of 3-Carboxycoumarins using 2-hydroxy benzaldehyde and Meldrum's acid

Heteropolyperoxo- and isopolyperoxo-tungstates, along with molybdates, have been utilized as catalysts in the oxidation of tertiary amines, alkenes, and alcohols,

employing hydrogen peroxide as a co-oxidant. (Bailey, Griffith, & Parkin, 1995) Zhu et al. investigated surfactant-like peroxotungstates and peroxomolybdates as catalysts for the oxidation of cyclohexene, cyclohexanol, cyclohexanone, and 1,2-cyclohexanediol into adipic acid using 30 wt.% hydrogen peroxide (H2O2). [11] These polyoxoperoxometalates serve a dual purpose, functioning both as catalysts and as phase transfer agents that facilitate the formation of emulsion droplets. These droplets, which are highly dispersed, mimic the behaviour of homogeneous catalysts, resulting in enhanced catalytic activity. (Scheme 5) At the droplet interface, the long hydrophobic carbon chains are organized, with catalysts containing peroxotungstate anions exhibiting superior efficiency. In comparison, peroxomolybdate-based catalysts show lower activity. Among the reactants tested, 1,2-cyclohexanediol achieved the highest yield of adipic acid.



Scheme 5: surfactant-type peroxotungstates and peroxomolybdates as catalysts for conversion of cyclohexanediol into adipic acid

Conclusions and Future Scope

Micellar media have emerged as a highly promising platform in the field of catalysis, providing distinct advantages in terms of reactivity, selectivity, and environmental sustainability. These systems utilize micelles, self-assembled aggregates of surfactant molecules to create unique microenvironments that enhance reaction rates and enable precise control over product selectivity. The hydrophobic cores of micelles can concentrate reactants, while their organized structures allow for selective interaction with catalytic species. As research progresses, deeper investigations into surfactant architectures, micelle morphologies, and their dynamic behaviour will unveil new catalytic opportunities. Tailoring the size, shape, and surface properties of micelles could optimize reaction pathways and expand their application to more complex transformations. By integrating micellar systems into chemical processes, it is possible to reduce the use of hazardous organic solvents, lower energy consumption, and minimize waste generation. This aligns seamlessly with the principles of green chemistry, offering a pathway toward more sustainable, efficient, and innovative industrial practices.

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Nanoparticles from Nature: Green Synthesis of Silver and Copper Nanoparticles Using *Pithecellobium dulce*

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Abstract

The green synthesis of nanoparticles has gained significant attention due to its environmentally friendly approach, utilizing plant extracts as reducing and stabilizing agents. This study explores the green synthesis of silver (Ag) and copper (Cu) nanoparticles from the leaf extract of the medicinal plant Pithecellobium dulce. The synthesis was carried out by mixing the plant leaf extract with metal salt solutions of silver nitrate ($AgNO_3$) and copper sulfate ($CuSO_4$) under ambient conditions. The formation of nanoparticles was confirmed through UV-Vis spectroscopy, which displayed characteristic absorption peaks at specific wavelengths corresponding to the plasmon resonance of silver and copper nanoparticles. The synthesized nanoparticles were further characterized using techniques such as FTIR, XRD, AFM, SEM, EDX and HRTEM. These results revealed the formation of spherical nanoparticles with an average size ranging from 10 to 50 nm. The antioxidant potential of the synthesized nanoparticles was evaluated against common bacterial strains, demonstrating notable activity. This study highlights the potential of Pithecellobium dulce leaf extract as a sustainable and eco-friendly source for the synthesis of metal nanoparticles with antimicrobial properties

Keywords: Green Synthesis, Silver Nanoparticles, Copper Nanoparticles, Pithecellobium dulce, Antioxidant Activity, Nanoparticle Characterization

Introduction

The term “medicinal plant” includes various types of plants used in herbalism ("herbology" or "herbal medicine"). It is the use of plants for medicinal purposes, and the study of such uses. The word “herb” has been derived from the Latin word, “herba” and an old French word “herbe”. Now a days, herb refers to any part of the plant like fruit, seed, stem, bark, flower, leaf, stigma or a root, as well as a non-woody plant. Earlier, the term “herb” was only applied to non-woody plants, including those that come from trees and shrubs. These medicinal plants are also used as food, flavonoid, medicine or perfume and also in certain spiritual activities.

Traditional systems of medicine continue to be widely practised on many accounts. Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several synthetic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments.

Treatment with medicinal plants is considered very safe as there is no or minimal side effects. These remedies are in sync with nature, which is the biggest advantage. Now, after finding the role of herbs in medicine, lots of consumers started the plantation of tulsi and other medicinal plants in their home gardens. Medicinal plants are considered as a rich resource of ingredients which can be used in drug development either pharmacopoeial, non- pharmacopoeial or synthetic drugs. A part from that, these plants play a critical role in the development of human cultures around the whole world. Moreover, some plants are considered as important source of nutrition and as a result of that they are recommended for their therapeutic values [1].

Why do plants have medicinal properties?

Plants produce many chemicals that are biologically active, not just in themselves, but also in other organisms. Some of these chemicals enhance their own survival. Below are several examples of active plant ingredients that provide medicinal plant uses for humans.

Alkaloids: This group is comprised of a wide variety of plants that contain nitrogen-bearing molecules that make them very active. Many of these plants have been used to create well-known drugs used for medicinal purposes. One such example, vincristine, which was derived from the Madagascar periwinkle (Catharanthusroseus), is used to treat some types of cancer.

Flavonoids: Flavonoids are found widely throughout the plant world and they have a wide range of medicinal uses and actions. They often act as pigments giving a yellow or white color to flowers and fruits. Some flavonoids have anti-viral and anti-inflammatory properties.

Minerals: Many plants have high levels of minerals because they can draw minerals from the soil and can convert them into a form that is more easily used by the human body. Mineral content is often the key factor in a plant‟s effectiveness as a medicine.

Phenols: Phenols are plant compounds that are thought to be produced to protect against infection and herbivory by

insects. They are often anti-inflammatory and antiseptic and can have anti-viral properties. Phenols vary in structure and range from salicylic acid (similar to aspirin) to complex sugar-containing phenolic acids.

Saponins: This group of active compounds obtains its name from the fact that like soap, they produce lather when placed in water. There are two main forms of saponins: steroidal and triterpenoid.

Tannins: Most plants produce tannins. Tannins serve as a deterrent to herbivory by insects and grazing animals given that that they provide a harsh unpalatable flavor. Tannins are also useful in curing leather because of their tendency to contract and astringe tissues by binding with precipitating proteins.

Vitamins: Many plants contain high levels of useful vitamins. Many well-known fruits and vegetables have high levels of vitamin C and beta-carotene. Lesser-known vitamin containing plants like watercress, rose hips, and sea buckthorn have high levels of vitamins B, C, and E.

Volatile oils: Volatile oils are extracted from plants and are used to produce essential oils that play a very important role in medicinal botany. These oils are often very complex and can be comprised of 100 or more compounds. These oils have manyuses. For example, tea tree oil is a strong antiseptic [2].

History and development of nanomaterials

Humans already exploited the reinforcement of ceramic matrixes by including natural asbestos nano fibers more than4,500 years ago [3]. The Ancient Egyptians were also using NMs more than 4000 years ago based on a synthetic chemical process to synthesize ≈5 nm diameter PbS NPs for hair dye [4] Similarly, "Egyptian blue" was the first synthetic pigment which was prepared and used by Egyptians using a sintered mixture nanometer-sized glass and quartz around 3rd century BC [5]. Egyptian blue represents a multifaceted mixture ofCaCuSi4O10 and SiO2 (both glass and quartz). In ancient geographical regions of the Roman Empire, including countries such as Egypt, Mesopotamia, and Greece, the extensive use of Egyptian blue for decorative purposes has been observed during archaeological explorations. In 2003, Samsung introduced an antibacterial technology with the trade name Silver Nano™ in their washing machines,airconditioners, refrigerators, air purifiers and vacuum cleaners,which use ionic Ag NPs [6].

Nanotechnology

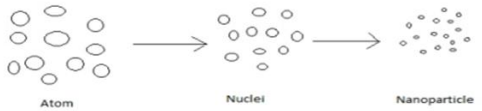
Nanotechnology an emerging field of nanoscience deals with nano size particles having a size of 1-100nm. These nanomaterials are considered as "smart" materials used for constructing nanocarriers, which plays a vital role in drug delivery systems and possess high biocompatibility nature [7]. Nanoparticles have received special attention due to greater surface area to volume ratio and highly reactive than macromolecules [8]. Employing nanotechnology, green method for the synthesis of nanoparticles provides tremendous advantages as it is free of toxic chemicals and eco - friendly.

Classifications of nanoparticles

Nanoparticles can be broadly classified into two groups: Organic nanoparticles and Inorganic nanoparticles. Organic nanoparticle is carbon nanoparticle (fullerenes) and inorganic nanoparticles are magnetic nanoparticle, noble nanoparticle (gold and silver), semiconductor nanoparticle (titanium oxide and zinc oxide). Especially inorganic nanoparticles have created attention towards itself due to its superior material properties with versatile functions. Due to nano size feature, it easily used for chemical imaging drugs agents and drug. Its versatile function used for the cellular delivery as they are widely available, rich functionality, good biocompatibility. This is also a good carrier of targeted drug delivery and controlled drug release [9]. it is a completely advantageous material foe medical science for example mesoporous silica combined with molecular medicines shows an excellent image on drug releasing. Gold nanoparticle is good carrier in thermo therapy of biological target [10]. Silver nanoparticle shows antimicrobial activity which heals the wounds and infectious disease.

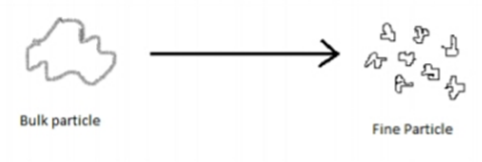
Traditionally, researchers generally used two methods for the synthesis nanoparticles such as Bottom-up approach: The bottom-up approach is a nano-architectural phenomenon of self-assembly of materials from cluster-to-cluster, molecule-to-molecule or atom-to-atom on top of a base substrate. The main concern in the bottom-up approach is the adhesion of the surface layers to the base substrate. The most commonly used bottom-up methods are wielding & riveting.

Fig1.1: Bottom High approach



Top-down approach: The Top-down method refers to a set of fabrication technologies starting with a block bulk material which share the same material with the base substrate. The most commonly used top-down methods are milling, drilling and grinding.

Fig1.2: Top-down approach



Common Medicinal Plants used for Nanoparticle Synthesis

The green synthesis method is used to produce the nanoparticles as it is cost effective and main advantage is its eco-friendly approach compared to other methods. Some specific plant parts or whole plant especially angiospermic plants are used for the greater synthesis of nanoparticles [11]. Many of them reported that plant like Musa sapientum [12] Clerodendruminerme [13] Coriandrumsativum [14] catharanthusroseus [15] Saururus Chinenis [16] are used for the synthesis of nanoparticles. Synthesis and Characterization of CuNPs using Capparis zeylanica leaf Extract. The leaf extract acts as both reducing and capping agent. The synthesized CuNPs were confirmed by the change of color after addition of leaf extract into the CuSO4 solution. The biosynthesized CuNPs were characterized by using UV-Visible analysis, FTIR, XRD, SEM, EDX and

TEM analysis. The synthesized CuNPs were in cubical structure with the particle size in the range between 50-100 nm. The antimicrobial study of the CuNPs was established using both gram positive and gram-negative pathogens [17]. The synthesized CuNPs showed zone of inhibition against *E. coli*. The leaf extract shows higher antioxidant activity as found by DPPH and hydrogen peroxide assay. The size and the morphology were confirmed by TEM [18]. A study has reported the anti-bacterial activities of Terminalia catappa bark against pathogenic bacteria and exhibited the growth inhibitory activity in a dose dependant manner [19]. In some other work, the biologically synthesized copper nanoparticles were tested for antibacterical activity against two human pathogens viz., E. coli and staphylococcus aures [20] One of the literature studies reveal the shape of the nanopartciles which addresses various form of triangular, cubic and hexagonal polyshaped AgNPs which was distinct while compared with AuNP which was appleared like spherical [21].

Plant Extract as a Reducing Agent for Metal Nanoparticle Synthesis

Of several biological methods available for the preparation of metal nanoparticles, leaf extract method is simple and cost effective. Because of their reducing ability of metal salts to nano metal particles, different leaf extracts were used. Most of the bio nanocomposites were made using metal nanoparticles as fillers. Of these, AgNPs and copper nanoparticles (CuNPs) were found to possess good antibacterial activity [14]. However, AgNPs are expensive so slowly shifting towards using CuNPs for antibacterial applications. Further, CuNPs can be used to form stable polymer nanocomposites due to their electrostatic interactions with the matrix [22]. There are several methods of generating metal nanoparticles such as physical, chemical and biological. Of these, biological method such as using leaf extract as a reducing agent is simple and economical [23]. The ability of leaf extract as a reducing agent was attributed to the presence of secondary metabolites in it. Most of the polymer composites and nanocomposites made using synthetic polymer matrices are non-biodegradable and pose many environmental problems. Hence, the trend is now shifted towards preparation of biodegradable nanocomposites using natural polymers. Most of the researchers concentrated on the synthesis of metal nanoparticles which can be subsequently used as nano fillers in different matrices to make nanocomposites. But often uneven dispersion of nanoparticles in a polymer matrix leads to their agglomeration. So whenever possible, it is advisable to in situ generate metal nanoparticles inside polymer matrices for their uniform distribution [24].

Silver Nanoparticles

The extraordinary optical properties of silver nanoparticles were used by glass founders as far back as in the time of the Roman Empire. This is evidenced by the so-called Lycurgus cup (4thcentury AD) now exposed in the British Museum. A detailed study of the composition of its bronze-mounted insets of stained glass, carried out in the late 20th century, revealed the presence of metal nanoparticles (with the average diameter of 40 nm) that consists of silver (70 %) and gold (30 %) alloy [25]. This

explained a remarkable feature of this bowl to change its color from red in transmitted light to grayish green in reflected light. In the preparation of this glass, nano silver was formed insitu.

Before the 1980s, the scientific and practical interest in silver nanoparticles was exclusively caused by the possibility of their use as highly dispersed supports for enhancing the signals from organic molecules in the Raman spectroscopy [26]. Fundamental studies carried out in the last three decade shows that silver nanoparticles exhibit a rare combination of valuable properties, namely, unique optical properties associated with the surface Plasmon resonance (SPR), well-developed surfaces, catalytic activity, high electrical double layer capacitance, etc. [27]. That's why they serve as a material in the development of new-generation electronic, optical and sensor devices. In the past 20 years, the trend miniaturization and the necessity of modernization of technological processes led to the substantial increase in the number of scientific publications devoted to the synthesis and ii of silver nanoparticles; at present, their synthesis is among the most actively developing trends of colloid chemistry.

Silver Nanoparticle Synthesis from and Leaf Extract

The Pithecellobium dulce extract and tissue culture derived callus have proved as reducing agents for synthesis of AgNPs. Presence of polyphenols and tannic acid plant derived compounds can effectively reduce the metal salts into nanoparticles. The variable size range of the nanoparticles is 5-20 nm. Approaching these plants based biological methods are single step and able to synthesize large quantity. The callus extract and the leaf extract of Pithecellobium dulce plant, derived silver nanoparticles have higher antimicrobial activity against the clinical pathogens, Pseudomanas aeruginosa, Staphylococcus aureus, Listeria monocytogenes, Micrococcus luteu and Klebsiella pneumonia and fungi Alternaria alternata, Candida albicans, Penicillium italicum, Fusarium equisetii [28].

Application of Silver Nanoparticles

Silver nanoparticles have more applications in many areas, including biomedical, materials science, and catalysis. This is because of their unique properties when compared with their bulk solid. This part of the literature will give a brief description.

Human Health

Nanoparticles have many different effects on human health relative to bulk material from which they are produced [29]. Increase the biological activity of nanoparticles can be beneficial, deterimental or both. Many nanoparticles are small enough to have an access to skin, lungs, and brain [30,31]. Exposure of metal containing nanoparticles to human lung epithelial cells generated reactive oxygen species, which lead to oxidative stress and damage of the cells [32,33]. A study on toxic effects of silver nanoparticles was done on zebrafish as a model due to its fast development and transparent body structure. The results show a deposition of particles on organs and severe developmental effects. The biocompatibility and toxicity of silver nanoparticles were exhibited by observing single silver nanoparticles inside embryos at each development stage. The types of abnormalities in

zebra fish were strongly dependent on the dose of silver nanoparticles [34].

Environmental

Silver nanoparticles are of great concern to wastewater treatment utilities and to biological systems. The inhibitory effects of silver nanoparticles on microbial growth were evaluated at a treatment facility using an extant respirometry technique. The nitrifying bacteria were susceptible to inhibition by silver nanoparticles, which could have detrimental effects on the microorganisms in wastewater treatment. The environmental risk of silver nanoparticles was recently investigated by determining released silver from commercial clothing. The sock material and wash water contained silver nanoparticles of 10–500 nm diameter.

Catalytic Action

High surface area and high surface energy predetermine metal nanoparticles for being effective catalytic medium. Growing small particles of silver have been observed to be more effective catalysts than stable colloidal particles. These growing particles catalyzed the borohydride reduction of several organic dyes. The reduction rate catalyzed by growing particles is distinctly faster compared to that of stable and larger silver particles, which are the final products of growing particles. Catalysis is due to efficient particle-mediated electron transfer from the BH4 ion to the dye. The catalytic activity of the particles depends on their size, E1/2 of the dye, and the dye-particle interaction. Catalytic activity of silver nanoparticles can be controlled by its size, as redox potential depends on the nanoparticle size [35].

Antimicrobial

Silver is a non-toxic, safe inorganic antibacterial agent being used for centuries and is capable of killing about 650 microorganisms that cause diseases. Silver has been described as being 'oligodynamic', that is, its ions are capable resistant a bacterostatic (growth inhibition) or even a bactericidal (antibacterial) impact. Therefore, it has the ability to exert a bactericidal effect at minute concentration [36]. It has a significant potential for a wide range of biological application such as antibacterial agents for antibiotic resistant bacteria, preventing infections, healing wounds and anti-inflammatory. Silver ions (Ag+) and its compounds are highly toxic to microorganism exhibiting strong biocidal effect on many species of bacteria but have a low toxicity towards animal cells.

Copper nanoparticles

In recent years, the preparation of copper nanoparticles has received increasing attention from many researchers since copper nanoparticles are viewed as possible replacements for Ag and Au nanoparticles because of their useful anti-microbial, anti-biotic and anti-fungal (fungicide) agent and for their potential electrical, dielectric, magnetic, optical, imaging, catalytic, biomedical and bioscience properties [37]. Although copper is one of the most widely used materials in various applications, its synthesis in nano sizes is challenging due to its high tendency for oxidation. Unlike gold and silver, copper is extremely sensitive to air, and the oxide phases are thermodynamically more stable. Therefore, the formation of a surface oxide layer on copper nanoparticles is inevitable. The presence

of copper oxides on the surface of nanoparticles is not desirable for many industries, such as electronics that count on copper as a good alternative for current expensive metals. The electrical conductivity of copper nanoparticles decreases dramatically if they become impure with oxide phases. One can rarely find a method in literature that produces pure copper nanoparticles, unless the whole procedure was done under an inert atmosphere [38]. The achievement in synthesis of pure copper nanoparticles by reducing copper salt in the presence of surfactant [39].

Application of Copper nanoparticles

Metallic nanoparticles can be used in heat transfer systems to improve efficiency. Fluids containing metallic nanoparticles with a thermal conductivity of about three times that of a pure fluid could double the fluid's heat transfer rate. It is reported that adding only 0.3 volume percent of copper nanoparticles, with average diameter of less than 10 nm, to ethylene glycol increased its thermal conductivity up to 40% [40]. A major problem facing fuel-cell technologies is formation of high levels of carbon monoxide (CO) which is produced during hydrogen production. One way to eliminate the CO byproduct is to combine it with water to produce hydrogen gas and carbon dioxide (CO2) in a process known as the "water- gas shift" reaction (See reaction below).

$$CO + H2O \rightarrow H2 + CO2$$

With the assistance of proper catalysts, the water-gas shift reaction can convert a large portion of carbon monoxide into carbon dioxide. For this purpose, to achieve greatest catalytic activity, nanoparticles (2 - 4 nm) of either gold or copper supported on a metal oxide (zinc oxide, ZnO and cerium oxide, CeO2) have been used. Although, gold nanoparticles show the greatest catalytic activity in water-gas shift reaction, copper is almost as reactive, and its cost is much lower [41].

Antibacterial activity

AgNPs are able to physically interact with the cell surface of various bacteria. This is particularly important in the case of Gram-negative bacteria where numerous studies have observed the adhesion and accumulation of AgNPs to the bacterial surface. Many studies have reported that AgNPs can damage cell membranes leading to structural changes, which render bacteria more permeable [42].

The correlation between the bactericidal effect and AgNP concentrations is bacterial class dependent [43]. Indeed, Pseudomonas aeruginosa and Vibrio cholera were more resistant than E. coliand Salmonella typhi, but at concentrations above 75 μg/mL, the bacterial growth was completely abolished [44].

AgNPs have been shown to be definitely an effective antibiotic against E. coli, S. typhi, Staphylococcus epidermidis and S.aureus [45]. Increasing scientific evidence has demonstrated that AgNP activity would depend not only on their concentration and size [46], but also on their shape [47]. The effect of nanoparticles with spherical, rod-like and triangular shapes against E. coli. They showed that all of them had antimicrobial activity, with the triangular nanoparticles being qualitatively more effective. Probably the triangular shape gives a greater positive charge to the nanoparticles, which together with the

active facets on a triangular-shaped particle is able to ensure a greater activity. It has been suggested that AgNPs also interfere with bacterial replication processes by adhering to their nucleic acids [46]. All factors which influence the activity of AgNPs (concentration, size, shape, UV radiation and the combination with various antibiotics) should be taken into consideration when preparing AgNPs for clinical use [48]. Notwithstanding the many conflicts in the literature regarding the effects of antibacterial AgNPs, it is likely that it is the result of a combined effect of each contributing feature, which provide a broad spectrum of antibacterial activity and decrease the probability of developing resistance [49].

Phytochemical screening

Among the 120 active compounds currently isolated from the higher plants are widely used in modern medicine, today 80 percent show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived [50]. The phytochemical interaction and trace components may alter the drug response in ways that cannot currently be replicated with a combination of few purative active ingredients. Pharmaceutical researchers recognize the concept of drug synergism but note that clinical trials may be used to investigate the efficacy of a particular herbal preparation, provided the formulation of that herb is consistent [51]. There is evidence that using some alternative medicines especially those evolving herbs, metals, minerals or other materials involves potentially serious risks including toxicity [52]. With the development of natural product chemistry, the potential of chemotaxonomy is now being increasingly obvious. The application of chemical data to systematics has received serious attention of a large number of biochemists & botanists [53]. The screening of plant extracts of plant products for antimicrobial activity has shown that higher plants represent a potential source of novel antibiotic proto types [54]. Hence during the present investigations phytochemical screening of certain native plants of Agra city is carried on with a view to analyse the presence of chemical constituents that included primary & secondary metabolites, with a view to recommend their application in pharmaceutical industry.

Enzyme

All enzymes are protein [55]. Enzymes are the proteins that are produced by living organisms to regulate their biochemical processes. Enzymes can be also known as catalysts that speed up biochemical processes without itself being consumed [56]. Enzyme can be classified into six major types according to the reaction types catalyzed. The six major types of enzymes are tabulated in Table 1.1 [57].

Class	Type of chemical reaction catalyzed	Example
Hydrolase	Hydrolysis reaction	Digestive enzymes
Isomerase	Rearrangement of atoms within a molecule	Fumarases
Ligase	Joining two molecules by forming a new bond.	Citric acid synthetases
Lyase	Nonhydrolytic removal of a groups	Decarboxylases, Aldolases
Oxidoreductase	Oxidation or reduction reactions which hydrogen or oxygen atoms are gained or lost.	Dehydrogenase, Cytochrome oxidase
Transferase	Transfer of function group	Transaminase

***Table 1.1: Classification of enzymes*.**

Enzymes with Special Characteristics

Special characteristics of microbial enzymes include their capability and appreciable activity under abnormal conditions, mainly of temperature and pH. Hence, certain microbial enzymes are categorized as thermophilic, acidophilic or alkalophilic. Microorganisms with systems of thermostable enzymes that can function at higher-than-normal reaction temperatures would decrease the possibility of microbial contamination in large scale industrial reactions of prolonged durations [58-60]. The quality of thermo stability in enzymes promotes the breakdown and digestion of raw materials; also, the higher reaction temperature enhances the penetration of enzymes [61]. The complete saccharification and hydrolysis of polysaccharides containing agricultural residues requires a longer reaction time, which is often associated with the contamination risks over a period of time. Therefore, the hydrolytic enzymes are well sought after, being active at higher temperatures as well as retaining stability over a prolonged period of processing at a range of temperatures. The high temperature enzymes also help in enhancing the mass-transfer and reduction of the substrate viscosity [62,63] during the progress of hydrolysis of substrates or65aw materials in industrial processes. Thermo philicxylanase are considered to be of commercial interest in many industries particularly in the mashing process of brewing. The thermo stable plant xerophytic isoform of laccase enzyme is considered to be useful for their applications in textile, dyeing, pulping and bioremediation [64,65].

Antioxidant

Antioxidant research is an important topic in the medical field as well as in the food industry. Many plants, particularly medicinal ones, have been extensively studied for their antioxidant activity in recent decades. Antioxidants from aromatic, spicy, medicinal, and other plants were studied to develop natural antioxidant formulations for food, cosmetic, and other applications [66]. It is believed that an increased intake of food rich in natural

antioxidants is associated with lower risks of degenerative diseases, particularly cardiovascular diseases and cancer [67]. There are three major classes of plant chemicals: terpenoids, phenolic, and alkaloids [68]. Among these three groups, phenolic compounds are the most important for dietary applications and the most extensively researched ([69]. Phenolic compounds include phenolic acids (hydroxybenzoic and hydroxycinnamic acids), polyphenols (hydrolyzable and condensed tannins), and flavonoids. These compounds can scavenge excess free radicals and effectively reduce oxidative stress, which protect plants, fruits, and vegetables and protect DNA, protein and lipids in the human body from oxidative damage. They have been used as antioxidants by humans, thus preventing diseases from being induced. Finding new and safe antioxidants from natural sources is of great interest for applications as natural antioxidants, functional foods, and neutraceuticals.

In the present study, three commonly used antioxidant evaluation methods such as DPPH radical scavenging activity, reducing power assay and phosphomolybdenum method were chosen to determine the antioxidant potential of seeds.

Aromatic plants are well known for their antioxidant and antimicrobial properties that prevent food degradation and alteration [70], as they are rich in phenolic substances, usually referred to as polyphenols, which are ubiquitous components of plants and herbs. Halliwell and Gutteridge [71] defined antioxidants as compounds that—when present in low concentration in relation to the oxidant—prevent or delay the oxidation of the substrate. Their importance in the safeguarding of health, and the protection from coronary heart disease and cancer, has recently been established, thus constituting them as functional food preservatives. Polyphenols are antioxidants with redox properties, which allow them to act as reducing agents, hydrogen donators, and singlet oxygen quenchers. Some show metal chelation properties [72,73]. In addition, some have antimicrobial activity [74].

Objectives

- To study the synthesis of silver copper nanoparticles from the leaf extract of the medicinal plant *Pithecellobium dulce*.
- To study the isolation of enzyme from the leaves of Pithecelobium dulce by standard methodology and synthesis silver nanoparticles from the enzyme.
- To study the formation and absorption properties of biosynthesized nanoparticles by UV-visible (UV-vis) spectroscopy techniques.
- To identify the functional groups of phytochemicals in the leaf extract by FourierTransform Infrared (FT-IR).
- To study the size, structure and phase synthesized nanoparticles by using X-ray diffraction (XRD) techniques.
- To study the surface morphology (shape and size) of the nanoparticles by Atomic force microscopy (AFM), Scanning Electron Microscopy (SEM) with Energy dispersive X-Ray Analysis (EDAX) and Transmission electron microscopy (TEM) techniques.

- To study the antioxidant activity of green synthesis silver nanoparticles from enzyme by phosphomolybdenum method.

Literature Review

- Hutchison et al. (2008) [75] Nanoscience involves the study of materials on the nanoscale level between approximately 1 and 100 nm in length in at least one dimension.
- Rosi and Mirkin et al (2005) [76] The study of how to control the formation of two- and three-dimensional assemblies of molecular scale building blocks into well-defined nanostructures or nanomaterials.
- Uskokovic et al (2008) [77] Nanotechnology is the application of science and technology to control matter at the molecular level, which is also referred to as the ability for designing, production, characterization and application to structures, devices and systems by controlling shape and size at the nanometer scale.
- Burda et al., (2005) [78] Nanotechnology emerges from the physical, chemical, biological and engineering sciences where novel techniques are being developed to probe and manipulate single atoms and molecules. Nanomaterials have broad applications in a variety of fields because of their unusual and size dependent optical, magnetic, electronic and chemical properties.
- Hodes et al, (2007) [79] Nanoparticles are characterized by an extremely large surface area to volume ratio, and their properties are determined mainly by the behaviour of their surface.
- Hsiao et al., (2006) [80] Nanobiotechnology is an emerging area of opportunity that seeks to fuse nano/micro fabrication and biosystem to the benefit of both. Increasing awareness towards green chemistry and other biological processes has led to the development of simple and eco-friendly approaches towards the synthesis of nanomaterial.
- Goyeret al, (1997) [81] Copper is one of a relatively small group of metallic elements that are essential to human health as it is a constituent of many enzymes involved in numerous body functions and is a constituent of hair and of elastic tissue contained in skin, bone and other body organs.
- Airey and Verran et al, (2007) [82] A number of recent studies have explored the potential benefit of using copper in place of stainless steel on surfaces to reduce bacterial loads in a number of settings including hospitals and the food industry.
- Moya et al., (2006) [83] Copper nanoparticles can easily oxidize to form copperoxide. If the application requires the copper nanoparticles to be protected from oxidation, the copper nanoparticles are usually encapsulated in organic or inorganic materials such as carbon and silica.
- Esteban-Cubillo et al., (2006) [84] Colloidal copper has been used as an antimicrobial agent for decades. Copper monodispersed nanoparticles (2-5nm) embedded into a polysilicate called sepiolite

(Mg8Si12O30 (OH)4(H2O)4.8H2O) haverevealed a strong antibacterial activity and were able to decrease the microorganism concentration by 99.9%.

- Cioffi et al., (2005) [85] Copper nanoparticles (about 6 nm) embedded in polyvinylmethylketone films exhibit a noticeable inhibitory effect on the growth of microorganisms (*E. coli* and *S. cerevisiae*).
- Theivasanthi and Alagar et al, (2011) [86] Almost all properties of nanoparticles are due to their small sizes and they are attracting a great deal of attention because of their potential for achieving specific processes and selectivity, especially in biological and pharmaceutical applications.
- A.Mills et al., (1997) [87] described Photocatalysis generally involves the process of photosensitization, where a photochemical reaction occurs in one chemical species due to the absorption of photonic energy by another species called photosensitize.
- C.Haefeli et al. (1984) [88] The first evidence of bacteria synthesizing silver nanoparticles was established using the Pseudomonas stutzeri AG259 strain that was isolated from silver mine.
- M. Husseiny et al., (2006) [89] There are some microorganisms that can survive metal ion concentrations and can also grow under those conditions, and this phenomenon is due to their resistance to that metal.
- R.vaidyanathan et al. (2010) [90] The enzyme converts nitrate into nitrite. In in vitro synthesis of silver using bacteria, the presence of alpha-nicotinamide adenine dinucleotide phosphate reduced form (NADPH) - dependent nitrate reductase would remove the downstream processing step that is required in other cases.
- P. Mohanpuria et al. (2008) [91] When in comparison with bacteria, fungi can produce larger amounts of nanoparticles because they can secrete larger amounts of proteins which directly translate to higher productivity of nanoparticles.
- P. Mukherjee et al. (2001) [92] Trapping of Ag+ ions at the surface of the quinine cells and the subsequent reduction of the silver ions by the enzymes present in the fungal system.
- A.Ahmad et al. (2003) [93] The extracellular enzymes like naphthoquinones and anthraquinones are said to facilitate the reduction. Considering the example of F. oxysporum, it is believed that the NADPH-dependent nitrate reductase and a shuttle quinine extracellular process are responsible for nanoparticle formation.
- A. Jha et al. (2009) [94] In the case of mesophytes, it was found that they contain three types of benzoquinones:cyperoquinone, dietchequinone, and remirin. It was suggested that the phytochemicals are involved directly in the reduction of the ions and formation of silver nanoparticles
- Look et al., (2001) [95] It is found in paints, cosmetics, plastic and rubber manufacturing, electronics andpharmaceuticals. More recently however, it has again gained large

interest for its semiconductingproperties.

- Lovely et al., (1987) [96] It can also be suitably scaled up for large-scale synthesis of nanoparticles. It is well known that biological systems can provide a number of metal or metal containing particles in the nanometer size range. The synthesis of magnetite nanoparticles by magnetotactic bacteria.
- Shang et al., (2007) [97] Although the protein may retain most of its native structure after adsorption on the NP surface, in some cases the thermodynamic stability of the protein is decreased, making the protein more sensitive to chemical denaturants such as urea.
- Zhang et al., (2009) [98] Recent study reported that some nanomaterials catalyze the formation of protein fibrils as evidenced from the fact that interactions between proteins and nanophase materials could induce modifications in protein structure, leading to the growth of extended assemblies.
- Jin et al. (2001) [99] It was reportedthat prismatic structure of AgNPs could be obtained by irradiation of a conventional40-W fluorescent light on previously prepared spherical particles (8.0 ± 1.7 nm).
- Metraux and Mirkinet al, (2005) [100] Compared with photo-induced synthesis, thermal synthesis (or chemical reduction methods) of silver nanoprism were reported to be able to achieve AgNPs of similar shape and size.
- Pal et al. (2007) [101] Synthesis of this specific structure was also appealing to consider due to a proposed mechanism in which different crystal facets may induce different extent of antimicrobial effects.
- Typical procedures for synthesis and characterization of truncated triangular silver nanoplates were reported by Chen and Carroll (2002) [102]. Three phases were involved in the synthesis route: seeding, growthand aging. First, sodium borohydride (NaBH4) was used to reduce Ag+ into Ag (0) with sodium citrate as stabilizing agent.
- Ahmad et al., (2011) [103] During glycolysis NAD (Nicotinamide adenine dinucleotide) formation occurs, which is a co-enzyme found in all living cells. NAD is an oxidizing agent which accepts electrons from other molecules and got reduce.
- The green synthesis of metal NPs, reduction, capping and stabilization steps occur and the biomolecules such as enzymes, proteins sugars etc. due to presence in the plant extract reported by Singh et al. (2015) [104].
- [105] Though the exact mechanism involved in AgNPs production by plants is not fully deciphered. It is believed that the biomolecules are involved directly in the reduction of the ions and formation of AgNPs (Jha et al., 2009).
- [106] The biochemical and molecular mechanisms of AgNPs green synthesis remain undiscovered, for instance biochemical mechanisms underscored the significance of phytoconstituents which may

mediate green synthesis (Chung et al., 2016).

- Li et al., (2007) [107] Silver ions are then reduced by proteins, lead to changes in their secondary structure and the formation of silver nuclei, consequently silver nuclei grow by the reduction of silver ions and their aggregation at nuclei.
- Safeopour et al., (2009) [108] AgNPs are used in the development of new technologies in the areas of electronics, material sciences and medicine and because of their extensive applications in various areas more research is being conducted on the AgNPs by the scientists throughout the world.
- Harikumar et al, (2016) [109] The results obtained from the effect of bacterial load indicated that there was a decrease in antibacterial activity as the bacterial concentration increased. Flow test was conducted for the antibacterial filter by passing contaminated water through the filter and no bacteria were detected.
- Sunitaojha et a, (2017) [110] reported the capping of phytochemicals and thermal stability of RcAgNPs were assessed by FTIR spectraand TGA analysis, respectively. It also showed antibacterial activity against both gram positiveand gram negative strains. RcAgNPs were non-toxic against normal cell line (mouse fibroblast cell line L929) at lower concentrations (80 μg ml−1.
- Shivan and payamalle and hosakatteni Ranjan amurthyet al, (2016) [111] The aim of present study was the evaluation of antibacterial activity of G. xanthochymus seed extracts against some pathogenic bacteria like Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa and Escherichia coli and to analyze the mechanism of its antibacterial action by atomic force microscopy (AFM).
- [112] Khalid et al., (2018) The medicinal importance of these plants depends upon the chemically vital and active substances that produce specific physiological action on the human body. Flavoniods, tannin, phenolic compounds and alkaloids are the most important bioactive components of plants.
- [113] Sathyaprabhu et al., (2018) The enzyme extracted from different parts of the sample show an optimum activity at pH 6 along with a molecular weight ranging between 60 to 100 kDa. In conclusion, the study suggests faba bean can serve as best source of protease enzyme.
- [114] Charalamposproestos et al., (2013). The antioxidant capacity of the plant extracts was measured by their ability to scavenge free radicals such as (a) DPPH(2,2-diphenyl-1-picrylhydrazyl) and, (b) ABTS (2,2′-azinobis-(3-ethylbenzothiaziline-6-sulfonate). The Folin-Ciocalteu method proved the existence of antioxidants in the aromatic plant extracts.

Method and Materials

Pithecellobium dulce

It originated from Mexico, then went to America, Central Asia and then to cooking, contains high wholesome esteem and various medical advantages for body. Besides being a viable normal

cure, it is more moderate contrasted with high-cost medicines in clinics and restorative centres. Studies have concluded that hydro alcoholic fruit extract of *Pithecellobium dulce* can be used safely for experimental and clinical trials. This study was carried out to evaluate acute and sub-acute toxicity profile of HAEPD in 2010. According to the studies performed in 2012, scientists have validated the antimicrobial potential of traditionally important plant, *Pithecellobium dulce*. The bark and pulp of Manila Tamarind is used as a traditional remedy against gum ailments, toothache, and haemorrhage. Bark extract is also used against dysentery, diarrhea, and constipation. An extract of leaves is used for gall bladder ailments and to prevent miscarriage. Seeds when grounds are used to cleanse ulcers. Numerous studies have been performed on anti-oxidant, anti-inflammatory, anti-diabetic, anti-cancer properties of Manila tamarind. It provides relief from pain, eczema, fever, cold, sore throat, pigmentation, acne and pimples.

Pithecellobium dulce

Collection of Plant material and preparation of extract

Pithecellobium dulce leaves collected from natural geographical landscapes of Thoothukudi, in India. The *Pithecellobium dulce* leaves were washed thoroughly then sliced into small pieces and 20g leaf was boiled with 100 mL of sterile distilled water for 15 min in a 500 mL beaker. The extract obtained was filtered through Watmann filter paper No.1. The filtrate was collected and stored at 4°C. Then the solution was used for the reduction of silver ions Ag+) to silver nanoparticles (AgNO3).

Preparation of silver nitrate solution

Seventeen milligrams (17 mg) of silver nitrate (Analytical grade) 99.9% AgNO3, MW = 169.87 g/mol) were weighed using electronic balance and transferred into 500 ml Erlenmeyer flask. The silver nitrate was slowly dissolved by gently swirling the flask containing distilled de-ionized water. After all the solid has dissolved, more water was slowly added to bring the level of solution exactly to a volume mark of 100 ml. The prepared 1 mM silver nitrate solution was stored at 4°C in amber colored bottle.

Synthesis of silver nanoparticles

A volume of 20 ml of aqueous extract of *Pithecellobium dulce* leaves was added to 80 ml of 1 mM of silver nitrate solution in 100 ml Erlenmeyer colored for reduction of Ag+ions and stabilization of AgNPs. The reactions were carried out in darkness (to avoid photo activation of AgNO3) at room temperature. Complete reduction of AgNO3to Ag+ ions was confirmed by visual change of colour from pale green to reddish brown indicated the formation of silver nanoparticles (AgNPs). The synthesis silver nanoparicles stored at 4°C for future use.

Preparation of copper sulfate solution

24.9mg of copper sulfate (Analytical grade) 99.9% CuSO4, MW = 249.68 g/mol) were weighed using electronic balance and transferred into 500 ml Erlenmeyer flask. The copper sulfate

was slowly dissolved by gently swirling the flask containing distilled de-ionized water. After all the solid has dissolved, more water was slowly added to bring the level of solution exactly to a volume mark of 100 ml. The prepared 1 mM copper sulfate solution was stored at 4°C in amber colored bottle.

Synthesis of copper nanoparticles

20mL of *Pithecellobium dulce* leaf extract was added to 80ml of 1 mM aqueous CuSO4.5H2O solution and kept under magnetic stirrer for 2hours (60°C). Complete reduction of CuSO4 to Cu2+ions was confirmed by visual change of colour from pale blue indicated the formation of copper nanoparticles (CuNPs). The synthesis copper nanoparticles stored at 4°C for future use.

Phytochemical screening

The active Phytochemicals present in the floral extract were determined by various tests.

Test for alkaloids

A fraction of extract was treated with Wagners test reagent (1.27g of iodine and 2g of potassium iodide in 100mL of water) and observed the formation of reddish-brown color. It indicates presence of alkaloids.

Test for Flavonoids

A small amount extract was treated with aqueous sodium hydroxide and hydrochloric acid and observed. No yellow orange color. It indicates absence of flavonoids.

Test for Tannins

Few mL of extract was treated with 10% alcoholic ferric chloride solution and observed the formation of blue colour solution. It indicates presence of tannins.

Test for Phenols

The fraction of extract treated with 5% ferric chloride and observed of deep blue color. It indicates presence of Phenols.

Test for Saponins

To the small amount of the extract, 10 mL of distilled water was added and shaken for about 30 seconds and observed the formation of foam, it indicates the presence of saponins.

Test for Steroids

2 ml of chloroform and concentrated H2SO4were added with the 5 ml aqueous plant crude extract. In the lower chloroform layer red color appeared that indicated the presence of steroids.

Test for oils and Fats

a. Spot test: A small quantity of extract is pressed between two filter papers. Oil stain on the paper indicates the presence of fixed oils.

b. Saponification test: A few drops of 0.5 N alcoholic potassium hydroxide solution is added to a small quantity of extract along with a drop of phenolphthalein. The mixture is heated on a water bath for 2 hours. Formation of soap or partial neutralization of alkali indicates the presence of fixed oils and fats

Test for Phytate

Four grams of ground sample was soaked in 100 cm3 of 2% HCl for 3 h and then filtered through two layers of filter paper 25 cm3 of the filtrate was placed in a 250 cm3 conical flask and 5 cm3 of 0.3% NH4SCN solution was added as an indicator, 53.5 cm3 of distilled water was then added to reach

the proper acidity. This mixture was titrated against FeCl3solution, which contains about 0.00195 g of Fe iron per cm3 of FeCl3 solution. The result was multiplied by factor 1.95 to obtain phytate P. phytate P result was multiplied by factor 3.55 to convert to phytate.

Test for Terpenoids

Take 1 ml of extract of each solvent and add 0.5 ml of chloroform followed by a few drops of concentrated sulphuric acid, formation of reddish-brown precipitate indicates the presence of terpenoids in the extract.

Test for Carbohydrates

Take 1 ml of extract, add few drops of Molisch's reagent and then add 1 ml of concentrated sulphuric acid at the side of the tubes. The mixture was then allowed to stand for 2 to 3 minutes. Formation of red or dull violet colour indicates the presence of carbohydrates in the sample extract.

Enzyme extraction

- It is very important to use fresh, desiccated ammonium sulfate. This ensures uniform and rapid dissolution.
- The day before use, place ammonium sulfate overnight in ca. 120°C drying oven in a large beaker or drying dish (ammonium sulfate decomposes at 220°C).
- Clean grinder carefully and grind dry ammonium sulphate to a fine powder. Wear a dust mask (if you don't need a mask, the powder is not dry enough).
- Use ground powder immediately. For 70% saturation use 43.6 grams/100 mLs.
- Add the powder slowly but steadily with thorough mixing. Do not allow clumps to form.
- Allow precipitate to form for 30 minutes at 4°C with stirring.
- Recover precipitate by centrifugation. Solutions highly saturated in ammonium sulfate are quite dense and it can be difficult to pellet the precipitate. For CBF3 prep, spin at 40K in type 45 rotor for 1 hour.
- Remove supernatant, respin briefly to clear remaining ammonium sulfate.
- Resuspend pellets in a volume of buffer equal to the volume of the extract.

Antioxidant assay method

Phosphomolybdenum assay

The antioxidant activity of samples was evaluated by the green phosphomolybdenum complex formation according to the method of Prieto (1999). This method is based on the reduction of phosphomolybdic acid to phosphomolybdenum blue complex by sodium sulfide. The obtained phosphomolybdenum blue complex is oxidized by the addition of nitrite and this causes a reduction in intensity of the blue colour.

Reagent preparation

Reagent was prepared by adding 0.588ml of sulphuric acid, 0.049g ammonium molybdate and 0.036g sodium phosphate. The final volume was made up to 10ml with Dis. H2O.

Working procedure

10mg of plant extract was dissolved in 1ml of DMSO. 100µl from the prepared sample was taken and 1ml of reagent

solution was added to it and incubated in a boiling water bath at 95°C for 90 min. After 90 min, the absorbance of the solution was read at 695 nm. Ascorbic acid (10mg/ml DMSO) was used as standard. The Phosphomolybdenum reduction potential (PRP) of the studied extracts were reported in percentage.

Instrumentation

UV-Vis spectrophotometer

The synthesized silver Nanoparticles were characterized by JASCO variant 630 spectrometer (fig 3.1) within a range of wavelength 200-900nm.

Principle of UV spectroscopy

UV spectroscopy obeys the Beer-Lambert law, which states that: when a beam of monochromatic light is passed through a solution of an absorbing substance, the rate of decrease of intensity of radiation with thickness of the absorbing solution is proportional to the incident radiation as well as the concentration of the solution. The expression of Beer-Lambert law is A = log(I0/I) = Ecl.

Where,

A = absorbance

I0 = intensity of light incident upon sample cell

I = intensity of light leaving sample cell

C = molar concentration of solute

L = length of sample cell (cm.)

E = molar absorptivity

From the Beer-Lambert law it is clear that greater the number of molecules capable of absorbing light of a given wavelength, the greater the extent of light absorption. This is the basic principle of UV spectroscopy.

Fig. UV spectroscopy

Fourier transform infrared (FTIR) spectroscopy

The silver nanoparticles were analysed by for the detection of different functional groups using Thermo scientific Nicolet iS5ATR-iD1 Spectrometer (fig 3.2). The FTIR was recorded in the range of 400–4000 cm-1.

Fig. FTIR Spectrometer

- In FTIR analyses, Infrared light from the light source passes through a Michelson interferometer along the optical path. The Michelson interferometer comprises a beam splitter, moving mirror, and fixed mirror. The light beam split into two by the beam splitter is reflected from the moving mirror and fixed mirror, before being recombined by the beam splitter.
- As the moving mirror makes reciprocating movements, the optical path difference to the fixed mirror

changes, such that the phase difference changes with time. The light beams are recombined in the Michelson interferometer to produce interference light.

- The intensity of the interference light is recorded in an inter ferogram, with the optical path difference recorded along the horizontal axis.

f **=2Vm υ/C** interferogram frequency

$\boldsymbol{v}$**m =**$\delta/2t$. mirror velocity

XRD Analysis

The phase variety and grain size of synthesized Silver nanoparticles was determined by X-ray diffraction spectroscopy (fig3.3) (Philips PAN analytical). The synthesized silver nanoparticles were studies with CUKα radiation at voltage of 30 kV and current of 20 MA with scan rate of 0.030/s. Different ph+ases present in the synthesized samples were determined by X′ pert high score software with search and match facility. The particle size of the prepared samples were determined by using Scherrer′s equation as follows

$$D \approx \frac{0.9\lambda}{\beta\cos\theta}$$

Where D is the crystal size, λ is the wavelength of X-ray, Θ is the Braggs angle in radians and B is the full width at half maximum of the peak in radians. The crystallite size of synthesized product was determined using X-ray diffractometer Bruker AXS D8 Advance operating at a voltage of 40 kV and a current of 30 mA with CuKα radiation operating between 10 and 80° of 2θ angles at scanning rate of 2° per min. Using scherrer equation one can calculate crystallite size from XRD data. Crystallite size= 0.94*X ray wavelength / beta* cos(theta)

Fig. XRD Analysis

Scanning Electron Microscopy (SEM)

This electron microscopy-based technique determines the size, shape and surface morphology with direct visualization of the nanoparticles. Therefore, scanning electron microscopy offer several advantages in morphological and sizing analysis. However, they provide limited information about the size distribution and true population average. During the process of SEM characterization, solution of nanoparticles should be initially converted into a dry powder. This dry powder is then further mounted on a sample holder followed by coating with a conductive metal (e.g. gold) using a sputter coater. Whole sample is then analyzed by scanning with a focused fi ne beam of electrons. Secondary electrons emitted from the sample surface determine the surface characteristics of the sample. This electron beam can often damage the polymer of the nanoparticles which must be able to withstand vacuum. Average

mean size evaluated by SEM is comparable with results obtained by dynamic light scattering. In addition, these techniques are time consuming, costly and frequently need complementary information about sizing distribution. In this research study, Joel JSM-6480 LV SEM (fig3.4) machine was employed to characterize the average particle size and sound structure of nanoparticles. Compositional analysis on the sample was carried away by the energy dispersive X-ray spectrometry (EDS) attached with the SEM. The EDS analysis of Ag sample was served by the SEM (JEOLJSM 5800) machine. The EDS normally reveals the presence of phases.

Fig. Scanning Electron Microscopy

Transmission Electron Microscope

Transmission electron microscopy techniques can provide imaging, diffraction and spectroscopic information, either simultaneously or in a serial manner, of the specimen with an atomic or a sub-nanometer spatial resolution. TEM operates on different principle than SEM, yet it often brings same type of data. The sample preparation for TEM is complex and time consuming because of its requirement to be ultra-thin for the electron transmittance. High-resolution TEM imaging, when combined with nano diffraction, atomic resolution electron energy-loss spectroscopy and nanometer resolution X-ray energy dispersive spectroscopy techniques, is critical to the fundamental studies of importance to nanoscience and nanotechnology. During the TEM characterization nanoparticles dispersion is deposited onto support grids or films. After dispersion they are fixed using either a negative staining material (phosphotungstic acid or derivatives, uranyl acetate, etc., or by plastic embedding). This is done to make nanoparticles withstand against the instrument vacuum and facilitate handling. Alternatively, nanoparticles sample can also be exposing to liquid nitrogen temperatures after embedding in vitreous ice. When a beam of electrons is transmitted through an ultra-thin sample it interacts with the sample as it passes through the surface characteristics of the sample are obtained.

The size and morphology of the synthesized AgNPs were determined by high resolution transmission electron microscopy (HR-TEM, JEOL JEM 2100). (fig 3.6)

Fig. Transmission electron microscopy

Atomic Force Microscopy

This technique is also known as scanning force microscopy (technique that forms images of surfaces using a probe that scans the specimen), very high-resolution type of scanning probe microscopy, with reported resolution on the order of fractions of a nanometer, more than 100 times better than the optical diffraction limit. The atomic force microscopy is based on a physical scanning of samples at sub-micron level using a probe tip of atomic scale and offers ultra-high resolution in particle size measurement. Depending upon properties, samples are usually scanned in contact or noncontact mode. During contact mode, the topographical map is generated by tapping the probe on to the surface across the sample and probe hovers over the conducting surface in non-contact mode. One of the prime advantages of AFM is its ability to image non-conducting samples without any specific treatment. The morphology was investigated by Atomic Force Microscope (AFM) with Nano surf Easy scan 2 AFM (fig 3.7).

Fig. Atomic Force Microscopy

Results and Discussion

UV-VIS Spectroscopic Analysis.

The UV-Vis absorption spectra of AgNPs prepared from leaves extract of Pithecellobium dulce are shown in Figure 4.1. The absorption band of AgNPs occurs at 426 nm. The AgNPs exhibit a yellowish-brown color in aqueous solution due to the excitation in UV-visible spectrum depending upon the particle size.

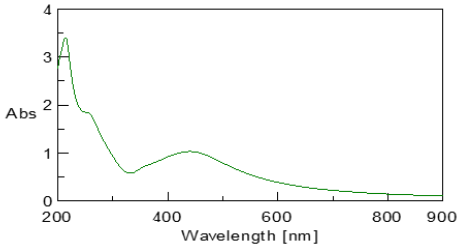


Fig. UV-Vis absorption spectra of AgNPs

UV VIS Spectroscopic analysis for CuNps

UV-VIS spectroscopy It is usually recognized that the UV-Vis spectroscopy could be used to examine the size and shape-controlled nanoparticles in aqueous suspensions. The reduction of copper sulphate to copper nanoparticles was monitored by measuring the UV-Visible spectrum of the reaction medium immediately after diluting a small aliquot of the sample into distilled water. Absorption spectra of copper nanoparticles formed in the reaction media has absorbance peak at 325nm (Fig 4.2).

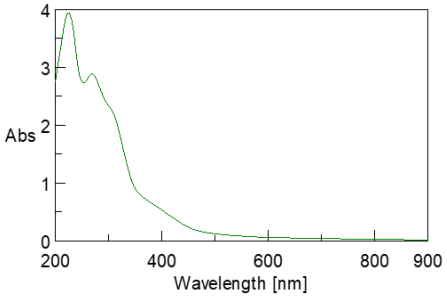


Fig. UV VIS Spectroscopic analysis for CuNps

UV-Visible spectral study in AgNps synthesized from enzyme

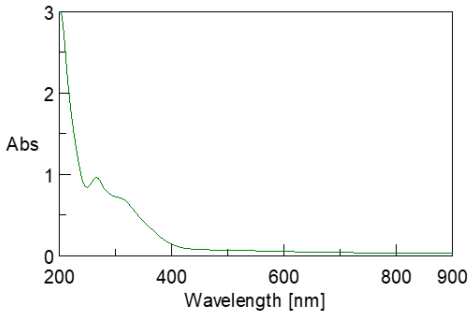


Fig UV-Visible spectral study in AgNps synthesized from enzyme

UV-visible spectroscopy is also of use to detect the presence of large particles (with a hydrodynamic radius higher than 200 nm) in a protein preparation. This can be done by monitoring the absorbance signal above 320 nm, where aggregate-free protein samples are not supposed to absorb light, and the signal can be attributed exclusively to the scattering of light by large aggregates present in the sample.

The UV/Vis spectrum of AgNPs showed a surface plasmon absorption band with maximum absorbance at 267, 314 nm (fig. 4.3).

FTIR Analysis.

The FTIR spectra were carried out to identify the possible biomolecules responsible for capping and reducing agent for the formation of metal nanoparticles. In Figure 4.4, FTIR spectra of silver and copper nanoparticles show strong absorption band at 1603 cm−1 and 1616 cm−1, respectively, and it is attributed to binding of NHC=O to metal ions. Other peaks include 2922 cm−1 (secondary amine),1383 cm−1 (C-N stretching vibration of aromatic amine),1138 cm−1, 821 cm−1, 764 cm−1, and 595 cm−1 for silver nanoparticles and 1383 cm−1, 1074 cm−1, and 601 cm−1 for copper nanoparticles. The presence of peak at 3186 cm−1 and3341 cm−1 could be due to O-H group in poly phenols or proteins or polysaccharide. It has been reported that proteins can bind to metal nanoparticles through the free amine groups or carboxylate ion of amino acid residues.

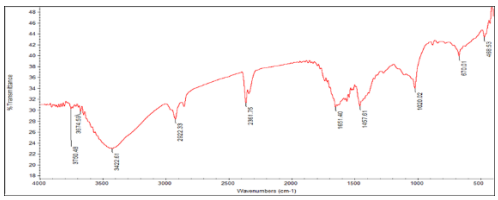
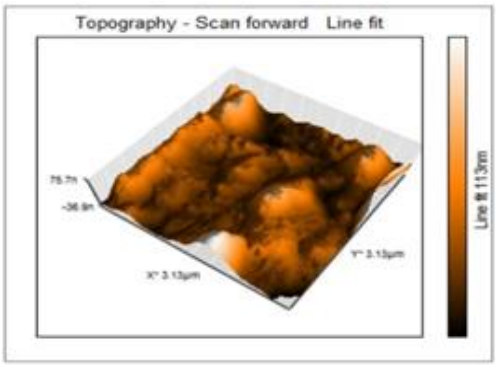


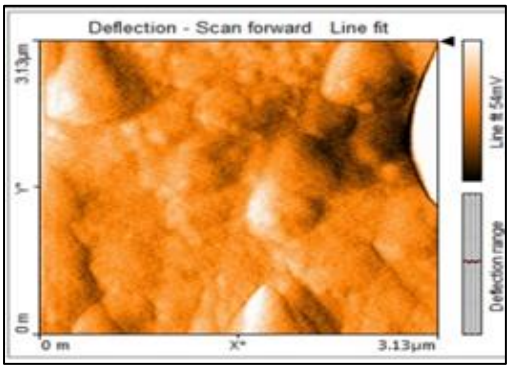
Fig. FTIR Spectrum of Pithecellobium dulce.

AFM Studies of AgNPs and CuNps

Topography of the silver nano particles synthesized from pithecellobium dulce extract were given in the Fig.4.5. Triangular shapes of different sizes were seen in the topography. Spherical shape was reported for the silver nano particles synthesized using aqueous solution of propolis.



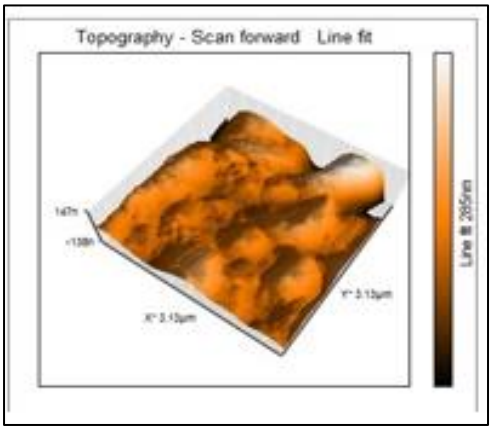
a) 3D view



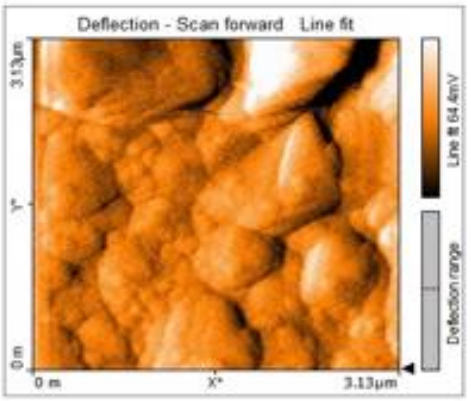
(b) normal view

The silver nanoparticle which was synthesized by pithecellobium dulce extract showed large agglomerated particles. Surface roughness of the silver nanoparticles synthesized from *Pithecellobium dulce*. This increase in roughness may be due to the formation of less agglomerated particles.

AFM images were taken using Nano Surf easy scan 2 AFM (BT02218).
Topography of the copper nanoparticles synthesized from pithecellobium dulce extract were given in the Fig 4.6. Triangular shapes of different sizes were seen in the topography.

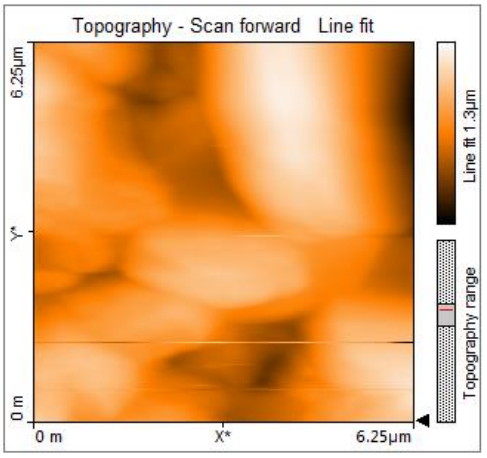


(a)



(b)

AFM studies of AgNPs from Enzyme
Oval shape particles of different diameters are clearly seen on the topography. This resulted due AFM topographies of silver nano particles prepared from Pithecellobium dulce leaf is given in the figure 4.7. to the aggregation of the particles. Surface is uneven with small peaks and small dents. Roughness values are calculated for the surface of area 39.37 pm2.



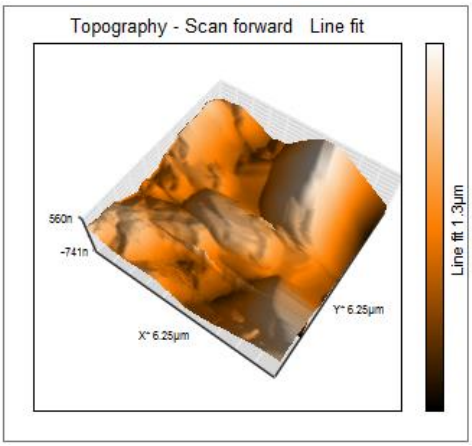


Fig 4.7

X-Ray Diffraction Analysis

The powder XRD of the metal nanoparticles is recorded between 2values 20∘ and 90∘and exhibits crystalline nature and is consistent with earlier reports showing possible peaks of silver and copper metal in Figure 4 [15, 25]. Bragg's diffraction peaks for silver nanoparticles are observed at 38.38∘, 44.48∘, 64.66∘, 77.56∘, and 81.66∘corresponding to 111, 200, 220, 311, and 222, respectively, representing face centered cubic structure of silver. Bragg's refection's for copper nanoparticles are observed in XRD pattern with value of 43.6∘, 50.7∘, and 74.45∘ representing 111,200, and 220 planes of FCC structure of copper. The average crystallite size of AgNPs and CuNPs was calculated to be about 31 nm and 26 nm respectively, using Scherer formula. Crystallite Size Calculation. The average crystallite size has been calculated by using Debye-Scherrer formula.

Table. X-Ray diffraction studies of AgNPs

pos[2Θ]	Height (cts)	FWHM left [2Θ]	d-spacing[Å]	Rel.Int[%]	size(nm)
51.2141	288.42	0.3921	6.621	98.73	23.54
58.3251	202.31	0.3824	6.5281	96.32	17.26
68.2492	201.14	0.3862	6.0814	82.48	15.14
72.8997	114.47	0.3984	5.2048	68.42	21.19
79.0433	61.84	0.2941	4.2804	51.58	31.17
82.8249	41.81	0.4102	4.182	28.01	41.07
99.3021	52.54	0.4201	4.084	21.92	17.81

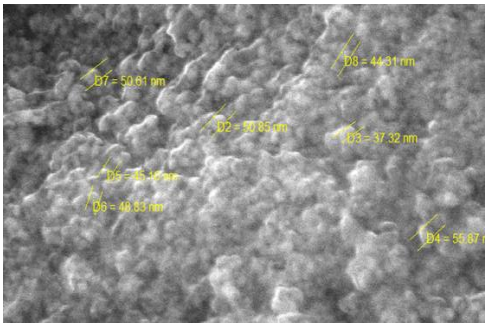
162.3211	41.51	0.4442	4.014	15.02	23.81
142.4284	28.54	0.4012	3.9942	11.92	32.81

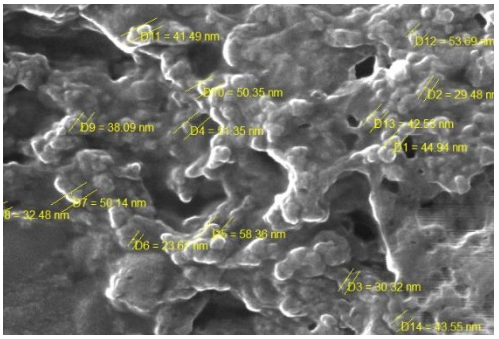
Table X-Ray diffraction studies of CuNPs

pos[2Θ]	Height (cts)	FWHM left [2Θ]	d-spacing[Å]	Rel.Int[%]	size(nm)
38.1759	200.85	0.3553	2.3551	31.98	24.72
44.3197	56.29	0.6764	2.0421	8.96	13.25
46.2811	338.76	0.1716	1.9601	53.95	52.61
54.8576	83.39	0.1698	1.6722	13.28	53.08
57.5224	89.84	0.1913	1.6009	14.31	49.5
64.5007	45.22	0.4181	1.4435	7.2	23.48
77.0516	55.22	0.9851	1.2367	8.79	10.77

SEM Analysis.

The surface morphological and nano structural studies using SEM are shown in Figure 4.8. The SEM micrographs clearly show well aggregates of silver nano-particles of Pithecellobium dulce with average particle sizes ranging from 20 to 65 nm and copper nanoparticles with 30–65 nm in size.

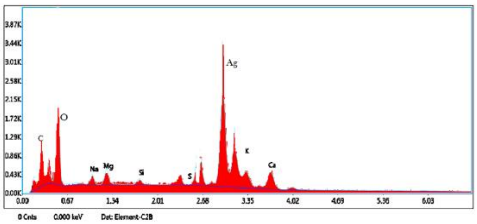




EDAX Analysis.

Below figure shows the elemental profile of synthesized silver and copper nanoparticles using leaves extract of Pithecellobium dulce. The EDX analysis of silver nanoparticles shows an intense signal at 3 keV indicating the presence felemental silver in examined samples. The elemental analysis of the silver nanoparticles shown in the figure revealeda strong silver signal (66.43%)

along with weak signals of O (22.22%) and Cl (8.12%). Furthermore, two small peaks of Si (1.67%) and Al (1.56%) were also observed in the examined sample. The EDX analysis of copper nanoparticles possesses metallic copper (19.09%) with some other impurities, that is,O (74.32%) and Si (6.59%). This includes elemental peaks at1.00, 8.00, and 9.00 keV for copper.



EDAX of AgNPs

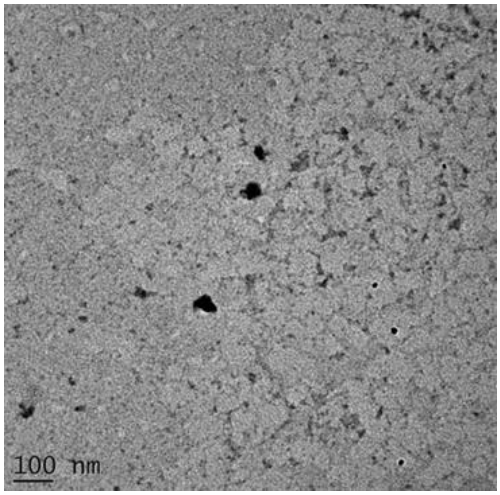
Element	**weight %**	**Atomic %**	**Net weight**
Ag	75	80.25	468.11
O	15	2.4	93.62
K	5	1.95	31.21
Ca	0.5	0.2	3.12
Na	0.9	0.198	5.62
Mg	1	0.24	6.24
S	0.9	0.288	5.62
Si	0.5	0.3	3.12
C	1.2	0.144	7.49

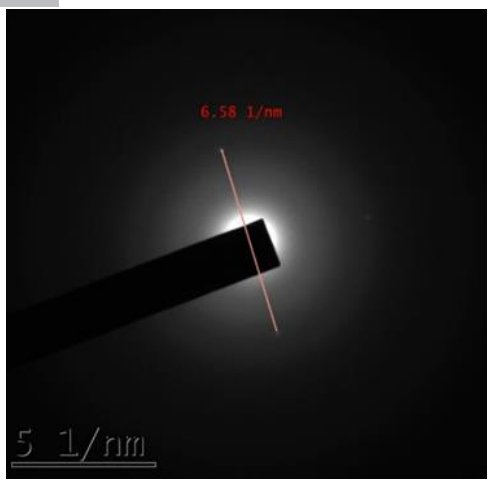
EDAX of CuNPs

Element	Weight %	Atomic %	Net. Weight
Cu	60.04	38.15	359.12
O	18.98	3.03	113.52
C	9.51	1.14	56.88
S	4.11	1.31	24.58
Cl	3.32	1.17	19.85
Ca	2.63	1.05	15.73
Mg	0.79	0.19	4.72
Na	0.4	0.09	2.39
Si	0.22	0.06	1.31

TEM Analysis of silver nanoparticles

TEM micrograph shown in below Figures revealed that the particles are spherical, oval, and well dispersed. The particle size of synthesized AgNPs is in the range of 100 nm and 50–100 nm, respectively. Figure 4.11 shows the Histogram of AgNPs of Pithecellobium dulce. It is evident that there is variation in particle sizes.





Histogram of AgNPs of *Pithecellobium dulce*. It is evident that there is variation in particle sizes.

Antioxidant activity

Total Antioxidant activity by Phosphomolybdenum method

% Antioxidant activity =
(1- (Abs Std –Abs sample/ Abs Std)) * 100

Total antioxidant capacity of silver nanoparticles from enzyme

Sample	Concentration µg/ml	OD @ 695 nm	% Antioxidant activity
Ascorbic acid	1000	1.500	
K-Ag enzyme	200	0.140	9.33
	400	0.295	19.67
	600	0.590	39.33
	800	0.750	50
	1000	1.124	74.93

Medicinal plants are a source for a wide variety of natural products, such as the phenolic acids,flavanoids, terpenoids and proteins which are very interesting for their antioxidant properties. The total antioxidant activity of the extracts was measured spectro photometrically. From the absorbance value, the potential of antioxidant activity was determined. The results presented in Table 4.5 was found to be good potential of antioxidant activities in silver nanoparticles synthesized from Pithecellobium dulce enzyme extract.

Conclusion

Silver and Copper nanoparticles were successfully synthesised using eco-friendly, rapid, simple and low-cost method. Synthesised nanoparticles were studied using visual observation, XRD, FTIR, AFM, TEM, UV-Vis and SEM techniques. Triangular shapes of different sizes were seen in the topography of AFM image of silver and copper nanoparticless. Some elongated oval shaped particles were present in the topography.

X-ray diffraction investigations of the synthesized AgNPs and CuNPs were crystalline nature. The SEM micrographs clearly show well aggregates of silver nano-particles of Pithecellobium dulce with average particle sizes ranging from 20 to 65 nm and copper nanoparticles with 30–65 nm in size. TEM micrograph revealed that the particles are spherical, oval, and well dispersed. The particle size of synthesized AgNPs is in the range of 100 nm and 50–100 nm, respectively.

The silver nanoparticles synthesized from enzyme Pithecellobium FTIR spectra indicated the presence of phytochemicals. which may be dulce

leaf extract showed the greater potential of antioxidant activities. Hence, we conclude that the leaf extract of Pithecellobium dulce can be used by various food and pharmaceutical companies.

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Benzimidazole Derivatives as Promising Anticancer Agents: Structural Insights and Therapeutic Potential

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Abstract

Benzimidazole (BZ) derivatives have emerged as promising anticancer agents due to their diverse biological activities and structural adaptability. These heterocyclic compounds exhibit significant anticancer potential by targeting various molecular pathways, including apoptosis induction, cell cycle arrest, tubulin polymerization inhibition, topoisomerase inhibition, and kinase modulation. Structural modifications of benzimidazole scaffolds have led to the development of potent derivatives with enhanced selectivity and reduced toxicity. Several benzimidazole-based compounds have demonstrated efficacy against different cancer types, including breast, lung, colon, and leukemia, making them attractive candidates for drug development. This review highlights recent advances in the design, synthesis, and mechanism of action of benzimidazole derivatives, emphasizing their therapeutic potential and future prospects in anticancer drug discovery.

Keywords: Benzimidazole, anticancer, structure-activity relationships.

Introduction

The chemistry of benzimidazole (BZ) has its roots in the pioneering work of Hoebrecker, whose contributions set the stage for future discoveries. Building on this foundation, Ladenburg and Wundt identified BZ as a novel heterocyclic compound, which later became a key component in modern medicinal chemistry. The structural significance of benzimidazole was further recognized in the early 1950s when 5,6-dimethyl-1-(α-D-ribofuranosyl) BZ was discovered as part of vitamin B12. Initially, benzimidazole derivatives were primarily identified in plant-based compounds, but their therapeutic potential expanded significantly with the development of anthelmintic agents for mammals. The 1960s marked a major breakthrough in the field, leading to the discovery of several clinically useful

benzimidazole-based drugs, such as thiabendazole and parbendazole. Despite the extensive research on benzimidazole derivatives, a critical analysis of current trends in medicinal chemistry, particularly in the field of anticancer drug development, remains limited. Over the past two decades, more than 15,000 research papers have been published on benzimidazole, yet comprehensive reviews focusing on its anticancer potential are scarce [1-4].

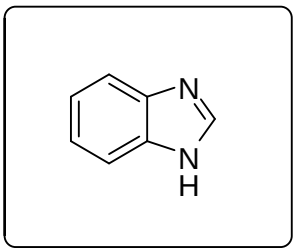

Figure 1: Basic structure of Benzimidazole.

Structurally, BZ (Figure 1) consists of a fused heterocyclic system that combines a benzene ring with an imidazole moiety. This conjugated aromatic framework has a molecular weight of 118.14 g/mol and undergoes tautomerization due to the presence of the imidazole ring. The five-membered imidazole ring contains two nitrogen atoms, giving BZ amphoteric properties and allowing it to exist in two equivalent tautomeric forms. These structural features enable benzimidazole to engage in diverse chemical reactions and biological interactions. Also known as 1H-benzo[d]imidazole, this core structure has played a crucial role in the synthesis of bioactive compounds with various pharmacological applications. Over the years, BZ derivatives have been widely explored for their antibacterial, antifungal, antiviral, antihypertensive, antidiabetic, anti-allergic, and anti-inflammatory properties. More recently, their anticancer potential has gained significant attention, with studies demonstrating cytotoxic effects on multiple human cancer cell lines, including leukemia, lung, prostate, melanoma, kidney, breast, and colon cancer [5-6].

The anticancer activity of benzimidazole-based compounds is primarily attributed to their ability to modulate key biological pathways, including DNA intercalation, enzyme inhibition (such as topoisomerase and tubulin polymerization), and apoptosis induction. Recent research highlights the significance of structural modifications in enhancing the biological activity of BZ derivatives. Specifically, substitutions at positions 1, 2, and 5 of the BZ ring have been found to significantly improve pharmacological effects, including anticancer potency. Modifications involving electron-donating and electron-withdrawing groups have also been explored to optimize selectivity, efficacy, and safety. Several benzimidazole-containing drugs are currently marketed for various therapeutic purposes. In the anticancer category (Figure 2), Selumetinib, a MEK inhibitor, is used for treating neurofibromatosis type 1-related plexiform neurofibromas, while Vismodegib, a hedgehog pathway inhibitor, is employed for the treatment of basal cell carcinoma [7].

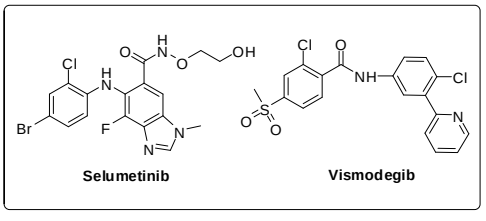

Figure 2: Benzimidazole-containing marketed anticancer drugs

Given its versatility and therapeutic potential, benzimidazole continues to serve as a valuable scaffold for drug development. Future research should focus on optimizing pharmacokinetics, minimizing toxicity, and identifying new molecular targets to maximize the therapeutic benefits of benzimidazole-based drugs. With ongoing advancements, benzimidazole remains a promising candidate for the development of next-generation anticancer agents.

Anticancer potential of benzimidazole derivatives

Garuti et al. conducted a comprehensive study on the synthesis of a novel benzimidazole-4,7-dione (BZ-4,7-dione) derivative, introducing a new chemical entity aimed at evaluating its antiproliferative potential. This research focused on investigating the inhibitory effects of the entire series of BZ-4,7-dione compounds on the proliferation of molt-3 cells, a human lymphoblastic leukemia cell line. Among the tested compounds, two derivatives, identified as compounds 1 and 2 (Figure 3), exhibited significant antiproliferative activity. Their inhibitory concentration (IC50) values were determined to be 1.32 μM and 2.63 μM, respectively, indicating their strong potential as anticancer agents against hematological malignancies [8]. In a subsequent study, Garuti et al. further explored the diverse antiproliferative activities of newly synthesized BZ-4,7-dione derivatives. A particularly noteworthy compound, designated as compound 3 (Figure 3), demonstrated remarkable antiproliferative efficacy when tested against SW620 cells, a human colorectal cancer cell line. With an IC50 value of 0.98 μM, compound 3 displayed superior potency compared to several standard chemotherapeutic agents. Notably, its antiproliferative action was found to be comparable to that of doxorubicin, a well-established chemotherapy drug, which exhibited an IC50 value of 0.72 μM. This finding suggests that BZ-4,7-dione derivatives could serve as promising alternatives or adjuncts to existing cancer treatments, particularly for aggressive colorectal malignancies [9].

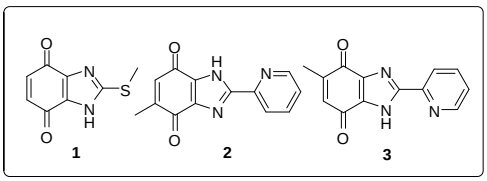

Figure 3: Benzimidazole derivatives (1-3) as anticancer agents

Beyond their antiproliferative effects, benzimidazole derivatives have also been investigated for their ability to inhibit protein kinases, which are critical regulators of cancer cell survival and proliferation. Chojnackie et al. focused on the role of BZ-4,7-dione compounds in anticancer therapy, particularly their potential as inhibitors of protein kinase 2 (CK2), an enzyme involved in various oncogenic signaling pathways. Their study identified two promising compounds, designated as compounds 4 and 5 (Figure 4), which exhibited the most potent CK2 inhibitory activity. The Ki values for these compounds were reported as 1.96 μM and 0.91 μM, respectively, highlighting their strong potential as targeted anticancer agents. Given their potent kinase-inhibitory effects, these compounds warrant further investigation as candidates for future drug development [10].

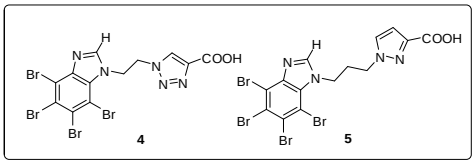

Figure 4: Benzimidazole derivatives (4-5) as anticancer agents

El-Gohary et al. conducted an extensive study on the development of novel benzimidazole (BZ) derivatives, aiming to evaluate their potential as anticancer agents. Their research focused on synthesizing a series of structurally modified BZ compounds and assessing their anti-tumor activity through in-vitro pharmacological studies. The primary objective of this study was to investigate the DNA-binding affinity of these newly synthesized derivatives, as DNA interaction plays a crucial role in anticancer mechanisms by disrupting essential cellular processes such as replication and transcription. Among the tested compounds, two derivatives, identified as compounds 6 and 7 (Figure 5), demonstrated particularly strong DNA-binding affinity. The inhibitory concentration (IC50) values for these compounds were determined to be 37.10 μM and 34.56 μM, respectively, indicating their potent cytotoxic effects against cancer cells. Notably, these values were found to be comparable to that of doxorubicin, a well-established chemotherapeutic agent, which exhibited an IC50 value of 32.35 μM in the same experimental setup. The close resemblance in potency suggests that these BZ derivatives may serve as promising alternatives or complementary agents to existing DNA-targeting chemotherapeutics.

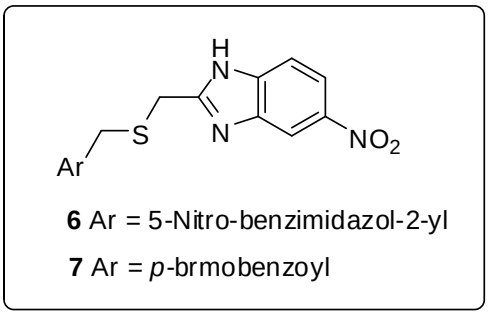

Figure 5: Benzimidazole derivatives (6-7) as anticancer agents

The significant DNA-binding affinity of compounds 6 and 7 suggests that these molecules could effectively interfere with cancer cell proliferation by inducing DNA damage, triggering apoptotic pathways, or inhibiting essential enzymes involved in DNA replication. Given their strong anticancer potential, these compounds warrant further investigation, including detailed mechanistic studies and in-vivo evaluations, to determine their therapeutic viability and safety profiles. Future research may also focus on structural modifications to enhance selectivity, reduce toxicity, and improve overall efficacy for potential clinical applications [11].

Yang et al. designed and synthesized a novel series of bis-benzimidazole (bis-BZ) derivatives, aiming to explore their therapeutic potential as anticancer agents. This strategic approach involved the development of structurally unique bis-BZ compounds with enhanced biological activity. Following the successful synthesis of these derivatives, the researchers conducted comprehensive in-vitro evaluations to assess their cytotoxic effects against various tumour cell lines. The primary goal was to compare their efficacy with existing chemotherapeutic agents and

determine their potential as viable alternatives in cancer treatment. Experimental studies confirmed that the newly synthesized bis-BZ derivatives exhibited potent anticancer activity. Notably, two compounds, designated as compounds 8 and 9 (Figure 6), demonstrated significant tumour cell inhibition, with IC50 values of 2.95 μM and 2.81 μM, respectively. These values indicate strong cytotoxic potential, comparable to that of cis-platin, a widely used platinum-based chemotherapy drug known for its effectiveness against various cancers. However, a critical advantage of compounds 8 and 9 over cis-platin was their reduced cytotoxicity towards normal cells, suggesting a more favourable therapeutic index and potentially fewer side effects in clinical applications.

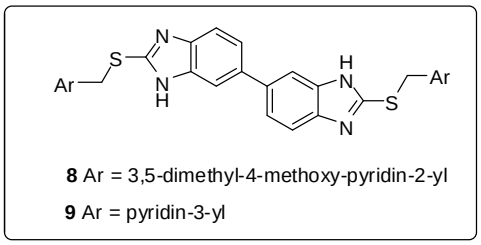

Figure 6: Benzimidazole derivatives (8-9) as anticancer agents

The promising anticancer activity of these bis-BZ derivatives suggests that they may function through mechanisms such as DNA binding, enzyme inhibition, or apoptosis induction, similar to other benzimidazole-based drugs. Their structural design, which allows for strong interactions with cancer cell targets while minimizing toxicity to healthy cells, positions them as valuable candidates for further preclinical and clinical investigations. Future research should focus on elucidating their precise molecular mechanisms, optimizing their pharmacokinetic properties, and evaluating their potential in combination therapy to enhance treatment efficacy while mitigating adverse effects [12].

El-Nassan et al. conducted an in-depth study focused on the synthesis of novel 1,2,4-triazino[4,5-a] benzimidazole (BZ) derivatives, aiming to expand the therapeutic potential of BZ-based compounds in cancer treatment. Their work not only introduced a new chemical scaffold but also provided a comprehensive synthetic strategy for the development of these derivatives. The primary objective of this research was to investigate the anticancer efficacy of the synthesized compounds, particularly against breast cancer cell lines, given the urgent need for more effective and targeted treatments. To evaluate their therapeutic potential, El-Nassan et al. tested the newly synthesized 1,2,4-triazino[4,5-a]BZ derivatives against MCF-7 cells, a well-established human breast adenocarcinoma cell line commonly used for anticancer drug screening. Among the tested compounds, compound 10 (Figure 7) emerged as the most potent, demonstrating significant cytotoxic activity against MCF-7 cells. Structure-activity relationship (SAR) analysis revealed that the superior anticancer activity of compound 30 could be attributed to the presence of an ortho-chlorophenyl moiety. This specific structural feature was found to enhance the compound's interaction with cellular targets, leading to increased antiproliferative effects.

The findings from this study highlight the promising potential of 1,2,4-triazino[4,5-a]BZ derivatives as targeted

anticancer agents, particularly for breast adenocarcinoma treatment. The identification of compound 10 as a lead candidate underscores the importance of structural modifications in optimizing anticancer efficacy. El-Nassan et al. emphasized the need for further research to refine these compounds, explore their detailed mechanisms of action, and conduct in-vivo studies to assess their pharmacokinetics and safety profiles. This study paves the way for future advancements in the development of BZ-based therapeutics for breast cancer and other malignancies [13].

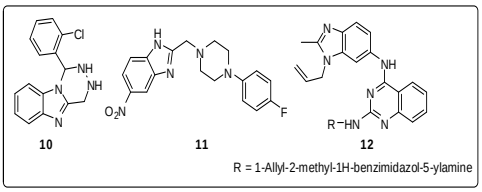

Figure 7: Benzimidazole derivatives (10-12) as anticancer agents

El-Gohary et al. introduced a novel class of benzimidazole (BZ) derivatives designed to exhibit multifunctional biological activities, including antimicrobial growth inhibition, quorum sensing disruption, and anticancer properties. Their study aimed to explore the potential of these newly synthesized compounds as therapeutic agents, particularly in the context of cancer treatment, while also investigating their effectiveness in combating microbial infections. The dual functionality of these compounds highlights the versatility of the BZ scaffold in medicinal chemistry. Among the synthesized derivatives, compound 11 (Figure 7) stood out for its remarkable anticancer activity. This compound, characterized by its unique chemical structure and diverse functional groups, demonstrated significant cytotoxicity against multiple human cancer cell lines, including liver, colon, and breast cancer. The inhibitory concentration (IC50) values for compound 11 were determined to be 0.022 mM for liver cancer cells, 0.014 mM for colon cancer cells, and 0.015 mM for breast cancer cells. These results suggest that compound 11 possesses potent antiproliferative effects, making it a promising candidate for further preclinical evaluation.

The strong anticancer activity of compound 11 is likely attributed to its ability to interfere with essential cellular processes, such as DNA replication, cell cycle progression, and apoptosis induction. Additionally, its antimicrobial properties and quorum sensing inhibition further enhance its therapeutic value by potentially preventing infection-associated cancer progression. El-Gohary et al. emphasized the need for continued research to optimize the pharmacokinetic properties, assess in-vivo efficacy, and evaluate the safety profiles of these promising BZ derivatives. The findings from this study underscore the potential of compound 11 as a lead candidate for the development of novel anticancer therapies, particularly for liver, colon, and breast cancer treatment [14].

Paul et al. developed an innovative synthetic strategy to produce a novel series of quinazoline-linked benzimidazole (BZ) derivatives, specifically designed to evaluate their potential as anticancer agents. This synthesis involved modifying the primary amine group within the quinazoline framework, allowing for the formation of unique chemical structures

with enhanced biological activity. The rationale behind this structural modification was to improve the compounds' interaction with cancer cell targets, thereby enhancing their therapeutic efficacy while maintaining a favorable safety profile. To assess the anticancer potential of the newly synthesized compounds, the researchers conducted extensive in-vitro evaluations against various cancer cell lines. Among the tested compounds, compound 12 (Figure 7) emerged as the most promising candidate, exhibiting potent anticancer activity against both colon and prostate cancer cell lines. The growth inhibitory concentration (GI50) values for compound 12 were determined to be 0.34 μM for colon cancer cells and 0.31 μM for prostate cancer cells. These low GI50 values reflect the compound's strong cytotoxic effect, suggesting its potential as a lead compound for further anticancer drug development.

The significant anticancer activity observed with compound 12 is likely attributed to its unique quinazoline-BZ linkage, which enhances binding affinity to cellular targets involved in cancer cell proliferation and survival. This structural advantage may allow compound 12 to interfere with critical pathways, such as cell cycle regulation, DNA replication, and apoptosis induction. Paul et al. emphasized the need for further studies to elucidate the precise molecular mechanisms of action, optimize pharmacokinetic properties, and evaluate the compound's efficacy in animal models. The promising results of this study highlight compound 12 as a valuable candidate for future development in anticancer therapy, particularly for colon and prostate cancer treatment [15].

Castillo et al. conducted an in-depth investigation into the pharmacophoric effects of copper-based benzimidazole (BZ) complexes, focusing on their potential as anticancer agents. Their research aimed to explore how the incorporation of copper ions into BZ structures could enhance the biological activity of these compounds, particularly in the context of cancer treatment. Copper, being an essential trace element involved in various cellular processes, has been known to exhibit cytotoxic effects when complexed with bioactive molecules, making it a promising candidate for anticancer drug design. Among the synthesized copper-BZ complexes, the thioether complex 13 (Figure 8) stood out for its remarkable anticancer potential. This compound exhibited a precise binding affinity with dimyristoyl phosphatidylcholine (DMPC) and dimyristoyl phosphatidylethanolamine (DMPE), two essential phospholipids found in cellular membranes. The strong interaction between complex 13 and these phospholipids suggests that the compound can effectively integrate into cancer cell membranes, thereby disrupting cellular integrity and promoting cytotoxic effects. This binding affinity is believed to play a crucial role in the compound's ability to induce apoptosis and inhibit cancer cell proliferation.

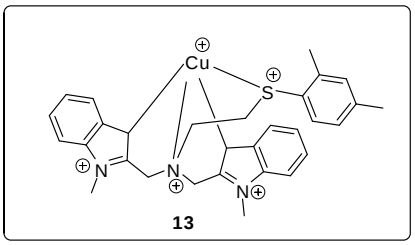

Figure 8: Benzimidazole derivative 13 as anticancer agent

Further in-vitro evaluations revealed that the thioether complex 13 demonstrated significant anticancer activity across various cancer cell lines. The compound's ability to target cancer cells while maintaining a favorable safety profile highlights its potential for further preclinical development. Castillo et al. emphasized the importance of continuing research to optimize the copper-BZ complexes, explore their molecular mechanisms of action, and evaluate their efficacy in animal models. The findings from this study underscore the promise of copper-BZ derivatives, such as complex 13, as potential candidates for the development of novel anticancer therapies [16].

Tropomyosin receptor kinases (TRKs) are a family of receptor tyrosine kinases that play a critical role in the development and function of the nervous system. However, aberrant TRK signaling, often resulting from chromosomal rearrangements and gene fusions, has been implicated in the pathogenesis of various cancers, including lung, colon, and thyroid tumors. As a result, TRK inhibitors have emerged as promising therapeutic agents for the treatment of TRK-driven malignancies. Currently, several Pan-TRK inhibitors are either in clinical use or under evaluation for their anticancer potential. These inhibitors target all three TRK iso forms—TRKA, TRKB, and TRKC - simultaneously, thereby effectively blocking TRK signaling pathways across different tumor types. Despite the therapeutic success of Pan-TRK inhibitors, their clinical application is often limited by off-target adverse events. These side effects arise from the inhibition of TRKs in non-cancerous tissues, leading to issues such as sensory neuropathy, dizziness, and gastrointestinal disturbances. As a result, patient compliance and overall treatment outcomes are compromised. To overcome this challenge, researchers have been striving to develop subtype-selective TRK inhibitors, which can specifically target individual TRK isoforms while minimizing off-target toxicity. However, the high sequence similarity among TRKA, TRKB, and TRKC has posed significant challenges in achieving this subtype selectivity.

To address this issue, Wang et al. designed and synthesized a novel, highly selective TRKC inhibitor, designated as compound 14 (Figure 9). This compound exhibited potent inhibitory activity against TRKC with an IC50 value of 13 nM, while demonstrating remarkable selectivity over TRKA and TRKB, with IC50 values of 1400 nM and 454 nM, respectively. The structural basis for this selectivity was elucidated through extensive molecular dynamics (MD) simulations, which revealed critical interactions between compound 14 and specific residues within the ribose-binding region of TRKC. Notably, the selectivity was attributed to unique hydrophobic interactions and the involvement of conserved water molecules, which stabilized the binding of compound 14 within the TRKC active

site. These findings highlight the importance of targeting the ribose region as a strategy for achieving TRK subtype selectivity. Wang et al. emphasized the need for further preclinical and clinical investigations to validate the therapeutic potential of compound 14, with the ultimate goal of developing safer and more effective TRK-targeted therapies for cancer patients [17].

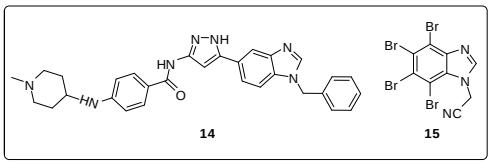

Figure 9: Benzimidazole derivatives (14-15) as anticancer agents

Chojnacki et al. conducted a comprehensive study focused on the development and evaluation of novel benzimidazole (BZ) derivatives with potential anticancer and proapoptotic properties. In their research, they synthesized a new polybrominated benzimidazole derivative, designated as compound 15 (Figure 9), through a series of targeted chemical modifications. Following the successful synthesis of this compound, the researchers further alkylated the parent structure to enhance its biological activity and evaluate its therapeutic potential. The anticancer and proapoptotic activities of compound 15 and its derivatives were assessed using two well-established human cancer cell lines: CCRF-CEM, a model for acute lymphoblastic leukemia, and MCF-7, a widely used breast cancer cell line. These cell lines were chosen for their relevance in evaluating the efficacy of novel anticancer agents and understanding their mechanisms of action. The compounds were tested at a concentration of 10 μM, a dosage commonly employed in preliminary cytotoxicity screenings.

The results of the study revealed that compound 15 exhibited significant anticancer activity, effectively inhibiting the growth of both CCRF-CEM and MCF-7 cells. Notably, the compound demonstrated potent casein kinase 2 (CK2) inhibitory activity, which is known to play a crucial role in cancer cell survival, proliferation, and resistance to apoptosis. By inhibiting CK2, compound 15 induced proapoptotic effects, promoting programmed cell death in cancer cells. These findings underscore the potential of polybrominated benzimidazole derivatives as promising candidates for the development of novel anticancer therapies. Chojnacki et al. highlighted the need for further investigations to optimize the structure-activity relationship (SAR) of these compounds and evaluate their efficacy in preclinical models [18].

Zhang et al. aimed to develop a novel molecular framework with potential antitumor activity by synthesizing a unique tetrahydrobenzodifuran-imidazolium salt. This innovative approach was designed to assess the compound's cytotoxic efficacy against various human tumour cell lines. The researchers hypothesized that incorporating the tetrahydrobenzodifuran moiety with the imidazolium salt could enhance anticancer properties by improving cellular uptake and binding affinity to critical molecular targets within cancer cells. The study identified compound 16 (Figure 10) as a lead candidate, demonstrating potent antitumor activity across all tested cell

lines. The IC50 values for compound 16 ranged from 1.06 to 4.34 μM, indicating strong cytotoxic effects at relatively low concentrations. This broad-spectrum activity suggested that the compound could effectively target multiple cancer types, making it a promising candidate for further development. The mechanism underlying the compound's efficacy was attributed to its ability to interfere with cellular proliferation pathways, ultimately leading to cell cycle arrest and apoptosis.

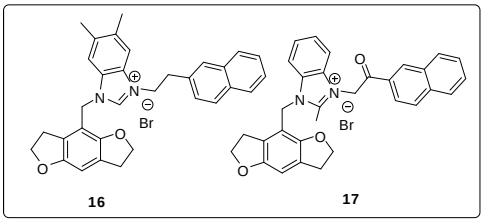

Figure 10: Benzimidazole derivatives (16-17) as anticancer agents

Among the derivatives tested, compound 17 (Figure 10) stood out for its remarkable selectivity and potency against specific cancer cell lines, including the SMMC-7721 hepatocellular carcinoma cell line and the MCF-7 breast cancer cell line. The IC50 values for compound 17 were found to be 2.7-fold and 8.4-fold lower than those of cis-platin, a commonly used chemotherapeutic agent. Further investigations revealed that compound 17 exerted its anticancer effects by inhibiting the G1 phase of the cell cycle, thereby preventing cancer cells from progressing to the DNA synthesis phase. Additionally, the compound induced apoptosis, promoting programmed cell death in tumour cells while exhibiting lower cytotoxicity toward healthy cells. These findings highlight the potential of tetrahydrobenzodifuran-imidazolium salts as promising candidates for future anticancer drug development, warranting further preclinical and clinical investigations [19].

Abd El-Meguid et al. designed and synthesized a novel series of 6-benzoyl benzimidazole (BZ) derivatives with the objective of developing multi-targeted molecules capable of inhibiting key receptor tyrosine kinases (RTKs) involved in cancer progression. Their research aimed to explore the anticancer potential of these compounds, focusing on their cytotoxic effects against cancer cells and their inhibitory activity against several critical molecular targets. Given the importance of receptors such as EGFR (epidermal growth factor receptor), HER2 (human epidermal growth factor receptor 2), VEGFR-2 (vascular endothelial growth factor receptor 2), and PDGFR-β (platelet-derived growth factor receptor beta) in the growth and survival of solid tumors, the study evaluated the most promising cytotoxic derivatives against these targets.

To assess the anticancer activity of the synthesized compounds, the researchers conducted an in vitro cellular toxicity study using HeLa cell lines, a well-established model for cervical cancer research. Among the tested derivatives, compounds 18 and 19 (Figure 11) demonstrated the highest cytotoxicity, with IC50 values of 1.62 ± 0.16 μM and 1.44 ± 0.06 μM, respectively. These results indicated that both compounds were more effective than the standard chemotherapeutic agent doxorubicin, which exhibited an IC50 value of 2.05 ± 0.03 μM under similar conditions. Further mechanistic investigations suggested that the cytotoxicity of

compounds 18 and 19 was associated with the induction of cellular apoptosis, cell cycle arrest at the G2/M phase, and an accumulation of cells in the pre-G1 phase. These findings highlighted the potential of the compounds to disrupt cancer cell proliferation through multiple pathways.

In addition to their cytotoxic effects, compounds 18 and 19 exhibited significant inhibitory activity against several key RTKs. Both compounds showed stronger suppression of HER2 activity (IC50: 0.25 ± 0.003 μM for compound 18 and 0.19 ± 0.004 μM for compound 19) compared to EGFR inhibition (IC50: 0.157 ± 0.007 μM for compound 18 and 0.109 ± 0.014 μM for compound 19). Notably, their inhibitory activity surpassed that of the standard EGFR inhibitor Erlotinib, which displayed IC50 values of 1.23 ± 0.005 μM for HER2 and 0.079 ± 0.001 μM for EGFR. Furthermore, compound 19 demonstrated superior multitargeting RTK inhibition, with its inhibitory activity against PDGFR-β and VEGFR-2 being 3.8-fold and 1.8-fold higher, respectively, than that of Erlotinib. These results emphasized the potential of 6-benzoyl BZ derivatives, particularly compounds 18 and 19, as promising candidates for the development of next-generation multitargeted anticancer therapies [20].

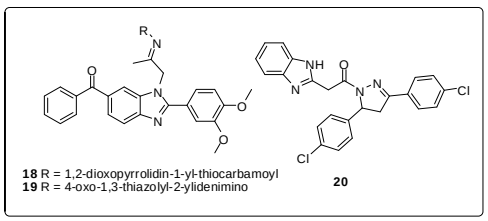

Figure 11: Benzimidazole derivatives (18-20) as anticancer agents

Recognizing the crucial role of epidermal growth factor receptor (EGFR) in cell signaling pathways associated with cancer progression, Akhtar et al. designed and synthesized a novel series of pyrazole-linked benzimidazole (BZ) derivatives through a cyclo-condensation reaction. This innovative molecular framework was strategically developed to explore its potential as an anticancer agent by targeting EGFR-related pathways. Following synthesis, the newly developed compounds underwent extensive in vitro biological evaluation to determine their antiproliferative effects against a panel of human cancer cell lines, including MDA-MB-231 (triple-negative human breast cancer), MCF-7 (hormone receptor-positive breast cancer), A549 (type II pneumocyte lung carcinoma), HaCaT (human keratinocyte line), and HepG2 (human liver carcinoma).

The study revealed that most of the synthesized compounds exhibited significant anticancer activity across the tested cell lines, with several derivatives demonstrating potent antiproliferative effects. Among the series, compound 20 (Figure 11) emerged as the most promising candidate, displaying the highest cytotoxic activity against A549 lung cancer cells with an IC50 value of 2.2 μM. Further mechanistic investigations indicated that the compound exerted its anticancer effects by inducing cell cycle arrest at the G2/M phase, thereby preventing cells from progressing to mitosis. This disruption in cell cycle progression was accompanied by the induction of apoptosis, leading to programmed cell death in the treated cancer cells [21].

Structure-activity relationship (SAR) analysis

Bis-benzimidazole derivatives, particularly in copper complexes, exhibit significant anticancer potential, with pharmacological activity influenced by structural modifications. Connecting nitrogen-containing heterocycles like isatin, pyrazolone, and piperazine via a methylene linker enhances broad-spectrum anticancer activity. The insertion of electron-withdrawing groups, especially nitro at the 5th position, significantly boosts potency. Substituting the ring nitrogen (N1) with short hydrocarbons and linking to a carboxylated triazole further enhances efficacy. Poly-bromination at the 4,5,6, and 7 positions and pyridyl methyl sulfanyl substitution, as seen in compounds 8 and 9, improve antitumor effects. Electron-withdrawing benzoyl groups, as in compound 7, elevate therapeutic potential. Thioether-linked bis-BZ, triazine-fused derivatives, and hydroxyethyl, dimethylamino, and ethoxycarbonyl substitutions at positions 1, 2, and 5, respectively, show potent tumor suppression.

Bis-BZ connected by a quinazolinyl bridge or bulky rings (e.g., naphthyl or dioxolobenzene) enhances anticancer activity. Linker length and hydrogen bonding capacity of carbonyl oxygen contribute to selectivity, while position 1 substitutions with alkyl nitrile or heteroaryl hydrazones improve biological response. Small alkyl groups at position 2 and methyl or benzoyl groups at positions 5 and 6 further elevate therapeutic efficacy.

Conclusion

Benzimidazole (BZ) derivatives have demonstrated significant potential as versatile anticancer agents due to their ability to target multiple cellular pathways, including apoptosis induction, cell cycle arrest, kinase inhibition, and topoisomerase inhibition. Structural modifications of the BZ scaffold have led to the development of potent derivatives with enhanced selectivity, efficacy, and reduced toxicity. Bis-benzimidazole, particularly in copper complexes, has shown notable affinity towards tropomyosin receptor kinases (TRKs), though with some side effects. The introduction of nitrogen-containing heterocycles, electron-withdrawing groups (such as nitro at the 5th position), and electronegative atoms in either aliphatic (thiomethyl) or heterocyclic (pyridyl) forms has significantly enhanced antiproliferative effects. Compounds featuring methylene-linked heterocycles, carboxylated triazoles, and bromine-substituted fused benzene rings have exhibited broad-spectrum anticancer activity across various cell lines.

Key findings suggest that the type and length of linkers connecting heteroatoms, as well as specific substitutions at positions 1, 2, 5, and 6 of the BZ core, play a crucial role in determining both anticancer potency and selectivity. Notable examples include 5,5′-bis-BZ with pyridyl methyl sulfanyl, electron-withdrawing benzoyl groups, and bis-BZ connected by quinazolinyl bridges, all of which have shown remarkable tumor-suppressing activity. Overall, the structure-activity relationship (SAR) insights gained from these studies highlight the potential of BZ derivatives as promising candidates for future anticancer drug development. Further preclinical and clinical

investigations are warranted to optimize these compounds for therapeutic use and to explore their efficacy against resistant cancer types.

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MODERN APPROACHES TO CHEMICAL SCIENCE: CONCEPTS AND TECHNIQUES

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Fe_2O_3/g-C_3N_4 Nanocomposites: A Synergistic Approach Toward Sustainable Photocatalytic Applications

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Abstract

Iron oxide (Fe_2O_3) nanoparticles have been studied extensively for their adjustable physicochemical characteristics, economic viability, environmental sustainability, and significant photocatalytic capabilities. This chapter examines current advancements in the sustainable synthesis of Fe_2O_3 utilizing natural resources and industrial or geological waste, in accordance with green chemistry principles. Particular focus is directed towards Fe_2O_3–graphitic carbon nitride (g-C_3N_4) nanocomposites, which demonstrate improved photocatalytic activity due to effective charge separation via Z-scheme and S-scheme heterojunction mechanisms. The characterization of these materials employs a diverse array of techniques, such as XRD, FTIR, SEM, TEM, UV–Vis, PL, XPS, EDS, VSM, TGA, and BET studies. The chapter emphasizes their importance in environmental remediation by examining photocatalytic processes, charge carrier dynamics, and the formation of reactive oxygen species (ROS), rendering them attractive materials for advanced applications.

Keywords: Iron oxide nanoparticles, nanocomposite materials, sustainable synthesis, photocatalytic applications, heterojunction mechanisms.

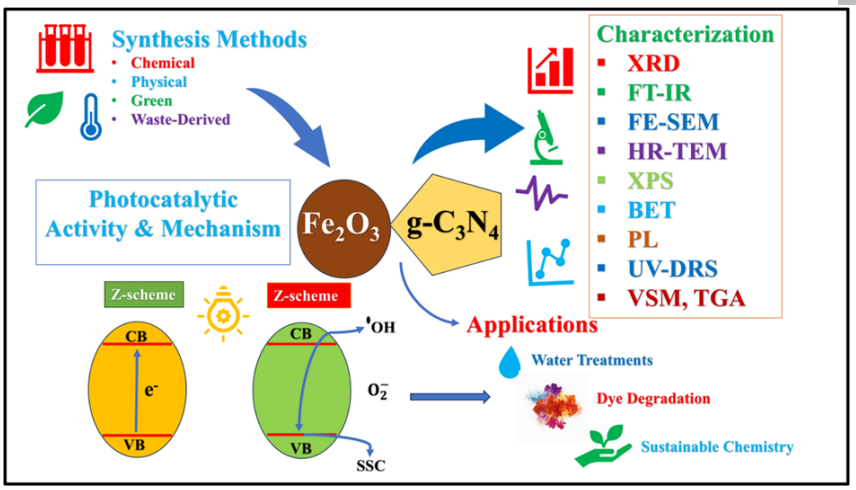


Fig.1-Graphical Abstract

Introduction

The worldwide need for renewable energy and environmental remediation technology has heightened the quest for efficient and sustainable solutions. Photocatalysis has garnered considerable attention for its capacity to utilise solar energy in the degradation of environmental contaminants and energy conversion. The essence of photocatalytic processes is the creation of efficient, stable, and environmentally benign photocatalysts [1]. In this context, iron oxide (Fe_2O_3), namely haematite, has emerged as a highly attractive nanomaterial.

Iron oxides exist in various crystalline forms, like magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) being distinguished by their magnetic characteristics, facilitating straightforward separation and recyclability in photocatalytic systems. Magnetite has a mixed-valence $Fe2^{+}/Fe^{3+}$ inverse spinel structure that makes it very good at conducting electricity. However, it has a very narrow bandgap (about 0.1–0.3 eV), which makes it less useful as a direct photocatalyst and less stable in reactive conditions [2]. Maghemite, is another form of iron oxide but it has a defective spinel-type Fe^{3+} oxide structure, displays a marginally higher bandgap (~2.0–2.2 eV) however is hindered by structural defects that enhance electron-hole recombination [3]. Conversely, hematite (α-Fe_2O_3), that has a rhombohedral crystal system and a moderate bandgap (~2.1 eV), is distinguished by its exceptional thermal and chemical stability, abundance, and strong visible-light absorption. It exhibits higher stability and efficiency compared to Fe_3O_4 and γ-Fe_2O_3 under photocatalytic conditions. Thus, Fe_2O_3 is the most extensively researched iron oxide for photocatalytic applications such as water splitting and dye degradation.[4]. However, the practical efficacy of Fe2O3 in photocatalytic process is limited by its inherent limitations, which include high recombination rate of photogenerated electron–hole pairs, limited electrical conductivity, and relatively short diffusion lengths for photo-excited carriers. To overcome

these limitations, researchers have investigated the formation of heterojunctions or composite materials, in which Fe_2O_3 is combined with other semiconductors to improve charge separation and photocatalytic activity [5]. In this context, choosing appropriate materials such as g-C_3N_4, which have comparable band structures and visible-light responsiveness, is crucial for building new composites with improved photodegradation performance. Graphitic carbon nitride (g-C_3N_4) is a polymeric, metal-free semiconductor that has garnered considerable interest in recent years for its prospective photocatalytic uses. Due to its relative bandgap of 2.7 eV, g-C_3N_4 may efficiently utilize visible light, rendering it a viable option for solar-driven redox processes [6]. Additionally, g-C3N4 has a two-dimensional layered structure made up of tri-s-triazine units connected by flat amino groups. This helps to keep the chemical stable and strong in both heat and oxidative conditions, sensitivity to visible light, and advantageous conduction and valence band. Nonetheless, despite these benefits, g-C_3N_4 is hindered by several inherent limitations that restrict its photocatalytic efficacy. The restrictions encompass a comparatively low specific surface area, inadequate electrical conductivity, and the swift recombination of photogenerated electron-hole pairs, which collectively hinder efficient charge separation and transmission [7]. To address these challenges, the development of g-C_3N_4-based heterostructures, particularly its composite with iron oxide (Fe_2O_3), has emerged as a promising strategy. Fe_2O_3 is a visible-light-active semiconductor with a narrow bandgap and good chemical stability. When integrated with g-C_3N_4, the resulting composite material exhibits a synergistic enhancement in photocatalytic performance due to enhanced charge carrier separation, reduced recombination rates, and enhanced light absorption in the visible spectrum [8]. The establishment of Z-scheme or S-scheme heterojunctions among the g-C_3N_4 and Fe_2O_3 further augments redox capacity by maintaining the robust oxidative and reductive potentials of both semiconductors [7]. These composites provide effective spatial separation of photogenerated electrons and holes, resulting in improved charge dynamics and increases photocatalytic activity. The resultant nanocomposite not only addresses the limitations of pure Fe2O3, g-C_3N_4 but also demonstrates improved photo-response and redox potential, rendering it exceptionally suitable for applications including dye degradation, water splitting, and environmental remediation [9,10]

Important Highlights of Fe_2O_3-g-C_3N_4 Heterojunction Multifunctional Nanocomposites

- **Enhanced Visible Light Absorption:** Light absorption is wider in the composite, improving solar energy use.
- **Increased Redox Capability via Z- and S-Scheme Mechanisms:** Keeps component oxidation and reduction potentials high for photocatalytic efficiency.
- **Eco-friendly Material:** Eco-friendly applications benefit from the non-toxic, stable, and abundant Fe_2O_3 and g-C_3N_4.

- **Cost-effective Synthesis:** Reduces production costs by synthesizing with raw ores, laterite soil, or plant extracts.
- **Photocatalytic Efficiency in Visible Light:** Degrades methyl orange, rhodamine B, and methylene blue well.
- **Useful for wastewater treatment:** Used to cleanse dye-contaminated industrial effluents under sunlight or fluorescent lamps.

Trends in Research and Development

Recent changes in the synthesis of Fe2O3/g-C_3N_4 nanocomposite show a move toward using environmentally friendly starting materials that come from waste, chemicals, and plants. Waste toner powder (Babar et al. [11] and industry waste water (Wang et al. [12] have been used as iron sources that work well. A cheap readily available raw natural material called laterite soil has been converted by acid leaching and calcination (Dissanayake et al; Sharma et al. [14,15]. As part of green synthesis, plant extract from Acalypha arvensis (Ble-Gonzalez et al., [15] and Moringa oleifera (Mateus et al. [16] plants have been investigated as ways to make materials more stable. For long-term photocatalyst development, these different methods are in line with the ideas of green chemistry and the circular economy.

Challenges and Future Scope study

- **Optimization of Green Synthesis Parameters:** Necessity for meticulous regulation of pH, precursor concentration, calcination temperature, and mixing ratios to enhance crystallinity, particle size, and photocatalytic efficacy.
- **Interface Engineering in Z-/S-Scheme Systems:** Inadequate regulation of charge carrier trajectories and heterojunction alignment in composites synthesized by simplistic or low-temperature techniques.
- **Photocatalyst Stability and Reusability:** Insufficient data regarding long-term structural integrity, recyclability, and resistance to photo dissolution in actual environmental circumstances.
- **Scalability and Industrial Viability:** The necessity for economical, energy-efficient, and scalable green synthesis methods for effective environmental remediation.
- **Mechanistic Understanding:** There is an insufficiency of comprehensive mechanistic investigations on photocatalysts employing modern methodologies such as in situ XPS, TRPL, EIS, and DFT simulations. These approaches can elucidate essential insights into charge transfer, separation efficiency, and material degradation.

Objectives

- To highlight the main photocatalytic properties of Fe_2O_3 that have been documented in the literature.
- To evaluate the limitations of pure Fe_2O_3 and the enhancements that can be achieved through the use of g-C_3N_4 heterojunctions.
- To provide a concise overview of environmentally friendly synthesis methods that employ natural and waste-derived materials.
- A comparison of the degradation mechanism performance of

photocatalytic dyes under UV and visible light.

- To study the electron–hole transfer processes regulated by Z-scheme or S-scheme pathways in nanocomposite materials

Data and Methodology

The advancement of photocatalysts using Fe_2O_3 and its composites with graphitic carbon nitride ($g\text{-}C_3N_4$) received significant interest owing to its potential uses in solar-driven environmental cleanup. This section provides a comprehensive overview of the synthesis strategies used in the production of Fe_2O_3, g-C3N4 nanoparticles and $Fe_2O_3/g\text{-}C_3N_4$ composites, emphasising the various approaches reported in recent research.

Comprehensive Synthesis Techniques for Fe_2O_3 Nanoparticles

A diverse range of synthesis methods has been documented for the fabrication of iron oxide nanoparticles. These can be classified into physical, chemical, and green (biogenic) methods:

Chemical Approaches

The predominant techniques encompass co-precipitation, sol-gel, hydrothermal/solvothermal, microemulsion, and combustion synthesis. These techniques provide the control of particle size, morphology, and crystalline phase by the modulation of factors like pH, temperature, ionic strength, and precursor concentration. Co-precipitation is especially beneficial because to its simplicity and scalability in a (Table.1)

Table.1: Common Chemical Methods for Synthesizing Iron Oxide Nanoparticles

Synthesis Method	Key Features / Advantages	Tunable Parameters	Limitations	References
Co-precipitation	Simple, scalable, low cost	pH, Fe^{2+}/Fe^{3+} ratio, temperature, time	Poor control over size/morphology	[17]
Sol-gel	High purity, fine particle size, good homogeneity	Sol concentration, aging time, drying temp	Time-consuming, organic solvents used	[18]
Hydrothermal	Crystalline, uniform shapes, low aggregation	Temperature, pressure, reaction time	Needs autoclave, high temp/pressure	[19]
Microemulsion	Narrow size distribution, nanoscale control	Surfactant, oil/water ratio, co-surfactant	Surfactant removal, low yield	[20]
Thermal decomposition	High crystallinity,	Ligand, solvent,	Expensive, requires organic	[21]

	monodispersity	heating rate	precursors	
Spray pyrolysis	Continuous process, spherical particles	Atomizer type, carrier gas flow	Equipment intensive	[22]
Sonochemical	Rapid reaction, reduced particle size	Ultrasonic frequency, power, duration	Limited scale-up	[23]
Reverse micelle	Good particle control, nanoscale synthesis	Micelle size, water content, surfactant	Complex setup, surfactant removal	[24]

Eco-friendly Synthesis: To conform to sustainable development objectives, the utilisation of plant extract-mediated (phytochemical) synthesis and bio-waste-derived precursors is on the rise. These technologies utilise natural reducing and stabilising chemicals, rendering the process ecologically friendly and economically efficient given in (Table.2)

Table.2: Eco-Friendly Synthesis Using Plant Extracts and Bio-Waste

S. No.	**Catalyst/Nanoparticle Synthesized**	**Plant Material Used**	**Application**	**Reference**
1	Iron oxide nanoparticles	*Moringa oleifera and chitosan*	Corn germination	[25]
2	hematite (α-Fe2O3)	leaf broth of *Psidium guajava* plant,	Dye degradation of organic pollutants	[26]
3	Magnetite (Fe_3O_4) and Hematite (a-Fe_2O_3	*Delonix regia* flower extract	Heterogeneous Photo-Fenton Degradation of Dye	[28]
4	Metallic nanoparticles (general)	Various plant parts (review)	Environmental remediation	[29]
5	Metal and metal oxide nanoparticles (Fe, Zn, Cu, etc.)	Leaves, peels, bio-waste (review)	Wastewater treatment, pollutant degradation	[30]

Physical Methods

Techniques such as thermal breakdown and high-energy ball milling are utilised, particularly for the synthesis of highly crystalline or large-scale quantities of nanoparticles. Nevertheless, these frequently necessitate increased energy input and are less preferred for sustainable chemical objectives. Each of these approaches facilitates the optimisation of fundamental material parameters like as particle size, surface area, and phase purity, which are crucial for photocatalytic efficacy listed in (Table.3)

Table.3: Physical Synthesis Techniques and Their Photocatalytic Relevance

Sr. No.	Synthesis Technique	Material Synthesized	Advantages	Limitations	Application	Reference
1	Thermal decomposition	Fe_3O_4, Fe_2O_3	High crystallinity, phase control	High temperature, energy intensive	Photocatalysis, magnetic recovery	[17]
2	High-energy ball milling	Fe_2O_3, ZnO, TiO_2	Scalable, solvent-free, simple	Wide size distribution, contamination	Photocatalysis, sensors	[31]
3	Pulsed laser ablation	Ag, Au, Fe	High purity, surfactant-free	Low yield, expensive equipment	Catalysis, surface coatings	[32]
4	Ultrasonic irradiation	TiO_2, Fe_2O_3, carbon materials	Controlled nucleation, low temperature	Low scalability	Environmental remediation	[23]
5	Arc discharge	Carbon nanotubes, metals	Nanotube formation, high energy materials	Risk of gas release, energy heavy	Hydrogen storage, catalysis	[33]

General Synthesis Methods for g-C_3N_4

The synthesis of g-C_3N_4 is extremely simple and generally entails the thermal condensation of nitrogen-rich precursors, like melamine, urea, thiourea, or dicyandiamide [34]. The precursors undergo polymerisation at high temperatures (often 500–600°C) in a muffle furnace, resulting in a layered, graphitic-like yellow powder of g-C_3N_4. Techniques like as doping, thermal exfoliation, or templating are frequently employed to enhance surface area, adjust electrical structure, and augment photocatalytic capabilities [35].

Formation of Fe_2O_3-g-C_3N_4 Nanocomposite

Iron oxide graphitic carbon nitride (Fe_2O_3-g-C_3N_4) composites are synthesised using various general techniques, each aimed at improving interfacial contact between the two semiconductors to facilitate enhanced charge separation and transfer listed in (Table.4)

- **Mechanical Mixing and Grinding:** The physical amalgamation of pre-prepared iron oxide (Fe_2O_3) and graphitic carbon nitride (g-C_3N_4) material, succeeded by thermal treatment, constitutes a straightforward and prevalent technique. It facilitates physical interaction and partial chemical bonding.
- **In-Situ Growth:** This method involves the direct synthesis of one component (often Fe_2O_3) in the presence of g-C_3N_4, facilitating improved dispersion and interface development.
- **Hydrothermal/Solvothermal Composite Synthesis:** These techniques ensure homogeneous dispersion of Fe_2O_3 nanoparticles on g-C_3N_4 nanosheets and facilitate the regulation of shape and crystallinity.
- **Ultrasonication-Assisted Blending:** This technique enhances the $Fe2O_3$ nanostructures are uniformly anchored on g-C_3N_4 sheets minimising agglomeration and augmenting photocatalytic interaction sites. These composite construction techniques aim to enhance the physicochemical synergy between Fe_2O_3 and g-C_3N_4, consequently augmenting photocatalytic efficiency under solar or visible light exposure.

Table.4: Synthesis Methods for Fe_2O_3 & Fe_2O_3/g-C_3N_4 Composites

Sr. No.	Synthesis Method	Material System	Key Features / Conditions	Advantages	Reference(s)
1	Co-precipitation	Fe_2O_3	Fe^{2+}/Fe^{3+} salts base (NaOH/NH_4OH), ambient or mild temp	Simple, scalable, cost-effective	[36]
2	Sol–gel	Fe_2O_3	Metal alkoxide precursor + solvent, gelation & drying	High purity, good control over particle size	[37]
4	Green synthesis (plant extract)	Fe_2O_3	Leaf/fruit extracts + Fe salts, low-temp heating	Eco-friendly, avoids toxic chemicals	[38]
5	Combustion synthesis	Fe_2O_3	Fuel (urea/citric acid) + Fe salts, high-temp ignition	Fast reaction, high surface area	[39]

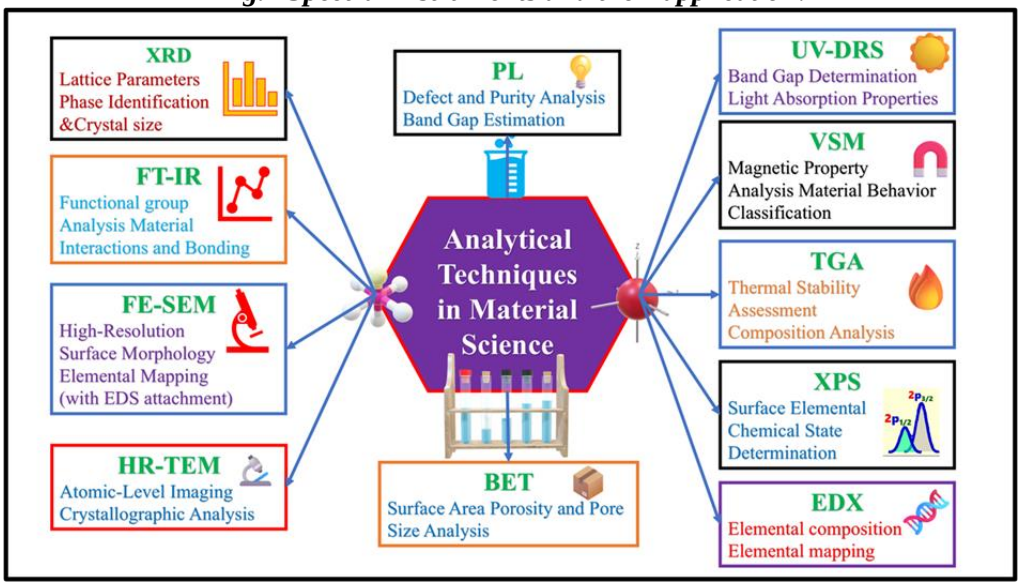
Result and Discussion:

Characterisation Technique

To evaluate the structural, morphological, optical, elemental, and magnetic properties of synthesised

Fe_2O_3, g-C3N4 nanoparticles and Fe_2O_3–g-C_3N_4 nanocomposites, a variety of sophisticated analytical methods used. Each technique serves a distinctive function in the verification of synthesis, composite interaction, and property-performance relationships Fig.2 illustrate the comprehensive use of analytical instruments and its applications.

Fig.2 Spectral instruments and their application.



Photocatalytic Mechanism

Photocatalysis involves the enhancement of a photoreaction facilitated by a catalyst. Photocatalysis operates by the production of electron-hole pairs in semiconductor materials upon exposure to light energy that meets or exceeds their band gap energy (Eg).

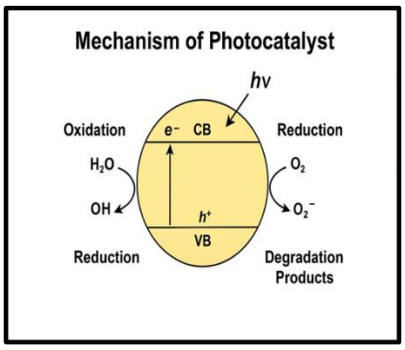


Fig.3 General Mechanism of Photocatalyst

Basic Mechanism of Photocatalysis

Photoexcitation

When a semiconductor photocatalyst such as Fe_2O_3 or g-C_3N_4 is exposed to light (UV or visible), electrons (e^-) in the valence band (VB) absorb energy and transition to the conduction band (CB), resulting in the formation of holes (h^+) in the VB.

- **Charge Separation and Migration:** The photoexcited electrons and holes migrate to the catalyst surface, enabling their involvement in redox processes.Surface Reactions: The photo-generated electrons convert oxygen (O_2) to superoxide radicals ($\bullet O_2^-$). The photo-generated holes oxidize water or hydroxide ions (OH^-) to produce hydroxyl radicals ($\bullet OH$).
- **Pollutant Degradation:** Reactive oxygen species (ROS) degrade

organic contaminants, such as dyes, into non-toxic byproducts including CO_2 and H_2O.

A Comprehensive Overview of the Different Types of Photocatalytic Mechanisms

By combining two semiconductors with distinct band structures, photocatalytic heterojunctions are designed to increase charge separation and boost photocatalytic efficiency. The energy band alignment and interfacial contact affect the redox potential and charge transfer channels. The following main categories of heterojunction mechanisms that are frequently documented in photocatalysis are listed below:

The Z-scheme heterojunction

The Z-scheme mechanism increases photocatalytic efficiency by enhancing charge separation and sustaining robust redox potentials. Two semiconductors selectively recombine electrons and holes in a process modelled after natural photosynthesis. The electron from the conduction band of $Fe2O_3$ recombines with the hole in the valence band of g-C_3N_4 in a g-C_3N_4/Fe_2O_3 Z-scheme. This can happen through direct contact or via a solid-state mediator such as reduced graphene oxide nanoparticles. The remaining electron in g-C_3N_4 and the hole in Fe_2O_3 possess significant redox potential for photocatalytic processes. These charge carriers produce reactive species such as ·OH and $\cdot O_2^-$ when exposed to visible light. This technology provides little energy waste and improved pollutant degradation efficacy. Consequently, Z-scheme photocatalysts hold significant potential for environmental remediation [40].

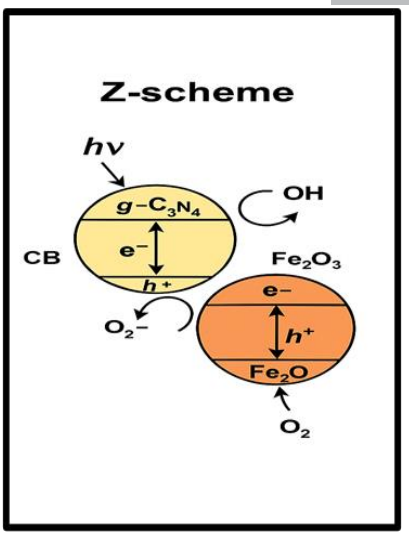


Fig.4 Z- scheme Mechanism

The S-scheme the heterojunction

The S-scheme is a powerful heterojunction that develops on the Z-scheme concept to improve charge separation. An internal electric field is produced by differences in the Fermi level between n-type and p-type semiconductors. This intrinsic field causes band bending, facilitating directional charge movement at the interface. Upon light irradiation, low-energy electrons and holes selectively recombine at the contact. High-energy electrons in the conduction band of the reduction photocatalyst and holes in the valence band of the oxidation photocatalyst are retained this "intelligent separation" leads to enhanced redox capacity and less charge recombination. In contrast to Z-schemes, S-schemes require no external facilitators, hence speeding the system. Consequently, S-scheme heterojunctions provide enhanced photocatalytic efficacy and interfacial control [41].

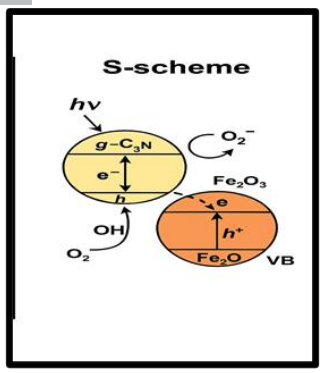


Fig.5 S-scheme

Parameter	Z-Scheme	S-Scheme
Charge Separation	Good	Excellent
Redox Power	High	Very High
Internal Electric Field	Indirect (mediator/contact-based)	Present (built-in)
Complexity	High	Complex
Visible Light Response	Strong	Excellent
Dye Degradation Efficiency	High	Very High
Remarks	Retains strong redox potential; efficient charge separation	Superior interface control; ideal for visible-light photocatalysis

Table: Comparative Analysis of Photocatalytic Mechanisms

Conclusion

$Fe_2O_3/g\text{-}C_3N_4$ heterojunction nanocomposites exhibit superior photocatalytic activity due to greater charge separation and the reactivity to visible light.The combination of Fe_2O_3's redox properties with g-C_3N_4's stability results in effective Z- or S-scheme systems. These heterojunctions inhibit electron–hole recombination and facilitate the production of reactive species. The green synthesis utilizing laterite soil, extracts of plants, and industrial byproducts promotes sustainable material advancement. These environmentally sustainable methods correspond with circular economy concepts and mitigate ecological damage. The composites demonstrate

promising efficacy in degrading dye and organic contaminants under visible light.
Simple synthesis techniques like as grinding, calcination, and activation make them scalable.
Characterization verifies the development of crystalline, stable, and functional nanostructures.
Despite advancements, obstacles persist in enhancing interfaces and augmenting recyclability.
Subsequent research should concentrate on empirical testing in real-world conditions and the assessment of long-term stability. Fe_2O_3-g-C_3N_4 complexes exhibit significant potential for sustainable photocatalytic applications.

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MODERN APPROACHES TO CHEMICAL SCIENCE: CONCEPTS AND TECHNIQUES

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Modern Approaches to Chemical Sciences- Concept and Technology

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Abstract

In the rapidly evolving landscape of chemical sciences, the integration of modern concepts and advanced technologies has revolutionized research and application across various domains. This chapter explores contemporary approaches that bridge traditional chemical principles with methodologies, emphasizing their impact on sustainability, efficiency, and interdisciplinary collaboration. By highlighting case studies and recent breakthroughs, this work aims to illuminate the symbiotic relationship between conceptual advancements and technological progress, illustrating how they collectively foster a deeper understanding of chemical phenomena and inspire future innovations. The integration of these modern approaches not only enhances the capabilities of researchers and practitioners but also promotes a more sustainable and responsible framework for addressing global challenges in health, energy, and environmental stewardship.

Keywords: Modern techniques, Chromatography, Ultra performance chromatography

Modern Analytical Techniques

Chromatographic Methods

Introduction

Chromatography is a crucial biophysical method that makes it possible to separate, identify, and purify a mixture's constituent parts for both qualitative and quantitative study. (Coskun, 2016) Chromatography is a general term that refers to a variety of techniques that enable the separation of closely related ingredients from complicated mixtures. The Russian botanist Mikhail Tswett developed the method of chromatography more than a century ago when he separated a solution of plant colours using a glass column filled with chalk. (R. J. Hamilton & Sewell, 1982) He used a procedure that included running solutions of several plant pigments, including chlorophylls and xanthophylls, through a glass column filled with finely split calcium carbonate in order to separate them. He adopted the method's name because the separated species showed up on the column as coloured bands (Greek chroma means "colour" and graphein means "writing"). (Chatwal & Anand, 2008) In 1941, A. J. P. Martin and R. L. M. Synge at Cambridge University, UK discovered partition chromatography for which there were awarded the Noble Prize in 1952.

The primary purpose of chromatography is to identify and/or separate the constituents of a chemical mixture. This method was developed because the mixture's chemical constituents had varying affinity for dissolving in an organic solvent and/or adhering to a surface. This method is extensively used in industry to separate and purify the constituents and corresponding products in a variety of organic syntheses. (Chatwal & Anand, 2008). Chromatography's widespread use in separation science may be attributed to its versatility in its numerous forms, as well as its ease of use and a relatively well-developed framework that allows for the operation of the many chromatographic procedures. (C.F.Poole, 1997). Chromatography, which separates the components of a mixture according to their distribution across two phases, is essentially a physical separation technique. A fluid (mobile phase) moves through or over the stationary phase, whereas the other phase—which might be a porous bed, bulk liquid, layer, or film—is typically motionless (stationary phase). (C.F.Poole, 1997) According to this method, the chromatography process is based on three components.

1. **Stationary phase:** This phase is always made up of a "solid" phase or "a liquid layer adsorbed on a solid support surface."
2. **Mobile phase:** "Liquid" or "gaseous component" always makes up this phase.
3. **Molecular separation I 2(Coskun, 2016):** The most used separation method in chemical laboratories, chromatography is used for analysis, isolation, and purification. It is also often employed in the chemical process industry as a part of both small- and large-scale manufacturing. At one extremity of the scale, hundreds of kilogrammes of material are processed into

recycled products per hour, while at the other end of the spectrum, tiny amounts of less than a nanogramme are separated and identified during analysis. (Chatwal & Anand, 2008)

Theoretical Principles Underlying Chromatography Technique

The two phases are selected so that the sample's constituents disperse to differing degrees between the stationary and mobile phases. The components that are firmly held in place by the stationary phase only move slowly when the mobile phase flows. On the other hand, elements that the stationary phase holds loosely move quickly. These variations in migration rates cause the sample's constituents to split up into distinct bands, or zones, which may be examined both qualitatively and numerically.

The partition or distribution is the foundation of all chromatographic techniques. The way a chemical distributes itself between two immiscible phases is described by the coefficient (K).ch (Chatwal & Anand, 2008) An equilibrium constant called a distribution constant, or even partition coefficient (Kc), which is the ratio of the concentration of the solute molecules in the stationary phase (cS) to that in the mobile phase (cM), is used to chemically describe a given component's tendency to interact with the stationary phase. I 7 (Fanali et al., 2016)

$$Kc = cS/ cM$$

The higher the value of Kc for a sample component, the more soluble it is and, consequently, the longer its retention time in the stationary phase. I 7 (Fanali et al., 2016)

Retention time (tR) is equal to the amount of time that any solute spends in the mobile phase, which is equal to the sum of the unretained peak time (tM) and the so-called adjusted retention time, which is the amount of time the solute spends dispersed in the stationary phase: I 7 (Fanali et al., 2016)

$$tR = tM + tR$$

Every analyte in a sample will exhibit a unique retention time. The duration for the mobile phase to travel through the column is referred to as dead time (tM). Both tR and tM can be easily acquired from the chromatogram. Every component has a duration of time tM in the mobile phase. (Chatwal & Anand, 2008)

The retention of a solute can alternatively be depicted using a retention factor (k), also known as a capacity factor, which reflects the duration that the solute interacts with the stationary phase relative to the time it engages with the mobile phase, based on the equation provided. I 7 (Fanali et al., 2016)

$$Rf\ (k) = tR/ tM$$

If the retention factor of an analyte is below one, the elution occurs too quickly to accurately pinpoint the retention time. Conversely, a high retention factor (over 20) indicates that the elution process is prolonged. The optimal retention factor for an analyte falls within the range of one to five.

K is quite helpful since it is independent of both volumetric flow rate and column shape. This indicates that any column of any shape running at any mobile phase flow rate will provide the same retention factor for a specific solute, mobile phase,

and stationary phase combination. (Chatwal & Anand, 2008)

The selectivity factor (α) is a measure that indicates how well two species (A and B) are separated on the column. I 7 (Fanali et al., 2016)

$$\alpha = Kb / Ka$$

where Ka stands for the distribution constant for species a, which elutes faster or is retained less strongly, and Kb for species b, which is retained more strongly. According to this definition, α is always larger than one. (Chatwal & Anand, 2008)

Theories of Chromatography

Two propositions have been presented concerning the speed of solute migration and the formation of peaks in the chromatogram. These propositions are known as the plate theory and the rate theory, also referred to as the kinetic theory.

Plate Theory

Based on the plate theory devised by Martin and Synge, a chromatographic column is made up of a series of distinct yet continuous horizontal layers known as theoretical plates. At each of these plates, a balance of solute occurs between the stationary and mobile phases. It is assumed that the migration of the solute happens via a series of stepwise transfers from one plate to the next below it. The efficiency of separation within a chromatographic column improves as the number of theoretical plates increases. This enhancement is due to the corresponding rise in the number of equilibrations. The number of theoretical plates, represented as N, serves as an indicator of column efficiency. If the column's length is L and the height equivalent of a theoretical plate is H, then N can be expressed as follows

The height equivalent of a theoretical plate (HETP) indicates the height of a segment of the column where the solution exiting the segment is in balance with the average concentration of the solute in the stationary phase throughout that section.

Rate Theory

The rate theory explains how factors such as the velocity of the mobile phase and the adsorption properties influence the width of an elution band. It also connects these factors to the time it takes for a solute to appear at the column's exit. The migration of solute molecules within a column occurs chaotically, with each solute molecule moving in a stop-and-start fashion, independently of others. When a molecule binds to the stationary phase, its downward movement along the column is briefly halted, even though the surrounding zone continues to progress. This means that one molecule might get temporarily stuck in the column while other molecules continue their migration. As a result, a molecule quickly alternates between being adsorbed and desorbed. The amount of time a molecule remains in either phase is highly erratic and relies on random energy gains from its surroundings that facilitate a reverse transfer. A particle can only migrate if it exists in the mobile phase, leading to irregular migration through the column. Consequently, some solute molecules may advance quickly while others trail behind. The cumulative effect of these erratic individual movements results in a symmetric distribution of velocities centered around an average value, which

characterizes the behavior of the typical or mean particle. The width of the zone increases as it moves down the column since more time is required for migration to occur. Therefore, the zone width correlates positively with the residence or retention time within the column and negatively with the velocity of the mobile phase. To optimize the use of a chromatographic column, it is essential to investigate the factors influencing how long a molecule is retained by either phase and the elements that contribute to zone spreading.

UPLC (Ultra Performance Liquid Chromatography)

Introduction

The development of packing materials used to accomplish separations has been one of the main factors driving the rise of this technology. (UPLC 3) (Swartz, 2005)

One crucial liquid chromatography (LC) method for separating various components in mixtures is high-performance liquid chromatography (HPLC). It has been in use for decades worldwide and is also utilized for the identification and measurement of chemical compounds during the drug development process. Waters introduced and trademarked Ultra Performance Liquid Chromatography (UPLC) in 2004 with the goal of achieving the aforementioned objectives. UPLC is based on tiny, porous particles (sub 2micron particles). (UPLC 1) (Chawla & Ranjan, 2016)

It is a process that uses a porous material and a solvent to separate a mixture of components into its constituent parts. (UPLC 4) (Gaikwad et al., 2020) The fundamental idea behind UPLC, a variation of HPLC, is that efficiency and, consequently, resolution rise with decreasing column packing particle size. According to the standard Van-Deemter equation, efficiency increases significantly if particle size is reduced to less than 2 µm and does not decline as linear velocities or flow rates increase. (UPLC 6) (Ashok et al., 2012) (UPLC 4) (Gaikwad et al., 2020) Significant improvements in sensitivity, resolution, and analysis speed are made possible by UPLC. By using small particles (less than 2.5µm) and mobile phases at high linear velocities, along with instrumentation that runs at higher pressure than that of HPLC, this system shortens the column's length, uses less solvent, and saves time. (UPLC 7) (ศักดิ์เพ็ชร et al., 2562) (UPLC 4) (Gaikwad et al., 2020) UPLC requires the use of porous particles that can tolerate high pressure in order to maintain retention and capacity comparable to HPLC; despite their high efficiency, these sub-2 µm (non-porous) particles have poor loading capacity and retention because of their small surface area. (UPLC 4) (Gaikwad et al., 2020) Using columns loaded with smaller particles and greater flow rates for faster separations with better resolution and sensitivity, this method fully utilizes chromatographic principles. (UPLC 4) (Gaikwad et al., 2020)

Principle

The basic principle behind UPLC and HPLC is the same and is dependent on the type of chromatographic sorbent used, which determines the method of separation (adsorption, partitioning, exclusion, and ion-exchange). (UPLC 4) (Gaikwad et al., 2020) The key distinction between UPLC and HPLC is the design of the column material

particle size, which is smaller than 2µm. (UPLC 5) (Taleuzzaman et.al.,2015)

The Van Deemter relationship, which explains the link between flow rate and plate height, is the core of UPLC. For long-term effects, the Van Deemter equation demonstrates that the flow range with smaller particles is significantly bigger than that with larger particles. (UPLC 4) (Gaikwad et al., 2020)

$$H=A+B/v+ Cv$$

Where, H = Height Equivalent to Theoretical Plate (HETP)

A = Eddy's Diffusion

B = Diffusion coefficient

C = Resistance to mass transfer coefficient

v = Linear velocity

Where A, B, and C are constants. v is the linear velocity, the carrier gas flow rate. The A term is independent of velocity and represents "Eddy" mixing. It is the smallest when the packed column particles are small and uniform.

Axial diffusion, or the molecule's inherent diffusion tendency, is represented by the B term. This term is divided by v since the influence is lessened at high flow rates.

Kinetic resistance to equilibrium during the separation process is the cause of the C term. The time lag required to transition from the gas phase to the packing stationary phase and back again is known as the kinetic resistance. A molecule on the packing tends to lag behind molecules in the mobile phase more when the gas flow increases. This term is proportional to v as a result. As a result, throughput and analytical speed can be increased without compromising chromatographic performance. (UPLC 4) (Gaikwad et al., 2020)

Instrumentation

For the UPLC approach to benefit from the increased speed, better resolution, and increased sensitivity offered by small particles, the fundamental instrument required to maintain a high tempo. To achieve the goal, a design including cutting-edge technology in the pump, autosampler, detector, data system, and service diagnostics was necessary. (UPLC 6) (Ashok et al., 2012)

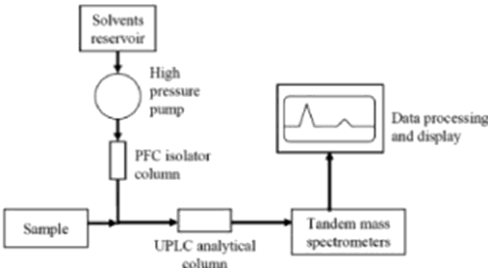

Fig: Schematic diagram of UPLC system (Taleuzzaman et.al.,2015)

It consists of the following-

Pumping devices

Sample Injector

UPLC Columns

Detectors

Pumping devices

For a 15 cm long column filled with 1.7 µm particles, the optimal flow rate and maximum efficiency can be achieved using a pump that can provide solvent at a higher pressure of about 15000 psi. Two serial pumps with a 1000 bar pressure limit and built-in solvent selector valves that can pick the precise

solvent ratio from up to four solvents are used in UPLC. (UPLC 6) (Ashok et al., 2012) Additionally, the delivery system needs to compensate for solvent compressibility across a broad pressure range and a range of solvents utilized in isocratic, linear, and nonlinear gradient elution. Vacuuming up to four eluents and two wash solvents removes the dissolved gasses. (UPLC 1) (Chawla & Ranjan, 2016)

Sample Injector

The insertion of the sample is crucial in UPLC. Neither automated nor manual conventional injection valves are built to withstand high pressure. (UPLC 5) Taleuzzaman et.al.,2015) The injector is used to add a little volume of solution containing the sample in the mobile phase in a precisely determined amount. Accurate and repeatable injections are required. (UPLC 1) (Chawla & Ranjan, 2016) The injection procedure must be comparatively pulse-free in order to protect the column from severe pressure fluctuations, and the device's swept volume must be kept to a minimum to minimize any band spreading. (UPLC 5) (Taleuzzaman et.al.,2015) The inject valve diverts flow from the needle to collect the sample from the vial when an injection is initiated. To extract the precise volume of sample needed, the needle is placed inside the vial and then brought back to the injection port. The injection valve rotates when the needle is pressed up against the port's internal sealing surface, pushing the sample down to the injection port. (UPLC 6) (Ashok et al., 2012)

UPLC Column

The small particles that make up the UPLC columns are smaller than 2µm. (UPLC 4) (Gaikwad et al., 2020) Since the bonded stationary phase is necessary to provide both retention and selectivity, the particles are bonded in a matrix. (UPLC Particles created using various technologies are packed into several kinds of columns utilized in UPLC. (UPLC 1) (Chawla & Ranjan, 2016)

There are four types of particle technology:

1. Charged Surface Hybrid [CSH]

2. Ethylene Bridged Hybrid [BEH]

3. High Strength Silica [HSS]

4. Peptide Separation Technology (PST).

Charged Surface Hybrid [CSH] particle technology

CSH Technology, makes use of low-level surface charged particles to improve peak sharpness and selectivity. With greater efficiency and chemical stability, a hybrid-based packing material technique produces sharp peaks, particularly for basic chemicals at low pH. The different kinds of CSH particles that are frequently utilized are CSH C18, CSH Phenyl Hexyl, and CSH Fluoro Phenyl. These columns have the following benefits which includes selectivity for positional isomers, halogenated and polar compounds (CSH-Fluoro phenyl), enhanced loading capacity (CSH C18), and complementary selectivity to straight chain alkyl phases (CSH-phenyl-hexyl). Additional benefits include enhanced batch-to-batch reproducibility, faster column equilibration following any change in the mobile phase's pH, and greater stability across a broad pH range. Basic chemicals, even in their ionized state,

can be analysed using columns based on CSH technology.

Poor peak shape and retention are frequently the outcome of evaluating basic chemicals in reversed phase and low pH circumstances. In contrast, CSH Phenyl Hexyl columns offer basic drugs an outstanding peak shape in an acidic mobile phase. (UPLC 1) (Chawla & Ranjan, 2016)

Ethylene Bridged Hybrid [BEH] particle technology

Hybrid particle technology [HPT], offers unparalleled performance and versatility. Without the disadvantages of inconsistent selectivity brought about by substitute materials like zirconia, organic polymers, and graphitic carbon, the XTerra particle was the first commercially available solution to address the problems (poor peak shape for basic compounds and column longevity due to chemical instability). Fast HPLC with small particles was created with the commercialization of 2.5µm XTerra particles, increasing chromatographic lab productivity worldwide. (UPLC 1) (Chawla & Ranjan, 2016)

The various types of BEH particle technology-based columns that are in widespread use are straight chain alkyl columns (BEH C18 and C8), embedded polar group columns (BEH Shield RP18), and UPLC BEH Phenyl (phenyl group tethered to the silyl functionality with a C6 alkyl) and BEH Amide columns.

A. BEH C18 and C8 Columns: Because they work across a broad pH range, these straight alkyl chain UPLC columns are the most popular. The greatest useful pH operating range is created by combining the poor pH stability of the trifunctional ligands with the high pH stability of the 1.7 µm BEH particles. (UPLC 6) (Ashok et al., 2012)

B. BEH Shield R18 Columns: They provide UPLC selectivity by enhancing the C18 and C8 columns. (UPLC 6) (Ashok et al., 2012)

C. BEH Phenyl Columns: Between the silyl functionality and the phenyl rings, they have a tri-functional C6 alkyl ethyl. (UPLC 6) (Ashok et al., 2012)

D. BEH Amide Columns: Excellent column life is achieved by combining BEH tiny particles with a trifunctionally linked amide phase. They make it easier to employ a broad pH range, such as pH 2 to 11. (UPLC 6) (Ashok et al., 2012)

These columns offer improved peak shape and more compatibility with 100% aqueous mobile phase (RP18); chemical stability, reproducibility, and peak shape (phenyl); superior efficiency, peak symmetry, and chemical stability (C8); and higher retention and selectivity (C18). (UPLC 1) (Chawla & Ranjan, 2016)

High Strength Silica [HSS] particle technology

HSS particle technology was created by an inventive synthetic approach that improves mechanical stability while maintaining pore volumes comparable to those of materials based on HPLC silica. This leads to a more sophisticated method that offers greater retention than the hybrid particles. The various types of HSS particles that are frequently used are HSS T3, HSS C18, HSS C18 SB, HSS PFP, and HSS CN. (UPLC 1) (Chawla & Ranjan, 2016) Ideal for planar aromatic, positional, halogenated

compounds (PFP), these columns offer balanced retention of polar and hydrophobic molecules (T3), remarkable peak shapes, enhanced retention (C18), and greater retention of basic compounds (CS 18 SB). They also offer ultra stable retention that works with both reversed-phase and normal-phase techniques (CN). (UPLC 1) (Chawla & Ranjan, 2016)

Peptide Separation technology

PST makes use of C18 BEH Technology TM particles, which have diameters ranging from 1.7 µm to 10 µm. The dimensions of the columns range from 50 mm to 250 mm in length and from 75 µm to 30 mm in internal diameter (i.d.). They are employed in all types of research and development projects that involve peptide separation and analysis. Sharp, symmetrical peaks are provided by the PST columns. (UPLC 1) (Chawla & Ranjan, 2016)

Detectors

To reduce the amount of separated solute that is wasted on the column, the detector used for the UPLC should be able to provide a high sampling rate with small attainable peaks (<1 s half-height peak width) and little peak dispersion. Due in part to the detection process, the UPLC technology offers separation sensitivity that is two to three times higher than that of the earlier analytical approach, HPLC. (UPLC 1) (Chawla & Ranjan, 2016)

The UV/visible detectors are used in UPLC analysis. (UPLC 5) (Taleuzzaman et.al.,2015)

The Acquity photodiode array (PDA) and Tunable Vis-UV (TUV) detectors are generally used in the UPLC have Teflon AF, which creates an internally reflective surface and increases light transmission efficiency by removing internal absorptions. These have a total internal capacity of 500nL, acquisition rates of 20 (PDA) and 40 (TUV) points, and route lengths of 10 nun. With UPLC, mass spectrometric detection has also been employed. (UPLC 1) (Chawla & Ranjan, 2016)

For regular analysis and method development, two tuneable UV-visible photodiode array detectors with the ability to detect and quantify trace impurities—ACQUITY PDA and ACQUITY PDA eλ detectors—are typically utilized. With a low noise standard of 10 Au and a broad range of spectrum analysis up to 500 nm (PDA detector) and 800 nm (eλ detector), these detectors have data speeds of up to 80 Hz. Low volume light guiding flow cells made of Teflon AF, which reduces internal absorption by employing the total internal reflection principle to increase the efficiency of light transmission, are used to prevent band spreading and concentration variance. (UPLC 6) (Ashok et al., 2012)

Other types of detectors are-ELS (Evaporative Light Scattering) detector and FLR (Fluorescence) detector. (UPLC 4) (Gaikwad et al., 2020)

ELS (Evaporative Light Scattering) detector

Empower or Mass Lynx software, which integrates a flow-type nebulizer suited for UPLC system performance, controls this detector. (UPLC 4) (Gaikwad et al., 2020)

FLR (Fluorescence) detector

With an excitation wavelength between 200 and 890 nm and an emission wavelength between 210 and 900 nm, this multi-channel, multi-wavelength detector also provides 3D scanning for simpler method development. (UPLC 4) (Gaikwad et al., 2020)

Advantages Of UPLC

Following are the various advantages of UPLC- (UPLC 5) (Taleuzzaman et.al.,2015)

- It reduces run time while increasing sensitivity.
- It provides LC analysis its dynamic range, sensitivity, and selectivity.
- The chromatogram shows resolved peaks.
- Multiple residue techniques are used.
- Quick analysis, precise quantification of analytes, and associated products.
- Analysis is accelerated up by using fine particles (2µm) for stationary phase packing.
- Both money and time are saved.
- Less Solvent consumption
- Using the resources already available, more products are analysed.
- It enhances sample throughput and makes it possible for producers to generate more material that continuously satisfies or surpasses product requirements, possibly doing away with unpredictability, failed batches, or the need for material rework.
- It provides real-time analysis in sync with production procedures.
- It ensures the quality of the final work, including testing before release.

Disadvantages Of UPLC

Following are the various disadvantages of UPLC-

- The primary drawback of UPLC analysis is the life of the columns; due to the particle size, significant pressure created during analysis. Increased pressure shortens the columns' lifespan. Increased pressure shortens the life of these columns and necessitates greater maintenance. Better analysis is achieved without the negative effects of high pressure when using a stationary phase of particles with a size of 2µm. (UPLC 5) (Taleuzzaman et.al.,2015)
- Furthermore, phases smaller than 2 µm are typically non-regenerable, which limits their utility. (UPLC 7(ศักดิ์เพ็ชร et al., 2562)

Green Analytical Techniques

In the chemical industry, methods that reduce feedstock consumption, reagent and energy consumption, and waste generation are commonly referred to as "green chemistry," "clean chemistry," "benign chemistry," etc. Eliminating dangerous substances by replacing them with safer alternatives is another objective of such procedures. Anastas created the idea of "green chemistry," which is an aspect of sustainable development. A subfield of green chemistry that focuses on various facets of chemical analysis is called "green analytical chemistry." (GAT 1) (Płotka et al., 2013)

Analytical techniques have historically frequently depended on hazardous chemicals and solvents, which can produce a substantial amount of waste

and provide hazards to both the environment and analysts. In order to overcome these obstacles, GAC optimizes analytical procedures to be more sustainable and safer by nature. (GAT 7) (Miladinović, 2024)

For a number of reasons, incorporating green chemistry into analytical chemistry courses is crucial which includes the following:

1. **Environmental Responsibility:** Analytical chemists need to be aware of how their job affects the environment and aim to reduce it by using sustainable methods.
2. **Safety:** Adopting green practices makes the environment safer for professionals and students equally by lowering exposure to dangerous chemicals.
3. **Economic efficiency:** Green techniques can lower expenses by consuming less energy and chemicals and producing less waste.
4. **Regulatory Compliance:** Understanding GAC guarantees that chemists of the future can create techniques that satisfy increasingly stringent environmental rules.
5. **Innovative Thinking:** Using green chemistry promotes creative problem-solving techniques and cultivates a mindset that prioritizes sustainability in addition to scientific achievement. (GAT 7) (Miladinović, 2024)

Principles Of Green Analytical Chemistry

1. Sample treatment should be avoided by using direct analytical procedures.
2. The objective is to have a few samples and few sample size as possible.
3. Measurements should be taken in situ.
4. Reagent use is decreased and energy is saved through the integration of analytical procedures and processes.
5. Automated and miniaturized methods should be selected.
6. Derivatization needs to be prevented.
7. Large-scale analytical waste generation should be prevented, and appropriate analytical waste treatment should be offered.
8. It is better to use multi-analyte or multi-parameter techniques rather than one analyte at a time.
9. Energy consumption needs to be kept to a minimum.
10. It is better to use chemicals that come from renewable sources.
11. It is necessary to replace or remove toxic reagents.
12. The Safety of the operator must be improved.

Green Sample Preparation

Sample preparation is regarded as an essential component of analytical procedures based on the identification, quantitative determination, and chromatographic separation of a broad range of analytes, particularly in samples with complex matrix composition.

Following are the ways leading to "greening" of sample preparation which are as follows-

- removing (or at least lowering) the quantity of reagents and solvents utilized in the analysis.

- reduction in the size of analytical processes and the downsizing of instruments.
- automation/robotization of sample preparation and integration of many processes.
- all containers used for sample preparation should be properly sealed.
- recovering and reusing solvents.
- use of green media, such as supercritical fluids, ionic liquids, or superheated water
- application of factors enhancing the effectiveness of sample preparation (e.g. elevated temperature and/or pressure, microwave and ultrasonic energy). (GAT 1) (Płotka et al., 2013)

Methods For Greeness Assessment

Following are the experimental methods or tools used to assess the greenness of the analytical methods-

1. National Environmental Method Index (NEMI)

NEMI is represented by a circle known as the "greenness profile," which is split into four equal portions. PBT, which stands for persistent, bio-accumulative, and toxic, is represented by the initial portion of the circle. The risky element is expressed in the second section. The corrosiveness and waste are expressed in the third and fourth sections, respectively. Each component can either be coloured green to represent the method's greenness or blank to represent its lack of greenness. (GAT6) (Patel & Patel, 2024)

2. Analytical Eco-Scale Assessment (ESA)

The Analytical Eco-Scale Assessment, the second evaluation method is based on total points, which may indicate how environmentally friendly the analytical process was. The eco-scale evaluation process is based on deducting penalty points from a starting point of 100. (GAT4) (Tobiszewski, 2016) By emphasizing the adverse effects of additives and excipients, such as hazardous solvents used in a procedure, as well as the effects on the environment and the energy used, a penalty point lowers the overall score, starting with 100 points.If the final score is more than 75 points, the strategy is considered green; nevertheless, if the final score falls between 50 and 75 points, the approach is considered acceptable. The green analytical technique is deemed inadequate if the score is less than 50. Hazard penalty points are calculated as follows: 0 penalty points and no pictogram indicate a non-hazardous chemical, 1 penalty point is awarded for a less serious hazardous chemical, and more serious danger is indicated when the points exceed 1. (GAT6) (Patel & Patel, 2024)

3. Green Analytical Procedure Index (GAPI)

In 2018, J. Potka-Wasylka introduced a novel tool known as Green Analytical Procedure Index (GAPI) that could evaluate the environmental friendliness of an analytical process from sample collection to the end product. According to the GAPI, every analytical procedure starts with sample collection, which is followed by a second phase that protects the sample from damaging chemical and physical changes. The third and last step then uses analytical methods to determine and quantify it.A particular

sign with five pentagrams could be used in GAPI to assess and quantify the low, medium, and high environmental impact associated with each phase of the approach, going from green to yellow to red. The red color denotes an environmentally unfriendly technique, the green color suggests a safe one. (GAT6) (Patel & Patel, 2024)

The Analytical Greenness calculator (AGREE)

AGREE is a comprehensive, adaptable, and uncomplicated evaluation method that yields an understandable and informative outcome. The parameters that are taken into consideration in AGREE are derived from the 12 GAC principles and converted into a single 0–1 scale. The fact that free software is readily available and simplifies its usage is one of this metric's benefits. (GAT6). (Patel & Patel, 2024)

Application

1. Biological Analysis

An ESI interface was used to link the constructed multi-dimensional LC system to a Q-Trap MS. The examination of the pharmacological effects of ginsenoside Rg3 on the urine metabolite pattern of tumor-bearing rats proved the system's suitability for metabonomics research. Urine was totally automatically separated after a single sample injection, first on an HILIC column and then on an RP C18 column. Both hydrophilic and hydrophobic metabolites were included in the combined chromatogram that was produced. 5,686 metabolite ions were generated by HILLC during the 52-minute separation, while 1,808 metabolites were formed by the RP separation. The metabolic information generated by RP and HILIC separation complemented the metabolic phenotype discrimination and helped identify potential biomarkers.The potential of multidimensional LC for thorough metabolic profiling studies is demonstrated by this column-switching method that combines HILIC and RP separations. [Ap1] (Wu et al., 2009)

2. Analysis Of Drugs

- **Antithrombin III**

To purify Antithrombin III from human plasma, immobilized-heparin chromatography remains the gold standard. One purification method involves passing cryo-poor plasma through a DEAE ion-exchanger to extract Factor IX, followed by immobilized heparin in a phosphate buffer with a pH that is nearly neutral and low ionic strength that binds Antithrombin III. Antithrombin III is eluted using 0.45 M NaCl or a higher salt with an x concentration of 31,34 after the gel has been cleaned with a buffer that contains 0.25 to 0.35 M NaCl. The starting plasma material for an alternate affinity-chromatographic procedure on immobilized heparin is Cohn ethanol precipitate IV-1[. Ap2] (Burnouf & Radosevich, 2001)

- **N-nitrosamines**

N-nitrosamines are frequently observed in food and the environment. The majority of them are recognized to be significant animal carcinogens.N-nitrosamines can be effectively analyzed using high-performance liquid chromatography.Foodstuffs, drinking water, rubber goods, medication formulations, tobacco, and tobacco smoke all include volatile nitrosamines.

In the human diet, the environment, and in vivo in the stomach or small intestine of experimental animals, secondary amines react with nitrosating substances like nitrite or nitrate to generate N-nitrosamines. Even at mg/kg concentrations, N-nitrosamines are hazardous. Therefore, it is crucial to have a sensitive and selective method for detecting these N-nitrosamines at low amounts. Ap5(Cárdenes et al., 2002)

- **Captopril**

Captopril is an ACE inhibitor, a class of anti-hypertensive medications that work by altering the renin-angiotensin system.Captopril is characterized by its weak chromophore, which prevents it from absorbing at the more beneficial UV-Vis spectrum. Captopril and similar compounds are detected in pharmaceutical tablet dosage forms utilizing an anion-exchange high performance liquid chromatographic (HPLC) technique that uses indirect photometric detection. Ap6(Mirza & Tan, 2001)

- **Ledipasvir**

One medication used to treat hepatitis C is called ledipasvir. Ledipasvir suppresses NS5A, a crucial viral phosphor protein involved in viral assembly, secretion, and replication. In contrast, sofosbuvir is converted to a uridine triphosphate mimic, which, when integrated into the RNA by the NS5B polymerase, functions as an RNA chain terminator. The reverse phase HPLC technique is used to estimate the amount of ledipasvir in its bulk drugs. Ap7 (Devilal et al., 2016)

- **Rivaroxaban**

An anti-clotting drug called rivaroxaban prevents blood clots from forming by acting at a critical stage in the blood-clotting process. The RP-HPLC method was created as a quality control measure to determine the amount of rivaroxaban in pharmaceutical dosage forms. A Phenomenex Luna 5 µm C18 100 Å LC Column was used for the separations, and UV detection was done at 249 nm. Ap8 (Bhatkar et al., 2024)

3. Impurity Profiling

As a result, chromatographic separation allows for real-time impurity structure determination, and isolation and characterisation are completed in a single step. Because bench-top instrumentation is readily available and offers several advantages, including versatility, sensitivity, the ability to profile substructural analysis, and the ability to quickly and selectively quantitatively determine the targeted compound even in mixtures, the use of hyphenated techniques for impurity determination is increasing. The sole drawback of hyphenated techniques is their high instrumentation costs, which prevents their widespread and widespread adoption, unlike HPLC, MS, or NMR systems. Although they can be utilized for other analytical objectives, these advanced techniques are currently primarily employed for the monitoring, characterisation, and detection of contaminants. Ap3(Jwaili, 2019)

4. Analysis of Drugs of Abuse

When used in conjunction with Headspace, GCMS is an effective analytical method for analyzing drugs of abuse. Analyses of amphetamines and their metabolites in urine and the amount of nicotine in prescription medications

are two examples of this kind of analysis. In SIM mode, GCMS in conjunction with chemical ionization and traditional headspace will provide a 20-fold increase in sensitivity. The consistent ionization produced by GC MS facilitates the comparison of identified chemicals with library data. Ap3(Jwaili, 2019)/Ap4(Eiceman et al., 2000)

5. Phenolic compounds

A popular analytical separation method that combines high resolution, simple automation, and low sample requirements is high-performance liquid chromatography (HPLC). The chromatograms of phenolic compounds at 280 nm are frequently used to study phenolic compounds because absorption at this wavelength is suitable for the detection of a large number of such compounds, which can be easily detected by HPLC due to its versatility and precision. Some phenolic compounds found in wine exhibit characteristic absorbances in the UV–vis region. The most common methods for analyzing phenolic compounds are reversed-phase C18 columns, a binary solvent system that consists of polar organic solvent and acidified water, and detection in the UV–vis range. Ap9 (Burin et al., 2011)

6. Ionic species

The need for automated or semiautomated analysis of chemical plant streams, environmentally significant waters like waste streams, rivers, and lakes, and biologically significant fluids like blood, urine, etc. is growing as a result of the rapidly rising demand for the identification of ionic species in a variety of aqueous environments. There are several instances where regular examination of common species, such as Li+, Na+, K+, NH4+, Ca2+, Mg2+, F-, C1-, Br-, I-, S042-, NOn-, Nos-, Po43-, etc., is constantly required. Ion exchange chromatography has been effectively used in a number of situations, and ion exchange resins are recognized to offer superior ionic species separations. Ap10(Small et al., 1975)

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Modern Approaches to Chemical Science: Concepts and Techniques

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Modern Synthetic Methods

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Abstract

Modern synthetic methods in chemistry are at the forefront of innovation, enabling the efficient and precise construction of complex molecules. This chapter provides an overview of the latest advancements in synthetic methodologies, emphasizing their significance in various fields, including pharmaceuticals, materials science, and organic chemistry. The integration of green chemistry principles in synthetic protocols is also highlighted, showcasing the shift towards more sustainable practices that reduce environmental impact. By examining recent breakthroughs and case studies, this work illustrates how modern synthetic methods not only inspire creativity in molecular design but also address the urgent need for innovative solutions in drug discovery, material development, and beyond. Ultimately, the continued evolution of synthetic methodologies holds the promise of overcoming current challenges in chemical synthesis and driving future discoveries.

Keywords: Methodologies, Modern Methods, Stereoselective, isomerism.

Introduction

Modern Synthetic methods start with "Darwin" truth of descent with modification main mechanism is much delayed which was natural selection of variation within Population. Since 1920-

1950 scientists Huxley coined termed "Modern Synthesis Methods"[1]. The traditional method of drug synthesis is very time-consuming process peoples are looking for alternate method of Synthesis of Drug molecules i.e. Modern Synthetic methods. This method is also known as Combinatorial Synthesis. This is novel method getting large number of compounds in short period of time. Industries adopt this method in 1990 but basic concept was introduced in 1963 advantage of combinatorial synthesis that large range of analogue has been synthesis using same reaction condition in some react vessels and also large number of products produced is larger than number of chemical steps taken.[2]

Modern synthetic methods are of two types

Solid-phase synthesis.

Solution- phase Synthesis

Solid-phase synthesis: This method has advantage that it is very for isolation of product which can be gained by filtering complete conversion of product from reactant toxic and safe handling of explosive regents. This method can be carried out by using parallel or split and mix procedure using insoluble polymer support. This Solid phase Synthesis involve following steps.[3]

a. Synthesis of heterocyclic compound
b. Synthesis of peptide & protein,
c. Synthesis of organic compound
d. Synthesis of inorganic compound

Solution phase synthesis: Some compounds are synthesis by this method using parallel or split and mix method. These processes involve multistep synthesis because it involves tedious purification in each step as compare to Solid phase Synthesis. So, majority of compound were synthesis by using solid-phase Synthesis. [4]

Synthesis of organic and peptide compounds: Researcher developed microwave assisted Synthesis of thirty-eight Microwave N-aroyl-N-aryl thiourea using solution phase synthesis. Compound were carried out against urease enzyme which act as target for lung carcinoma later from this analogue were prepared from raw material using same conditions.

Synthesis of Inorganic compound: Synthesis of inorganic compound are vital material for different application such as photovoltaic catalytic & thermoelectric process. Solution phase-synthesis is used in novel method of synthesis nanoscale transition metal tellurides by interaction of colloidal metal nano particles & telluride's

Yongchun found the new method for nanoparticles through microwave-assisted, heating at low temperatures, hydrothermal/solvothermal using solution-phase synthesis. Thus, combinatorial chemistry is useful for several molecules & Screening of their pharmacological activity using solid & solution phase technique. These methods are useful for lead identification & optimization, synthesis of peptides oligonucleotides, organometallic small proteins, inorganic molecules & Polymer chemistry. In recent days these methods are useful for medicinal compound preparations.5

1. Organometallic chemistry

Organometallic chemistry is Synthesis, structure and reactivity of chemical

compounds that contain metal carbon bonds. These compound of often used as homogeneous catalyst. Organometallic compound is which contains at least one bond between metallic element & carbon atom belonging to organic molecule such as silicon, tin, boron, are known to form organometallic compound which are used in industrial chemical reactions.[6]

History of organometallic chemistry

1760	**The first complex organometallic chemistry occurs in United States, England, and Germany during 3rd quarter of the XXth Century It is in Paris military pharmacy however discipline was introduced in 1760**
1900-1950	**Grignard, Sabatier, and Catalysis in Germany**
1950-1960	**The Discovery of Ferrocene and the boom of organometallic chemistry**
1961-1981	**Discovery of multiple metal-carbon bonds and golden age of catalysis**
1970-1985	**Activation of C-H bonds in hydrocarbons - Sigma bond metathesis and H_2 as a ligand**

Properties of organometallic compounds

1. Metal carbon atom band is highly covalent in nature
2. Organometallic compound exists in solid form especially aromatic compounds
3. Compound is highly electropositive metals such as Sodium, Lithium which are highly volatile
4. Organometallic compound found toxic to human.
5. These are reducing agents especially compound of electropositive metals
6. Complexes formed by organometallic compound are useful in synthesis of many organic compounds

Let us start with special properties of ferrocene which makes electrochemical applications. Ion atom of ferrocene is completely delocalized on highest occupied molecular orbital of ferrocene. So, electron density is maximum in ferrocene molecules. If you remove on electron, it is an ion which is depleted of electron, primarily and is nonbinding orbital.

Special properties & applications organometallic compound have been used is quite large we will discuss few topic-like sensors, deposition of metal organic chemical way and Nonlinear optics[7]

a. **Sensors:** It has been designed these are Amperometric sensors in other words they measure the current flow that is there is electrochemical setup. To detect & have quantity specifies you have an enzyme which specially oxidize glucose but enzyme itself not capable of transferring that electron to electrodes so electrode may be modified using ferrocene substituted species which allows implantable version of a glucose sensor
b. **Organometallic polymers** Femrene can be used as catalyst for on electrochemical reaction there must be way of coating this electrode with organometallic species use of single molecule functionalized and coated onto electrodes, these can be connected to organic legend and that

is cyclopentadienyl legend. that is present on ions or connecting it through the metal. In other words, it is possible for us to generate a polymeric species where metal along is linked one after another.[7]

c. **Optical Properties:** Now let us move to electrical properties to electronic properties. Optical properties of organometallic compound are similar to other chemical compounds.
d. Many other organometallic compound to respond to light in linear way. Light following on molecule. Molecule Scatters light and and outcome light with lower intensity. Organometallic compound transmit light with lower intensity because some of photons of light absorbs organometallic Compounds.8

Methods of Synthesis: There is various method of synthesis of organometallic compound. but few are discussed here. It includes Direct Reactions, Reductive Carbonylation and Photolysis and Thermolysis

Direct Reactions: For synthesis of nickel purification (Mond's Process), Tetracarbonyl nickel and penta-carbonyl iron were discovered in 1988. The synthesis of tetracarbonyl nickel were industrial importance because reaction is irreversible

$$Ni + 4CO \xrightarrow{25^{o}C} Ni[co]_4 \xrightarrow{\text{Distillation}} Ni + CO$$

The Simplest metal carbonyl compound is neutral binary compound these may be mononuclear or poly nuclear. Majority of metal carbonyl are low Melting Point and Solid that can sublimate in vacuum. Some compounds are volatile liquids. Other compound of mononuclear metal carbonyl is prepared by direct metal carbonyl are prepared of at appropriate temperature & pressure.[9]

Reductive Carbonylation's: Both the type of carbonylation is Synthesis by this method. In this transition metal in a high oxidation state is reduced to Zero-oxidation state in presence of carbon monoxide gas (CO) These reactions are performed at very high pressure in steel compartment. To reduced possibility of accident the compartment is explosion free located on top floor of chemistry building Some typical metal Carbonyl Synthesis are shown as follows[10]

$$CrCl3 + Al + 6[CO] \longrightarrow CrCO]3 + AlCl3$$

$$Re_20_7 + 17CO \xrightarrow{uh} Re_2[CO]10 + 7CO2$$

Photolysis and thermolysis: other than these two methods Carbonyl Compound can also be synthesis by route called photolysis photochemical bond cleavage occurs during Synthesis.[11]

$$2Fe[CO]_5 \longrightarrow Fe_2[CO]_9 + CO$$

The Ligands:

Given the convention according to which all the ligands are considered as neutral, there are two classes of ligands. First, there are ligands bringing one or several electron pairs to the metals; they are even ligands and are designated as L or Ln, n being the number of electron pairs given to the metal. Then, there are ligands bringing one electron or an odd number of electrons to the metal, i.e. the radical type ligands; they are designated as X (one electron) or XLn (odd number of electrons). The L or Ln ligands do not accept valence electrons from the metal to make the metal-ligand bond, because

the bond involved is of the donor-acceptor type. On the other hand, the X or XLn ligands require one valence electron from the metal to form the metal-ligand bond. Thus, the M-X bond resembles the covalent bond in organic chemistry as each partner brings one electron to form the bond electron pair. The triplet carbenes or alkylidenes (CR2), oxo (oxene O) and nitrido 24 part i – structures of the transition-metal complexes (NR) are biradicals that form a double bond with the metal, and will therefore be considered as X2ligands, whereas the singlet carbenes give a pair of electrons to the metal, and they are thus considered as L ligands[12]

Ligands are of following types.

Types of ligands	Examples
1-electron radical type x ligand	H, F, Cl, Br-I
2-electron X_2 biradical type ligand	CH, $=CR_2$, =NR (Amido)
2-electron L ligands	H_2O, H_2S, R-OH, R-SH.
3- electron x_3 ligands (trivalent)	=CR, =N (Nitrido), = P (Phosphodo)
3- electron radical LX ligands	-CH=CH-CH_2. CHCHCH
4-electron L_2 ligands	-CH_3-O-CH_2-CH_2-O-CH_3 (DME)
4-electron LX2 ligands	M=N-R
5 electron L_2X radical ligand	C_5H_5, C_6H_7
5- electron LX_3 ligands	M=N
6-electron L_3 ligands	C_6H_5N (Pyridine)
6- electron L_2X_2 ligands-(divalent)	N_4 ligands porphyrins
7- electron L_3X radical ligands	C_7H_7
2- ligands	Lewis's acids., BH_3, $AlMe_3$

2. Selective Bond Formation

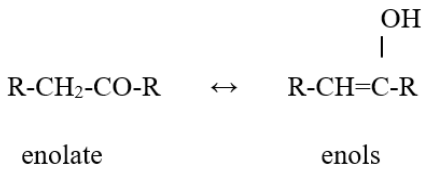
Selective bond formation involves

Carbon-carbon single bond: Formation of this bond is having very importance because it involves many useful procedure & additions of organometallic species of enolates to electrophiles as in Grignard reaction, aldol reaction, Michel reaction alkylation reaction & coupling reaction. Such as reaction have been finding useful application.[14]

Alkylation Reactions of enolate and enamines. The acidity of the C-H bonds in these compounds is due to combination of inductive effect of unsaturated group and resonance stabilization of anion formed by removal of proton. The sequence of more to less is as follows

NO_2>COR>SO_2R > CO_2R > CN > C6H5

Acidity is increase by electronegative substituents and decrease by alkyl group. Removal of proton from α carbon atom of carbonyl compound with base gives. enolate anions. These enolate anions involve in many carbonyls' reaction such as aldol condensation & bimolecular nucleophilic displacement reactions. Enolate anion are different from esters which are equilibrium with carbonyl compound



faster alkylation of enolates anion can achieved by DME (1, 2 dimethoxyethane DMSO (Dimethyl Sulfoxide), DMF (Dimethyl formamide) Presence of HMPA or triamine or tetra amine also enhance rate of alkylation's alkyl halide both primary, secondary, alkyl or benzyl halide create alkylation of enolate ions. It better to treat enolate ions with toluene p-sulfonate, mathone sulfonate and trifloro methane sulphonate rather than halides.15 Under Mitsunobu conditions, primary and secondary alcohol can be used to alkylate enolates attack of enolate ions on alkylating agents take by SN2 reactions mechanism & thus its inversion of alkylating configuration. A Common problem in direct alkylation of ketones is formation of di or poly alkylated product. Difficulty can be avoided by addition of DME to excess all alkylating agents The enolate therefore rapidly consumed before equilibrium take place. Formation of polysubstituted product often result in decreased in yield of desired monoalkyl compound. Poly alkylated product is that enolate of alkylated ketones are more reactive. Dimethyl zinc gives very good yield for mono alkylated [14]

Product have been obtained under these conditions. Alkylation of symmetrical ketones or ketones that can enalize in one direction only gives mono cyclic alkylated product with unsymmetrical ketones two different mono alkylated product may be formed by two structurally isomeric enolate anions.[16]

Several methods have been used to improve selectivity in the alkylation of unsymmetrical ketones and to reduce the amount of polyalkylation. One procedure is to introduce temporarily an activating group at one of the _-positions to stabilize the corresponding enolate anion; this group is removed after the alkylation. Common activating groups used for this purpose are ester groups. For example, 2-methylcyclohexanone can be prepared from cyclohexanone. The 2-ethoxycarbonyl derivative is obtained from the ketone by reaction with diethyl carbonate (or by reaction with diethyl oxalate followed by de carbonylation). Conversion to the enolate anion with a base such as sodium ethoxide takes place exclusively at the doubly activated position. Methylation with iodomethane and removal of the ketoester group with acid gives 2-

methylcyclohexanone, free from poly alkylated products.[17]

Conjugate addition reactions of enolates and enamines: add an alternate type of alkylation occurs on addition of these nucleophiles to electrophilic alkanes Such as α and β unsaturated ketones, ester or nitriles- Monoalkylated carbonyl compound high yield can be obtained. [18]

As conjugate addition reaction is an equilibrium process there must be force for formation of product otherwise starting material may be recovered. New anion formed in this reaction can be abstracted proton from original carbonyl compound therefore base only be present as catalyst. Alternatively, anion be trapped by addition of alkylating agents to generate two carbon-carbon bands in single operations.

Although presence of protic solvent aids these protons transfer steps, protic solvent is not necessity for addition reactions. A large variety of different accepters - can be used in addition reactions electron with withdrawing groups is commonly ester or ketones.19

Aldol reaction: Reaction of these carbon nucleophiles with aldehydes is generally known as aldol reaction These reactions for making carbon-carbon bond reaction products are β hydroxy carbonyl compounds which are common in many natural products [17]

Asymmetric methodology with enolates and enamines: Excellent levels of asymmetric induction in various carbon–carbon bond-forming reactions, such as alkylation, conjugate addition, and aldol reactions, are possible using a suitable chiral enolate and an achiral electrophile under appropriate reaction conditions. An interesting example of the alkylation of amino acids without loss of optical activity has been reported.[20]

Organolithium reagents: Organolithium reagents are used extensively in organic synthesis, either as a base or as a nucleophile They react with electrophiles and the extent of reaction via proton abstraction or nucleophilic attack depends on the structure of the organolithium species, the electrophile and the conditions employed.

Organolithium species are conventionally written as R Li; however, they are often aggregated structures with significant covalent carbon–lithium bond character. Coordinating solvents such as THF, Et2O or N, N, N_, N_-tetramethyl ethylenediamine (TMEDA) can reduce the degree of association of the organolithium species compared with non-polar solvents such as hexane and this can affect the reactivity of the organolithium species. Many simple alkyl lithium reagents are available commercially, often as a solution in a non-polar solvent. However, many reactions with organolithium species are done in ethereal solvents, normally at low temperature (−78 ◦C) to avoid problems with abstraction of a proton from the ethereal solvent by the basic alkyl lithium species.

Alkyl lithium species are good bases and a common use is the abstraction of a more-acidic proton. For example, addition of n-butyllithium to a solution of diisopropylamine in THF gives lithium diisopropylamide (LDA), a common base. Abstraction of a more-acidic proton attached to a carbon atom can also be affected with n-butyllithium, or with stronger bases such as sec-

butyllithium [EtCH(Me)Li], tert-butyllithium or the complex formed between n-butyllithium and potassium tertbutoxide

In addition to their basic properties, organolithium species can act as powerful nucleophiles in carbon–carbon bond-forming reactions. The synthetic utility of organolithium reagents can, however, be limited by the ease with which alkyllithium species act as a base. Despite this, alkyllithium species are well known to act as nucleophiles with a range of electrophiles, including aldehydes, ketones[18]

Organomagnesium reagents: commonly referred to as Grignard reagents. Typically, a Grignard reagent is formed by reaction of an alkyl halide (RX) in ethereal solvent with magnesium to give the species R-Mg-X. An alternative procedure involves the formation of an organolithium species and its conversion to the Grignard reagent with magnesium bromide. The ethereal solvent co-ordinates to the magnesium atom and the Grignard reagents are in equilibrium with the dialkylmagnesium species R2Mg and MgX2 (Schlenk equilibrium). Aryl and alkenyl halides can also form Grignard reagents, normally using the more effective coordinating solvent THF.[18]

1. Stereoselective Synthesis

An important goal in organic and medicinal chemistry is the continuous development of new synthetic techniques to create new chemical entities in a stereoselective way.21 Due to its ability to produce molecules with high enantiomeric purity and biological importance, stereoselective synthesis has been gaining popularity as a useful technique.[22] The designers of molecular structures are synthetic chemists. Although the early masters of organic synthesis focused mostly on the simple constitution of chemical bonds, it became clear that the three-dimensional structure—that is, the configuration of a molecule—presents an equally essential, and occasionally even more critical, difficulty. The well-known statement by Robert Ireland, "stereo-chemistry rears its ugly head,"[23]

For the creation of a novel stereo genic center with a determined absolute configuration, enantioselective (asymmetric) catalysis has proven to be the most elegant and effective method. By carefully selecting an enantioselective transformation, synthetic chemists can disregard a molecule's inherent Dia stereoselectivity in addition to making it easier to create chiral compounds with high enantiomeric excess (ee). Reagent control has saved many late-stage total synthesis attempts and has emerged as a helpful technique to address the problems so vividly outlined by Ireland. Enantioselective catalysis is a significant area of chemistry nowadays, particularly organic chemistry, and it is expanding at an astounding rate. The fact that two pioneers of enantioselective Organocatalysis, David MacMillan and Benjamin List, were awarded Nobel Prizes in 2021 for their significant contributions to enantioselective catalysis has served as a catalyst for the discipline. A selection of current enantioselective catalysis research projects has been compiled in this special issue of the Journal of Organic Chemistry, "Modern Enantioselective Catalysis in Organic Chemistry," to which authors from all over the world

have graciously contributed. This issue's administrative decision to concentrate on non-photochemistry approaches was made primarily to avoid conflict with a recent JOC issue that discussed advancements in photocatalysis.[24]

Enantioselective catalysis

As enantioselective catalysis has grown in popularity as a field of study and has been the focus of numerous conferences, symposia, and monologues, it can be difficult to provide many fresh or uncommon initial remarks. However, it's necessary to provide certain fundamental definitions. Enantioselective catalysis is the process of producing a specific enantiomer of a chiral product from achiral reactants in a catalytic, selective, and reproducible manner. Despite the fact that catalyst precursors can be a different matter, as discussed further below, enantioselective catalysts are always chiral and non-racemic. If a rigorously achiral or racemic chiral catalyst were to generate a non-racemic product, it would yield equal amounts of each enantiomer after a statistical number of repetitions. According to the previous definition of enantioselective catalysis, this does not satisfy the reproducibility requirement.[25]

General Principles and Concepts

- **Isomerism**

The phenomenon known as isomerism occurs when certain compounds with the same chemical formula have different shapes due to the varying arrangements of their atoms. Isomers are substances that have the same chemical formula but distinct structural characteristics. Moreover, isomers share the same molecular mass. The essential significance of molecule shape and structure in organic chemistry is demonstrated by the idea of isomer-ism. Since isomers might differ in their chemical, physical, structural, and biological characteristics, it is critical to be able to identify them. [26]

- **Constitutional (Structural) Isomers**

The molecular structure is described using two levels of comparison. Substances with the same atom count but different molecular connections are included in the first level, which does not include three dimensions. Constitutional (structural) isomers are isomers that have various functional groups and/or bonding patterns (e.g., branching) because of differences in the order in which atoms are joined to one another. A two-dimensional space may be used to represent the composition of molecules (number, kind, and connection of atoms). Chain isomerism, positional isomerism, functional isomerism, metamerism, and tautomerism are the five forms of constitutional (structural) isomerism.[27]

- **Strategies in synthesis**

- **Linear**

All stereochemistry in a lot of linear syntheses is set in relation to an initial stereocenter. Some of these synthesises produce racemic end products despite the targets having multiple stereos enters. Nowadays, enantioselective synthesis is used in the majority of natural products.[28]

Scheme 1

- **Convergent**

A convergent synthesis is one in which two intricate building elements are

combined later on. Enantiomerically pure and in the proper absolute configuration are prerequisites for each building block.[29]

Scheme 2

- **Iterative**

In an iterative synthesis, complex compounds are created using comparatively few reagents and conditions by repeatedly using comparable building blocks and reactions. Enantiomerically pure and correctly arranged building blocks are required. An additional significant example of this synthetic approach is peptide synthesis.[30]

Scheme 3

- **Late-stage functionalization and semi-synthesis**

Derivatives and semi-synthesis have long been prepared by the selective reactions of complicated molecules with chemical reagents. An important field of current study is the development of new reagents that affect the chemoselective and regioselective functionalization of complex compounds; these reagents or catalysts are frequently chiral.[31]

Scheme 4

- **Asymmetric vs. racemic synthesis**

A target molecule is created as a 50/50 mixture of enantiomers during a racemic synthesis. The right diastereomer (with the right relative configuration) is generated if the target has several chiral centers. Only one of the end product's two potential enantiomers is prepared during asymmetric synthesis. Several methods can be used to do this, such as: A target molecule is created as a 50/50 mixture of enantiomers during a racemic synthesis. The right diastereomer (with the right relative configuration) is generated if the target has several chiral centers

Only one of the end product's two potential enantiomers is prepared during asymmetric synthesis. Several methods can be used to do this, such as:

1. **Chiral pool (chiral beginning materials):** an enantioenriched starting material, like sugar or amino acid, is the source of at least one stereo enter.
2. **Resolution:** a combination of enantiomers is separated using catalytic (typically enzymatic), chemical, or chromatographic methods. At any point during the synthesis, this can be done.
3. **Chiral auxiliaries:** new stereo enters are introduced in a specified relative configuration (substrate control) using an enantiopure appendage. Later, this appendage is taken out and frequently recycled.
4. **Enantioselective synthesis:** a chiral reagent that does not itself end up in the result is controlled to add new stereo enters. Catalytic, enantioselective synthesis is the term used when sub stoichiometric amounts of the chiral reagent are utilized.[31]

Importance of asymmetric catalysis

1. **All enantioenriched molecules derived from natural sources**

Only enantioselective reactions employing chiral, enantiomerically enriched reagents or catalysts, or other chiral starting materials, can produce an enantiomerically enriched chiral product. Since all genetically encoded amino

acids are L-configured (typically (S)), the natural world is enantiomerically enriched. Additionally, most Natural sugars D-formatted. There were extremely limited techniques for creating chiral chemicals prior to the development of asymmetric catalysis. Advances in biocatalysis and asymmetric catalysis have significantly increased the chiral pool.32 The following are a few easily accessible, naturally occurring chiral compounds:

In the pharmaceutical sector, enzymes are frequently employed as good enantioselective catalysts. The fact that enzymes are only available in one enantiomer and that only one enantiomer of the final product can be generated is a constraint.[33]

There are many theories on the genesis of enantiomerically pure amino acids, making it an active subject of study. The arrangement of the molecules in nature appears to have no discernible cause other than chance. [34]

2. All new pharmaceuticals must be single enantiomer

All novel chemical entities (drugs) must be approved as single enantiomers, according to a 1992 directive from the US Federal Drug Administration (FDA). In the past, enantiomer combinations were marketed despite the fact that the two enantiomers frequently exhibited entirely different biological activity.[34]

Catalysis

A catalyst speeds up a chemical reaction. It accomplishes this by bonding with the molecules undergoing the reaction and letting them react to produce a product that separates from the catalyst and remains unchanged, making it ready for the subsequent reaction. In actuality, the catalytic reaction can be defined as a cyclic event in which the catalyst takes part and, at the conclusion of the cycle, is recovered in its initial form.[35]

Photoredox catalysis

One of the areas of organic synthesis that is expanding the fastest is visible light-mediated Photoredox catalysis. A photoactive catalyst usually engages in single electron transfer reactions with organic substrates and absorbs visible light. This is a gentle, cost-effective, and eco-friendly method to encourage organic transformations based on radicals and maybe open up novel reaction pathways.

The most extensively researched photoredox catalysts are ruthenium and iridium complexes. Tris(2,2'-bipyridine) ruthenium (II) and tris [2-phenylpyridinato-C 2 N] iridium (III) are typical instances. The ligand-centered π^* orbital in these complexes has a lower energy than the metal-centered eg orbital, which makes them special.[36]

Examples

Below are a few significant early instances that helped pave the path for the current development in this sector. Ru(bpy)3Cl2 as the catalyst and BNAH as a stoichiometric reducing agent were used to reduce electron-poor alkenes in one of the first instances of visible light Photoredox catalysis.[37]

Scheme 5

Using Ru(bpy)3Cl2 as a photocatalyst, Fukuzumi and colleagues presented an early example of reductive dehalogenation of α-bromocarbonyl compounds.[38]

Scheme 6

Photoredox reactions catalyzed by ruthenium or iridium complexes

Photoredox-catalyzed reactions can be classified according to whether the substrates undergo a net oxidative, reductive or redox neutral transformation. For net oxidative or net reductive reactions, a stoichiometric oxidant or reducing agent is required, whilst in redox neutral processes substrates will undergo both single electron reduction and oxidation as part of the reaction mechanism.

Net oxidative reactions

Formation of iminium ions via Photoredox catalysis

Tertiary amine substrates can undergo two-electron oxidation to produce iminium ions. Because they are good electron donors, tertiary amines can easily undergo single-electron oxidation to produce aminium radical cations. A reducing agent can absorb a hydrogen atom to create an iminium ion because the α-protons of an aminium radical cation have a low C-H bond dissociation energy. A second single electron oxidation can produce the iminium ion after the aminium radical cation undergoes αdeprotonation to create an α-amino radical.[39]

Scheme 7

New carbon-carbon bonds can be formed when nucleophiles react with imidium ions produced by photoredox catalysis. The aza-Henry reaction, which is catalyzed by photoredox and involves an iminium ion intermediate, is an early example. The final oxidant in this net oxidative reaction is oxygen.[40,41]

Scheme 8

Oxidative cyclizations

Benzothiazoles and indoles have also been synthesized using photocatalysis using oxidative cyclization, where oxygen serves as a final oxidant.[42]

Scheme 9

Net Reductive reactions

When a stoichiometric reducing agent is present, Photoredox catalysis is used to reduce the substrate in net reductive reactions.

Alkene reduction

Electron-poor alkenes have been reduced using Photoredox catalysis, using 1-benzyl-1,4-dihydronicotinamide (BNAH) as the stoichiometric reductant. The excited ruthenium catalyst and the resulting Ru(I) complex are reduced by BNAH, which subsequently reduces the electron-deficient alkene.[37]

Scheme 10

Ring opening/allylation

The stoichiometric Hantzsch ester and an iridium photocatalyst have been utilized to simultaneously allylate and open keto epoxides.[43]

Scheme 11

Reductive dehalogenation

Photoredox catalysis can be used to achieve reductive dehalogenation in mild conditions. DIPEA serves as the terminal reducing agent in a reductive quenching cycle that drives the reaction. The DIPEA is the main source of hydrogen for the radical intermediate, according to labeling studies.[44]

Scheme 12

Reductive dehalogenation produces radical intermediates that can be utilized

to create C-C bonds. One instance is the use of activated halides to functionalize furans, pyrroles, and indoles.[41]

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MODERN APPROACHES TO CHEMICAL SCIENCE: CONCEPTS AND TECHNIQUES

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Polymeric nanoparticles – Based topical delivery system for the treatment of dermatological diseases

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Abstract

Skin problems are among the primary reasons for dying, and can have a big impact on people's health. Traditional treatments often fail because of long treatment times, rush of the conditions, and systemic side effects, especially because of ineffective medicine delivery. Nanomedicine offers a new way to deliver medicine to targeted areas using bitsy carriers like polymeric and lipidic nanocarriers, nano-mixes, and advanced technologies like carbon nanotubes. This discussion focuses on the failures of conventional treatments for skin condition, like psoriasis, vitiligo, & skin cancer.

Recent studies show that topical treatments using nanoparticles effectively treat different skin diseases. These styles combine the advantages of direct skin operation with the effectiveness of small medicine carriers to show promise for better skin condition operation. The composition explains how medicines are delivered through the skin and how they work. When the skin's hedge is damaged or inflamed, like in skin cancer, nanoparticles still have trouble getting through the towel. Nanoparticle-based topical delivery systems can help with skin problems by combining the benefits of nanosized medicine carriers with direct ways of working.

Keyword: Nanoparticle, Nanocarriers, dermatological disease, transdermal, topical delivery, skin cancer, routes of penetration, skin disease

Introduction

Polymeric nanoparticles are at the leading edge of many innovative drug delivery concepts because of their exceptional control over physiochemical characteristics like dimension, form, structure, charge, and surfaces activity. By overcoming a range of biological obstacles, polymeric nano-particles can also precisely target particular bodily regions [1]. Polymeric nanoparticles are especially notable for improving bioavailability of drugs as well as targeted shipment at the location of activity. The one that corneal layer of the epidermis is principally in charge of the skin's barrier function Moreover, to regulating the flow of substances into the epidermis. The layer of skin barrier refers to the topical delivery technique. It is employed to deliver medications or active ingredients through the epidermal barrier. Over the past ten years, nanoscale drug carriers have garnered a lot of interest. It is employed to deliver medications or active ingredients through the epidermal barrier. In the last ten years, nano sized carriers of drugs have garnered a lot of interest as potential topical pharmacology solutions. Among the most researched systems are nanoparticles and nanospheres. micelles, liposomes and micellar-like nano-particles, and nano emulsions of solid lipids We talk about nanoparticles composed of non-biodegradable polymers (like polyacrylates) and biodegradable polymers (like chitosan) Moreover, synthesized substances that degrade (such as poly lactide-co -glycoside) and poly-caprolactone). [2] Since the medications target the stratum of the skin, topically applied therapies hold promise for the treatment of skin conditions like psoriasis, contact dermatitis, and skin malignancies. The theme of this research is medication delivery systems based on topically administered polymeric nanoparticles. In addition to acting as a permeation barrier, the stratum corneum layer of human skin offers a unique pathway for the delivery of medications and other active components. These substances can be delivered via inter-cellular intra-cellular and Appendageal transverse routes either topically (into the layers of skin) or over dermally (enters the bloodstream and the subcutaneous tissues). To improve Skin penetration both passive and reactive permeation augmentation Many strategies have been employed to boost accessibility. The pathophysiology, etiology, and superficial therapeutic methods used in dermatology disorders, including skin malignancies, are then discussed. Both contact dermatitis's and psoriasis's

Skin Barrier

The greatest organ in both the human body and its own body is the skin. In addition to acting as a barrier against penetration, the layer of strata corneum of human skin provides a unique pathway for the distribution of medications and other active components. The skin on the soles of feet and palms of shoes, and the top portion of the back is the thickest (over 5.0 mm), whereas skin on the eyelids is the thinnest (less than 0.1) [3]. The techniques to spread the medicinal nano-

particles, especially to sick hair and skin's follicles opening, even if skin serves as a tangible obstacle to stop penetration of particles. Lipid carriers—solid lipid nano-particles and nano-emulsions with a diameter of 300 nm—are the foundation of the majority drug's delivery particle technologies now considered microparticle. [4]

Stratum corneum

The outermost layer corneum is protective layer of epidermis, is made from the dead, dried-out cell known as corneocytes (brick-&-mortar configuration).

Controlling the diffusion of molecules over the skin is among the epidermis primary transdermal barrier activities.

Chemicals from the outside environment and water loss (TEWL) from the interior to the exterior One of 2 pathways—intracellular through an epidermal lipid matrix or transcellular through corneocytes—can be utilized for the diffusion via the epidermal layer. A number of factors influence the rate of dispersion over the stratum corneum, including:

- The lipid matrix's unique lamellar structure and how it interacts in vivo with keratinocyte protein components such as scaffolding proteins and tight connections
- The quantity, size, cohesion, and thickness of the stratum corneum layers of corneocytes determine the diffusion path's length.

Subcutis

The majority of the subcutis is made up of adipocytes, or fat cells. Adipose tissue (the fat tissue) plays a vital role in thermoregulation because it produces heat and creates an insulating layer. Additionally, the subcutis serves as a mechanical barrier, shielding deeper components like bone from mechanical shocks like hysteria. [5]

Skin appendages (or adnexa of skin)

Skin appendages are anatomical pores and skin-associated systems that serve a particular characteristic consisting of sensation, contractility, lubrication and heat loss in animals. In human beings, a number of the more not unusual pores and skin appendages are hairs (sensation, warmness loss, clear out for breathing, protection), arrector pilli (clean muscles that pull hairs straight), sebaceous glands (secrete sebum onto hair follicle, which oils the hair), glands for sweating (which could launch sweat that smells strongly (apocrine), or faintly (merocrine or cutaneous), and nails (which give safety).

Appendages of skin are typically found next to the skin and are produced from it. [6]

Drug Penetration Pathways via Skin

Numerous investigations have been carried out to ascertain how topical substances enter the skin. Drugs must essentially diffuse through the preserved epidermis in order for them to be permeabilized to the skin. In addition, sweat glands and hair follicles, which comprise roughly 0.1% of the skin's overall area, create thrust paths through the intact epidermis (Illel, 1997). The stratum corneum frequently controls how well a medication penetrates the skin. It is proposed that medications can pass through this entire barrier via two distinct pathways: transcellular and intercellular. [7]

Transcellular Route

- Through cells of the stratum corneum and epidermis
- Challenging due to hydrophobic barriers

Intercellular Route

- Between the cells through lipid-rich domains.
- Favoured by lipophilic drugs but hindered by the tortuous path

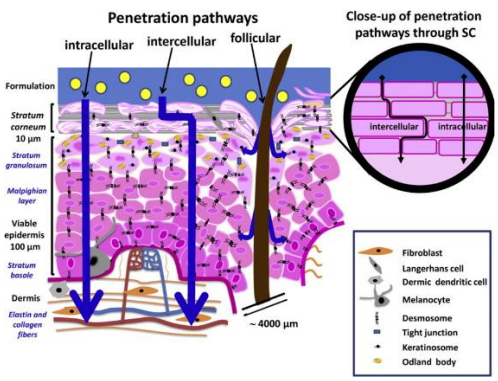
Trans appendageal (Shunt) Route

- Through hair follicles, sweat, and sebaceous glands
- Useful for certain drugs, especially macromolecules

Subcutaneous Route

- Direct delivery into subcutaneous tissue via injections
- Bypasses skin barriers, not typically used in TDDS

Graphical abstract



Different Dermatological Disease

Pathological changes in the skin can be inflammatory, neoplastic, traumatic, hormonal, degenerative, or even genetic [9]. Numerous dermatological issues are brought on by infectious skin diseases that are bacterial, fungal, or viral. This infiltration of inflammatory T cells leads to Psoriasis's, topic dermatitis, and contact dermatitis caused by allergies are examples of long-term inflammatory skin conditions. [10] Drugs can be topically administered to the skin using transdermal delivery technology. In contrast to intravenous and oral administration, it has a more ideal effect when treating common dermatoses (like vitiligo, psoriasis, skin cancers, etc.) [11]. To treat a variety of illnesses, Transdermal medication administration can also introduce drugs into the blood circulation [12]. It can prevent gastrointestinal adverse effects and first-pass metabolism, providing the benefits of ease of use, simplicity, and substantial patient satisfaction in contrast to traditional methods including subcutaneous, intravenous, and oral injection [13]. Because of developments in molecular science and the development of novel delivery technologies, transdermal administration technique has demonstrated an excellent deal of promise & benefits of the therapy of dermatitis. Psoriasis can range in intensity from small, isolated patches to full body coverage.

Psoriasis

Psoriasis affects the life of many individuals and is prevalent everywhere in the world [14]. The primary characteristics of psoriasis are thickened skin, alteration in the layers of the skin, dilated blood vessels, and tiny bleeding points. It is an ongoing skin condition disorder arised by an overactive immunological system [15,16]. These signs make the life of patients more difficult, producing pain, discomfort, and psychological problems. Injured skin lesions are a primary indication of psoriasis, which is a chronic, non-contagious dermatosis [17, 18]. Erythro-dermic, guttate-related, inverted,

pustular, and plaques are the 5 major type of psoriasi's [19].

Pathophysiology

The skin's epidermal layer develops abnormally greatly & quickly in psoriatic.[20] The pathogenic process of psoriasis leads to both excessive skin cells and abnormal skin cell formation, particularly in wound healing. [21]

Diagnosis

The look of the skin is most typically used in order to make a diagnosis of psoriasis. Psoriasis is erythematous, scaly deposits, papules, or regions of skin that tend to make one feel itchy and painful. [22] Most of the time, no specific blood examination or test are required to make the diagnosis. [21] [23].

Causes

1. Genetic
2. Lifestyle
3. HIV
4. Microbe
5. Medication

Transdermal drug delivery technology can offer very safe and effective treatment of psoriasis, which is usually a relapsing and remitting disease requiring frequent treatment. MTX can partially relieve psoriasis, but its effect is slow, can cause liver damage, and frequently results in symptom recurrence after its withdrawal, restricting its application. In addition, transdermal drug delivery tech. based on nano-medicines able to go beyond the issues of the conventional topical drug-delivery systems, like low dermal permeability and infectious therapy, because psoriasis is often a relapsing and remitting disease requiring frequent treatment. A peptid -coated Cur-loaded liposome's (CRC-TD-Lip) was designed to enhance cure of psoriasis & accelerate the absorption of Cur. Furthermore, transdermal drug delivery techniques can be applied for more universal treatment of psoriasis. To increase the therapeutic activity & enable the drug to penetrate the thick skin of psoriasis patients, Shen-et-al. designed HA --modified liposomes with the M T X & blended with microneedle's (HA-MTX-Lipo-MNs). [24].

Melanomas

The melanoma is among the most fast-developing cancerous tumours', is defined by slow survival rate, higher metastasis's, high recurrence, & malignant growth. It is induced by the fast growth of melanocytes, the pigmented cells of the skin [25]. Melanoma in damaged by the sunlight is also categorized as either low or excessive CSD lie on the histology of accumulative sun damaging (CSD) of the peritumoral skin. Low-CSD melanomas are superficially diffused melanomas, while high-CSD melanomas are malignant freckle-like nevus and proliferative melanomas that induce connective tissue. In [26]

Pathophysiology

As the melanocytes grow uncontrollably, the first stage of the melanoma is formed. between the epidermis, the outermost layer of pores and skin, and the dermis, the second layer of pores and skin, are melanocytes. whilst the tumor is much less than 1 mm thick and extends to the base of the epidermis, it's miles within the radial growth segment.[27] it's miles extremely not going this early cancer will spread to the

rest of the frame due to the fact the cancer cells haven't yet gained access to the blood vessels deeper within the skin. cancer surgical procedure can commonly cast off the cancer totally if the melanoma is located at this stage. [Reference needed]

The behavior of the tumor cells drastically changes as cancer cell starts to flow in a different different direction, entering the papillary dermis & the epidermal layer vertically upward. [28]

Cause

1. Gene mutation
2. Metastasis

The most frequent cause of melanomas is DNA damage by UV radiation from the sun. Additionally, there is a genetic component. [29] [30] Melanoma also develops in region of the skin that receive minimal exposure to the sun, like mouth, palms of the hands, soles of your feet, & genitalia. [31] Melanoma is more common in patients with a dysplastic nevus syndrome or familial a typical multi mole-melanoma.

One unique therapeutic method is the use of nanocarriers. Though ICG has been used in therapeutic applications, its use is restricted due to the instability of aqueous solutions. In a 12-hour skin penetration experiment, Lee et al.'s chitosan-coated ICG liposomes showed a two-fold total recovery of ICG (in contrast to free ICG). The very last formula confirmed a wonderful growth in ICG's mobile absorption and photocytotoxicity in B16/F10 cancer cells. moreover, it substantially multiplied ICG's pores and skin permeability, that's nice for topical melanoma PDT. [32]. via developing peptide TD-changed vemurafenib-loaded liposomes (Vem-TD-Lip), it changed into established that in male mice, transdermal management of Vem-TD-Lip successfully centered and inhibited subcutaneous cancer. additionally, it turned into shown that dermal administration of Vem-TD-Lip became more powerful than oral and intraventricular administration in minimizing most important organ harm (discern 7A) [33]. This observe presented a unique technique for using vemurafenib to target and suppress subcutaneous melanoma.

Vitiligo

A condition called vitiligo causes some skin to appear lighter. The lighter regions enlarge over time. The illness can impact any area of the skin on the body. Additionally, it may appear on the inside of the hair and lip. Normally, melanin controls the color of skin and hair. When the cell's that make Vitiligo develops when melanin dies or stops functioning. Although vitiligo can affect people of any color, people with dark or black skin may notice it more than others. The illness is not lethal and cannot be spread. You might feel anxious or self-conscious about it. Vitiligo-affected skin can have its color restored with treatment. It does not, however, prevent the patches from returning or from losing more skin color.

Causes

Melanocytes, the pigment cells that generate melanin, the pigment found in eyes, hair, and skin, can be damaged or stop producing it, which results in vitiligo. Affected skin patches lighten or turn white. Why these pigment cells die or stop functioning is unknown to us. It might be because of:

1. An autoimmune ailment, which is an immune system disease
2. Genealogical history
3. An incident that sets things off, such tension, a bad sunburn, or skin injuries like coming into contact with chemicals [34]

Pathophysiology

Studies strongly suggest that vitiligo is caused by alterations in the immune system However, the fact that several Theories have been put out as possible catalysts.[35][36] It has been suggested that vitiligo is a complex illness in which environmental variables and genetic susceptibility both contribute.[35] Skin cells may start the cytokine-releasing unfolded protein response and mounts an immune activity , since it is thought that harmful environmental chemicals can interfere with redox reactions required for protein folding. [37][38]

The development and advancement of nanotechnology provides ideas and hints for creating novel vitiligo treatment approaches. However, not much research has been done to examine the potential by using of nano-technology in the treatment of the vitiligo. With a focus on liposomes, noisomes, nanohydrogel, and nanoparticles, we present and evaluate recent research on nano delivery methods for the treatments of vitiligo. By improving penetration or increasing medication loading efficiency, this research made important strides. Based on these investigations, three concepts have been suggested for vitiligo therapy with topical nano-drug delivery systems: facilitating melanin regeneration, improving drug retention, and promoting transdermal penetration.[39]

Skin Cancer

The most frequent cause of irregular skin cell growth is being in the sun. However, areas of the skin that aren't typically exposed to the sun can potentially acquire this prevalent type of cancer.

The three most common forms of skin cancer are as follows. Melanoma, basal cell carcinoma, and cutaneous squamous cell carcinoma. Malignancies that start in the skin are known as skin cancers. The formation of abnormal cells that are invasive and capable of spreading to other areas of the body is the cause of these cancers. [40] It happens when skin cell proliferation increases and malignant growths are present. Prolonged exposure to ultraviolet (UV) rays from tanning beds and sunshine is the most common cause of skin cancer. The most common cancer in humans to be diagnosed is skin cancer. [41] [42, 43].

Diagnosis

Doctors utilize histopathological examination and biopsy to diagnose.[44] Several non-intrusive techniques exist for detecting skin’s cancer, including photographic methods, terahertz imaging, optical coherence tomography, dermatoscopy, ultrasound, confocal imaging, Raman spectroscopy, fluorescence, tape peeling, electrical bio-impedance, thermography, and imaging with multiple wavelengths, computerized analysis, and terahertz spectroscopy.[45] Aside from inspecting the skin, dermatoscopy is able to diagnose basal cell carcinoma.[46] The use of optical coherence tomography (OCT) to diagnose squamous cell carcinoma or melanoma is unclear. OCT may prove to be beneficial when identifying carcinoma of basal cells

However, additional evidence is necessary to establish.[47]

Pathophysiology

The most changeable risk factor Sun exposure is connected to the emergence of NMSC and melanoma. UV exposure comes in three different forms: UV-A, UV-B, & UV-C. UV-A (about 90%) and UV-B (about 10%) make up the majority of sunlight [48]. The majority of UV-C radiation is absorbed by the atmosphere. When UV-A, which has an extended wavelength (320–400 nano-meter), reaches the dermis, free radicals are created. UV-B ray, whose wavelength is shorter (290–320 nm), creates thymine dimers and can penetrate the stratum basale of the epidermis. Both UV-A & UV-B are responsible for cancer formation. UV - A, however, is considered more important. UV-rays induce cells damage, apoptosis, & impairment of the DNA repairing mechanism's, result DNA mutations.

Causes

1. Age

The likelihood of getting cancer increases with age. This may be because damage to the cells has been building up during your lifetime. Also, resistance and defences in the body to abnormal cells may weaken as you get older.

2. Chemical carcinogen

A carcinogen is something that could damage a cell (chemical-based, radiation, etc.) and increase the likelihood of it becoming malignant. The more exposed you are on average, the higher the risk. Examples include:

Tobacco

People who smoke have a higher chance of developing bladder, pancreas, oesophagus, mouth, throat, and lung cancers.

substances found in the workplace, such as formaldehyde, benzene, and asbestos.

3. Lifestyle factor

4. Infection

There are some germs (viruses and bacteria) that cause specific cancers. For example, individuals who possess recurring hepatitis-B virus infections or with the Hepatitis C pathogen have raised danger of liver cancer. Another is the association of the human papillomavirus (HPV) with cancer of the cervix.

5. Immune system

People who have a weakened immune system are more likely to get some cancers. For example, individuals with AIDS, or individuals who are having immunosuppressive treatment.

6. Genetic makeup [49]

Topical treatment for skin cancer

It is possible to treat skin cancer with multifunctional nanoparticles or combining them with cutting-edge technology like CRISPR and immunotherapy in combination with This paper may be useful to researchers, physicians and politicians interested in treating skin cancer by nanoparticles. The 5th most prevalent worldwide cancer, skin cancer has negative impact on both economic as well global health. Skin cancer statistics have been made worse by industrialization genetic manipulation and drastically increasing environmental changes. The effectiveness of current treatment methods for skin cancer has decreased and patient compliance has decreased as

a result of problems with cost, toxicity and bioavailability. These problems include radiation for surgery, chemotherapy immunotherapy, targeted treatment, and traditional chemotherapy. Because nanotechnology can work with materials These have generated great interest in a variety of biomedical applications because of their size range of 1 to 1000 nm, including cancer therapy [50][51].

The materials at nanoscale have special physicochemical characteristics that can increase the effectiveness of cancer treatments significantly. Numerous nanomaterials have been extensively used to treat skin cancer, including nanofibers [52], nanosuspension [53], nano-emulsions [54], and nanoclay [55].

Nanomaterial based topical treatment for skin cancer

Nanomaterials serve both as therapeutic agents and drug transporters; thus, they can tremendously impact cancer treatment outcomes [56]. Considerable amounts of various nanomaterials are utilized to treat skin cancer, although nanoparticles (NPs) are especially known for their improved skin permeabiliity [60], evasion of the reticuloendothelial system (RES) [59], and passive tumor cell targeting through the increased permeablity and retention {EPR} effect [57,58]. Polymer & lipid-based NPs are the two further classifications of NPs in addition to Inorganic NPs, which are used for their special qualities that include passive evasion of skin and organ boundaries [62,63]. The Specialized NPs used to serve as therapeutic molecules and drug transporters are the inorganic NPs [61]. However, it is noted that polymer and lipid-based NPs are more efficient in permeable skin organ and tumor targeted delivery of an extensive range of solubilized therapeutics in rigid controlled manner [62,63].

- **Inorganic nanoparticles for skin cancer therapy's**

Nanoparticles fall within one of 2 categories: organic & inorganic. Inorganic NP species include metal as well as metal oxides. Nanoparticles of titanium oxide, iron oxide (Fe3O4), and silver and silver (Ag) oxide of titanium Metal oxide nanoparticles include zinc oxide & copper oxide (CuO).

Because of its improved therapeutic efficacy, decreased risk of drug tolerance and minimal adverse effects, the combination of nanotechnology with cancer therapy has garnered a lot more attention. Encapsulating anticancer treatments using Nano carriers that are inorganic have improved the medicinal worth of the medications resulting in greater antitumor action, when compared to traditional cancer therapy. These NPs are found in metal oxides, carbon dioxide ceramics silica and other materials. [64] Metal oxides are the sources of these

The most promising options for treating skin cancer are inorganic nanoparticles (NPs) because to their distinct physicochemical properties, which include their small size, large surfacearea, bio-activity, biocompatibility, & functional ability. Inorganic nanoparticles have been found by researchers to possess an innate therapeutic capability that enables them to eliminate cancer cells autonomously, hence obstructing treatment [65,66].

They can also use active or passive targeting to deliver a variety of therapeutic medicines to tumor locations.

However, they can also function as photosensors or photothermal, which are then used in photo-dynamic therapy (PDT) or photothermal therapy's (PTT), respectively [67].

1. Silica nanoparticles that are mesoporous

According to the International Union of Pure & Applied Chemistry (IUPAC), mesoporous silica nanoparticles (MSNs) are a specific version of NP characterized by an ordered arrangement of uniformly- sized mesopores in periodic order of silica with pore sizes between 2 and 7 nm and an average diameter between 50 and 300 nm [68,69]. MSN formation occurs via supramolecular assemblies of surfactants wherein micelles are formed when above a certain critical micelle concentration {CMC}. The next step involves condensation of silica precursors onto the surface of the micelle forming a hybrid organic-inorganic system. Removal of the template surfactant can occur through solvent extraction or calcination to create mesopores for the produced material. The unique features resulting from such MSNs in their production give them very wide applications in biomedicine. Some of the properties include dual-function surfaces: an inner porousable surfaces and an outer surface, very huge specific surface region, a tunable particle size, pore volume, an aligned porous structure and excellent biocompatibility, and biodegradability. MSNs exhibit very high loading capacity of drugs with its specific permeability to skin as a very huge advantage as applied oncology measures.

2. Cerium oxide nanoparticles

Cerium oxide NPs (CeO2 NPs) that are a special type of metal oxide which along with redox control and enzyme activity has been shown to be beneficial in many areas of biomedicine including cancer treatment. They have been employed in a number of biomedical applications, including the therapy of cancer and have shown to be quite promising. Reacting with the ROS levels is one of the main ways CeO2 NPs, with the help of their enzyme mimic activity, which includes the process involves the involvement of oxidative dismutase's (SOD), catalase, which (CAT), photosynthetic enzyme, oxidase, peroxide, and deoxyribonuclease I (DNase I). While cerium, which occurs in two distinct oxidation forms, Ce3+ (reduced) and Ce4+ (oxidized), functions as an antioxidant in healthy cells, it is oxidant found in cancerous cells and mostly generates R0S in acidic pH environments. The primary causes of their excellent performance are their oxygen vacancies on the surface of the mineral cerium oxide and their Ce3+/Ce4+ self-regeneration cycle [70]. To explain the role of these nanoparticles in cancer, many experiments have been carried out. The caspase-9 activation was detected when the caspase-3 was initially cleaved to its active form. CeO2 NPs, for example, were responsible for the formation of ROS in the tumor cells due to their increased activity on the mitochondrial-contained DNA which then broke and triggered cell death through the mitochondrion-mediated pathway involving the activator of this process [71].

3. Zinc oxide nanoparticles

The metal zinc is one that belongs to OR is the first among the list of the many transition metals which might be the most in number but is entirely the most abandoned metal in our body next to the iron that relatively is only a very small element. It is an important and crucial substance in the body to give help in the performance of various cell functions and to keep cellular homeostasis.[72] Nanoparticles of zinc oxide (ZnO) are widely recognized as a hopeful material for bio-medical applications as they have a natural source and are, overall, less toxic than other NPs. Due to both large ratio of surface area to volume & the small size of individual particles, the ZnO nano-particles are inherently cytotoxic to cancer cells. In the existing literature, it is widely accepted that ZnO NPs provoke cell death primarily by promoting ROS generation. This, based on ZnO nanoparticles' ability to act as semiconductors, is in turn a major contributor to the generation of ROS which induces cancer cell death through apoptosis. It discovered that ZnO NPs have the capacity of both PTT and PDT. [73-75] They have also been linked to a number of conjugated drugs that produce cancer death and can further be made with different polymers & peptides to result in actively tumor targeting and better skin permeation (cutaneous skin tumor-targeting).

4. Silver nanoparticles

Because of its physicochemical characteristics, including their Surface plasmonic resonance, stability of chemicals, high electrical conductivity, and tiny particle size (used in the PTT), silver nanoparticles (AgNPs) have garnered increased attention as a possible anticancer drug [76]. The silver ion's existence has been identified as the cause of AgNPs' biological action. AgNPs that are smaller than 100 nm have a tendency to penetrate tumors at their highest concentration by taking advantage of their leaky vasculature. By using the glucose-provided energy in the medium and causing oxidative stress within the cancer cells, AgNPs have shown remarkable antitumoral efficacy. According to research, Autophagy, apoptosis, and anti-angiogenesis (angiogenesis triggered by VEGF exclusively) are the most frequent mechanisms by which AgNPs have anticancer efficacy [77,78]. AgNPs also have a lesser skin penetrating ability because A significant proportion of free ions precipitate as sulfide of silver in the stratum corneum, the outermost layer of skin, making it more effective than other metallic nanoparticles, such gold [79]. AgNPs' use in the therapy of cancer of the skin is backed by research that shows that coating or functionalizing them with different polymers and peptides improves their skin permeability.

5. Carbon nanotubes

The cylindrical nanostructured carriers known as CNTs, or carbon nanotubes, are created by rolling graphene sheets [80]. The distinct mechanical, electrical, thermal, and structural characteristics (PTT) of the CNTs make them suitable candidates for cancer therapy. By employing the substantial surface area of carbon nanotubes (CNTs), which enables them to carry significant amounts of anti-cancer drugs, by either sorption or disulfides as linkers. Additionally, CNTs can be modified with stimuli-responsive materials to accomplish regulated drug delivery [81,82]. the potential of CNTs' skin permeability to administer

medicinal substances transdermally. However, it has been discovered that CNTs cannot penetrate the skin on their own. The enhanced However, there hasn't been much research done on the permeability of CNTs' skin under iontophoresis and lipid/polymer functionalization [83]. Biomedical researchers are encouraged to investigate their potential in treating skin cancer by all of these evidences.

6. Gold nanoparticals

Throughout times, medical professionals had used gold in the colloidal form for a wide range of purposes. Scientific studies of gold nanoparticles (AuNPs) were first published by Faraday in 1857. Since then, a great many numerous types of biomedical applications of gold nanoparticles have been observed. Of course, the prospects of efficient and cost-effective cancer therapy are one of the most important ones today [84, 85]. Besides, their easy, affordable, and trustworthy synthesis methods make them an attractive research area as well. According to study data, gold particle smaller than 100 nm are the most effective ones in selectively focusing and absorbing into the tumors [86]. In both classical and transgenic systems, the tumor growth-limiting factor, angiogenesis, was also found to be inhibited by AuNPs. This study implied that the AuNPs attached to the heparin-binding growth factors, which are the most important ones in angiogenesis, like bFGF, or basic fibroblast growth factor & blood vessel permeability factors and VEGF (vascular endothelial growth factor)-165, thus preventing their action, are the first and the most known ones when it comes to the inhibition of angiogenesis. This process decreases the phosphorylation rate; therefore, it restrains the growth of endothelial/fibroblast cells [87,88].

- **Polymer-based nanoparticles for skin cancer therapy**

Specialized drug carriers known as polymer-based nanoparticles (NPs) are made from natural / synthetic polymers and are between 10 and 1000 nm in size.To manage the dimensions and characteristics of the NP, reduce drug loss as well as early NP degradation, and create materials that are simple to manufacture and store, a variety of polymers have been utilized in NP creation. The polymeric outer shell can prolong blood flow or target area persistence by protecting the NPs from proteins intake, notably opsonin clearance [89]. Polymers employed in biomedical applications are biodegradable even though they are solid; most common polymers hydrolyze, or cleave, enzymatically, in biological fluids. Larger polymers' molecular weight gradually decreases as a result, enabling the therapeutic to be released from the system under regulated conditions and ultimately leading to the polymer's total elimination [90]. PEG, polycyanoacrylate, and polyglycerols are the most widely utilized surface polymers [91].

The two main categories of polymer-based NPs are nanospheres (solid matrix system) and nanocapsules (cavities enclosed by a polymeric shell or branch). Furthermore, according to their shape and polymer characteristics, they are further divided into other categories, such as micelle’s, dendrimer, polymer-somes, polyplexe’s, etc. [92]. The anticancer agents (genes, monoclonal antibodies, hydrophilic and lipophilic

medications, etc.) can be conjugated, adsorbed, entrapped, or encapsulated by these NPs for regulated release, active/passive tumor focusing, physiological defence, and enhanced tumor uptake, all of which could significantly enhance cancer treatment [93,94].

Many researchers then expressed great curiosity about creating anti-cancer medicines feeded with polymer-based NPs to treat skin cancer situations because of their straightforward manufacturing method, biocompatibility, biodegradability, and lower cost.

1. Polymeric micelles

Polymer micelles (PMs) are evolved colloidal debris with a diameter range of five to 500 nm, usually manufactured from amphiphilic di- or tri-block copolymers. The additives of PMs encompass triblock copolymers, such as polyethylene oxide, graft copolymers, together with G-chitosan and stearic acid, and di-block co-polymers, such as polyethylene glycol, additionally known as PEG, and polystyrene, which swiftly self-bring together in aqueous media at critical micellar concentration (CMC) to shape a hydrophilic shell and a hydrophobic core [95,96]. because the water-loving shell offers PMs a stealth characteristic, the hydrophobic core of PMs significantly aids in encasing a selection of lipophilic anticancer medicines. because the stealth property prevents the PMs from coming into RES, they remain available on the tumor site for an extended time period in the systemic flow. In contrast to different medication carriers, their tiny particle length facilitates superior tumor uptake thru the leaky vasculature. The advent of micelles for the remedy of skin cancer has exploded due to those superior characteristics.

2. Dendrimers

macromolecules made of hyperbranched polymers with distinct dimensions and forms, dendrimers are made up of countless branches that branch off from a central core to form a structure resembling a tree. Dendrimers' branched layers are referred to as "generations" (G) [97,98]. PEGylated dendrimers [100], poly ether co-polyester dendrimer’s [101], poly-propyleneimine) dendrimers [102], peptide-dendrimers [103], and poly(amidoamine) (PAMAM) dendrimers [99] are a few of its prevalent varieties. no matter being categorized as polymer-primarily based nanoparticles, dendrimers have a distinct structure made up of 3 fundamental components: a primary core, repeating branching devices, and terminal organizations. The hedgehog signaling (Hh) pathway plays a vital position in the survival, differentiation, and proliferation of most cancers cells and is mainly energetic in an expansion of cancer kinds, along with pores and skin most cancers [104]. for this reason, the healing agents that potently inhibit the Hh pathway offer an efficient treatment possibility towards cancer.

3. Polymeric nanoparticles

A capacity to encase, transport, dissolve, or adsorbed anticancer medications for sustained release, tumour targeting, therapeutic moieties defence, & other applications makes polymeric nanoparticles (NPs) straightforward and uncomplicated carrier systems [105]. The shape of NPs can distinct from tiny capsules (storage systems) to nanospheres (matrices), depending on

the preparation technique. The therapeutically medicines merely distributed across the system of particle-matrix in nanospheres. On the other hand, a uni-polymeric membrane enclosing an aqueous or oily cavity contains medicinal substances in nanocapsules [106]. Furthermore, poly. (Lactide-co-glycolide.) [PLGA] [107], poly'lactide [PLA] [108], polycapro-lactone (PCL) [109], PLGA)-polyethylene glycol (P E G) [110], alginate; [111], gelatin [112], albumen [113], and other biodegradable synthetic & natural polymers are the mostly frequently used to create this type of NP.

- **Lipid-based nanoparticles for the treatment of skin cancer**

"Fat" seems to be just another word for "lipid." Lipids are a compound that are soluble in the substances of alcohol (C2H5) 2O, and chcl3, but are not soluble in water. [14] Lipids were critical building blocks of human cells. Lipids were the main constituents of both plant & animal cells, together with proteins & C(x)H(y) (Cx(H2O) y). Cholesterol and triglycerides are both classified as lipids. Lipid are rapidly gotten and maintained on the system. Besides being a major constituent of the cells, it functions as an energy marker. Lipids include steroids (e.g., cortisone), waxes, neutral fats, and fatty acids. Compound lipids (liver complexed with another type of chemical molecule) include glycolipids, phospholipids, and lipoproteins. Lipids are small molecules that can be described as amphiphilic or aquaphobic. Indeed, Certain lipids' aquatic nature enables us to create membranes, gigantic uniflagellar liposomes and vesicles stepping up with a watery substance. Lipids from biological sources are composed of 2 kinds as "building blocks," or the concept biological sub-units," isoprene & ketoacy'l groups. California Emulsion of Lipids, Liposome's, & S LN Structure Lipids have been paid much attention that act as carriers since the beginning of the pharmaceutical age. They have very low oral absorption due to their high hydrophobicity [114]. Lipid nanoparticles (LNPs) are also used for drug administration and were discovered to have more advantages in nanoparticle-based delivery systems than polymer nanoparticles [115]. An alternative term for LNPs is "Nano safe" delivery systems because they are lipid-based carrier systems consisting of lipids that are physiological and/or bio-degradable [116]. Solid lipid nanoparticles (SLNs) are a widely used method of LNP synthesis, having been established in the early 1990s [117]. The delivery route was developed due to the many benefits of earlier carriers like polymeric nanoparticles, liposomes, and emulsifiers [118]. S L Ns are distinguished from liposomes by the ease of obtainment & scaling-up procedure, formulations' GRAS (Generally Recognized as secure) characteristics, and the absence of polar chemicals [119].

1. Solid lipid nanoparticles

These have fixed dimensions extending from 1 to 1000 nanometers. Particles are usually between 150 and 300 nanometer in size. SLNs range size from 1 -- 1000 nm, which are solid submicronic colloidal nanocarriers. Most of particle's are published in size ranges of 150–300 nm. Polymeric nanoparticles and other drug delivery methods provide another set of strategies for controlled releases [120]. The solid SLN matrix that they

developed allows them to mix the benefits of polymeric nanoparticles, liposomes, and micronized emulsifiers by means of improving stability and reducing drug mobility [121]. SLNs are created via substituting a solid lipid, or possibly a combination of solid lipids, for the liquid lipid (oil) phase in an emulsion of water and oil. lastly, the truth that SLNs remain solid at body temperature and room temperature is any other critical characteristic [122]. these drug transport systems include 0.1–30% (w/w) solid lipid in aqueous environments. [123] The SLNs consist of solid form lipids such as complex glyceride blends, free fattyacid's, free fattyalcohol, higher purity triglycerides, & also wax, (typically recognised physiological lipids). Furthermore, more complicated structures may be employed [124].

2. Nanostructured lipid carriers

Since lipids are the Swiss knife of biocompatible polymers, lipid-based nanoparticles have proven to be efficient for dermatological therapeutic applications. Nanostructured lipid carriers (NLCs) have aroused great interest in joint treatment of skin conditions owing to their potent therapeutic effects, improved drug stability, penetration, and retention. There I also describe the properties of NLCs and methods they are topically used for curing skin diseases. NLCs have attractive potential to use as advanced drug delivery agents to treat bacterial infections, dermatitis, psoriasis, and skin cancer. Its use in cosmetics has created a whole new avenue of skin care. Its clinical status and safety demonstrated potential for commercial acceptance, as did its approaches to developing valuable drugs. [125]. NLCs lipid-based nanocarrier of the second generation, created SLN by blending Lipids, both liquid & solid. NLCs were formulated to addresses drawbacks associated with SLNs and have a high drug loading capacity and also it is used to prevent medication discharge while being stored by stopping the melt crystals of lipid in NLC formulation by the addition of liquid lipids. Strong lipid nanoparticles (SLNs) are formed by lipids i.e solid, whereas nano -structured lipid carrier's (NLCs) are made from lipids, both liquid & solid, like glyceryl dioleate, ethyl oleate, iso propyl myristate, & glyceryl tricaprylate. Colloidal carriers have very similar mean particle sizes (10–1000 nm) to SLNs, and this also depends on both the encapsulating lipids and the preparation [126].

3. Liposomes

Liposomes are nanometer-sized particle primarily made from phospho-lipids and cholesterol with demonstrated progress in the biocompatibility and vectorized payload disposition with minimal injury. The cationic phospholipids are amphiphilic, being self-encapsulated by their lipid-soluble ends to form circular lipid bilayers, thus making it possible to contain water-insoluble medications. The head of phospholipids, which is soluble in water, forms an outer surface and a central watery core that can accommodate aquaphilic molecules. Liposomal encapsulation of additional therapeutic substances may be through multiple chemical linkers on the liposomal surface or charge-charge interaction. These include liposomes, enable the delivery of lipid & water-soluble therapeutic medicines at

maintained efficacy, and are some of the best nanotechnology cancer cures. While DOX wrapped in PEGylated liposomal material (Doxil®) was actually the first established nanodrug that was authorized by the FDA at 1995, over six liposomal drugs have been authorized through the Foods and Drug Administration to treat cancer. Based on the success of liposomes in chemotherapy, liposomes have emerged as one of the popular targeted delivery tools in chemoimmunotherapy. Liposomes are the earliest and most widely used nanocarriers for delivering cancer drugs, and they have demonstrated considerable clinical promise; however, their lack of sufficient build-up and permeation of the tumors interstitial spaces space severely impedes medicinal effectiveness [127].

4. Niosome

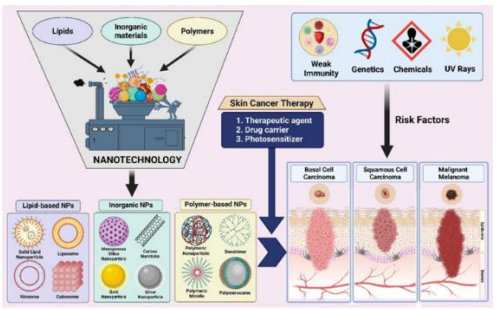
Niosomes are vesicles that assemble themselves composed of cholesterol and Surfactants that are not ionic or another amphiphilic compounds and were first described in the early 1970s. Niosomes are formed by nonionic surfactants, which are amphiphilic molecules with nonpolar tails and polar heads in their structure. This nonionic surfactant is more stable and less hazardous than anionic, cationic, and amphoteric surfactants [128]. Additionally, it serves as a p-glycoprotein inhibitor, with cresol reducing cell surface hemolysis and irritation, and increasing permeability and solubility [129].

Niosomes have emerged as highly efficient and novel drug carriers as compared to liposomes, presenting several benefits including enhanced surfaces adherence, availability, penetration through the skin, and sustained release property, & increased stability of drugs upon encapsulation [130]. In addition, niosomes are less toxic enabling controlled delivery of entrapped drugs [131].

Applications for cancer treatment

LBNPs, or Lipid-Based NPs, are an extensively used family and used in diverse applications including BreC therapy [132]. In addition to their versatility, liposomes are attractive vehicles owing to their marked biocompatibility and capability to encapsulate diverse cargos. LBNPs are currently utilized in multiple studies, and some of them (such as Abraxane и Doxil) have already received permission as BreC treatment [133,134]. section summarizes latest key developments regarding LBNPs that have been increasingly used in the management of prevalent cancer types.

Graphical abstract



Targeted drug delivery of nanoparticle in topical treatment

Patch for drug administration in the treatment of skin cancer

Recently, medicine- shipping patches have attracted attention from multitudinous scientists due to their capacity to supply mending composites to the systemic sluice in addition to to the point of mileage inside the pores and

skin for the treating a no. of skin ails which include cutaneous most cancers (135). those medicine- shipping topical/ transdermal patches can be distributed with untied or NP- imbibed anticancer rectifiers for topical remedy of pores and skin most cancers. To treat carcinoma, song et al. presently set excrescence antigen- feeded ethosomes & bedded them in silk fibroin (SF) poly vinyl alcohol (PVA)- grounded nanofibrous patch (136). on this paper, the authors face- modified Mannosylated polyethyleneimine is used by ethosomes to broadly target dendritic cells. The findings discovered that their evolved nano - fibrous patch considerably restricted excrescence smash in a murine carcinoma model. when both the vaccination patch andanti-PD-1 had been given together, the creatures showed an excellent further effective response towards carcinoma, attesting that vaccine andanti-PD-1 must beco-administered for pores and skin most cancers healing efficacity. also, mRNA vaccines & anti PDL1 siRNA- feeded ethosomes had been generated via the identical group of experimenters and incorporated into an SF- grounded completely electro- spun transdermal patch of cancer (137). at the same time as topical/ transdermal patches possess the capability to treatment skin cancer, the maximum good sized negative aspects of the invention approach, lading cure, andnon-customizable patch length for important remedy are some that want addressing. in this regard, Shao et al. lately delved the efficacity of a substantiated 3- D printable topical patch for the therapy of different pores & skin diseases beneath dermoscopy guidance (138). supposedly, depending at the character traits of the case inclusive of the size and vicinity of the lesion, the hydrophilic & lipophilic drugs may be brought directly at the patch with patterns using an inkjet printer. Such a system could doubtlessly resolve the demanding situations in traditional patch fabrication, thereby advancing the field of dermal cancer treatment.

Skin cancer treatment using a microneedle patch

MNs (microneedles): medication shipping equipment with needle heights among hundred and two thousand μm [139]. professionals label them as 0.33-technology topical/transdermal drug delivery structures. They stand out for his or her unique potential to get above the shortcomings of various topically and transdermal forms together with gels, creams, ointments, widespread patches, sprays, and others [140]. The "the stratum corneum," the skin's strongest barrier, is broken down by these MN patches. This permits them to introduce a huge variety of most cancer pills or nanoparticle-loaded remedies right away into the dermis to treat cancer of skin. Plus, whilst pores and skin cancers spread, those MNs provide a gentler manner to move different drug-filled nanoparticles into the bloodstream. This bypasses the need for more invasive methods like shots into veins, under the skin, or into muscles [141–143]. In earlier work, Demartis and his team created Rose Bengal (RB) loaded transferosomes (T) to tackle the absorption issues in treating skin melanoma [144].

Microneedles (MNs) have brought about a big change in transdermal drugdelivery system [TDDS] starting new phase in medicinal treatment [145,146,147].

These tiny needles, which can be as short as a few tens of micrometers or as long as a few thousand, allow drugs to go straight into the tissues under the skin. They do this by getting past the SC barrier, which helps drugs work better and causes fewer side effects [148,149]. MNs come in different materials and designs to suit many different uses [150,151,152]. They've shown great promise in treating skin problems [153–155]. MNs can put drugs right where they need to go, which means treatments can focus on one area without affecting the whole body as much. This works well for things like skin tumors that aren't deep skin that's inflamed, wounds, and even cosmetic skin issues. When drugs are put inside MNs, they often work better, cause fewer problems, and can control things like how collagen forms and how blood vessels grow. People have come up with new ways to put inorganic chemicals biological parts, cytokines, or biomedicines into MNs to make treatments work even better [156,157,158,159].

When making MNs, the materials need to be tough and meet these requirements:

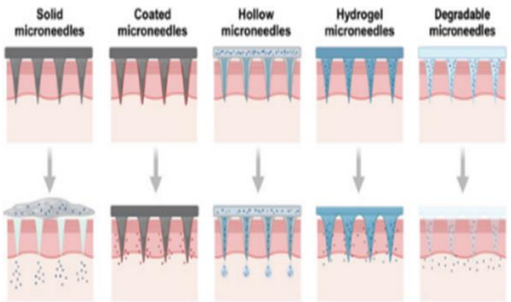
1. Great compatibility with the body and no toxicity
2. Stability of the material that doesn't reduce how well the medicine works
3. Enough strength to pierce the skin without breaking
4. Easy to use in many ways and shape as needed
5. Ability to dissolve in skin while controlling how fast the drug is released.

As technology has improved, it's now possible to make lots of MNs. Many MN devices have moved on to testing in people, and some new designs are now for sale [160].

It's worth mentioning that most MN products for sale are in skincare, which has gotten companies very interested. Several new products have come out, to be used for things like making skin lighter, reducing wrinkles, and treating scars [161,162]. Even with these cool steps forward, we still need to do more research on how to use MNs for skin problems.

Microneedle classification

Microneedles are divided into five groups according to how they are administered transdermally: solid, coated, hollow, hydrogel, and dissolvable.



Summary and perspective

The skin's ability to absorb and use medications has greatly improved because to nanoparticles. Because they can act as drug carriers, improve skin permeability, and aid aid Regarding the medical management about skin cancer, nanoparticles that are effective candidates for the skin cancer therapy. Additionally, the development of personalized medicine makes it possible to use AI to create more precise and tailored treatment regimens. New techniques for transdermal medication delivery systems will appear as biotechnology and material science

develop. These techniques will improve the drug's efficacy and fundamentally alter how medication is administered going forward, resolving a number of current delivery and absorption problems. As of right now, employing nanoparticles to treat aggressive and metastasized skin malignancies is a straightforward process. These methods can be administered through oral, intravenous, transdermal, or even intra-tumoral routes. When it comes to early-stage skin cancer, treatments like gels, creams, or microneedling—where tiny needles are employed—are quite effective. These options are generally safe and have minimal side effects. Nanotechnology is particularly intriguing, as it has numerous applications, including the development for "nanomedicines" that improve treatment of skin diseases & address shortcomings of older medications. Over the years, nanomedicines have progressed from basic polymer systems to sophisticated vesicular lipid carriers, providing notable advantages over conventional treatments for serious skin issues.

Transdermal drug delivery devices are set to revolutionize how we take our medications and manage health problems, especially the more complex ones. The concept of personalized medicine, which prioritizes individual requirements, drives the advancement of these transdermal systems, enabling more precise and customized treatment options.

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