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Green Medicines in Drug Discovery

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Abstract

The process of finding new leads for medicines using natural products is challenging. It discusses bioactive composites generated from natural resources, including phytochemical analysis, characterization, and pharmacological investigation. The success of these resources in the process of discovering unique and effective pharmacological combinations that may help mortal coffers is the primary focus. Natural goods have long been employed as a source of medicinal compounds, and they have shown promising results. Only natural product medicine development makes a substantial contribution to the scientific justification of natural resources. Nature has historically given medical components, and a surprising number of current medicines may be traced back to their natural origins. Businesses have long employed traditional herbal remedies to treat a wide range of illnesses, and the variety of natural products they sell has influenced the development of new medications. There is a growing need for novel chemical variety in webbing due to the creation of contemporary protein-based molecular targets. The continuous debate over the world's biodiversity, whose maturity has not yet been established, will make natural goods crucial to addressing this demand. There are still several obstacles to overcome, such as creating and implementing suitable high-output webbing bioassays, increasing the potency of bioactive molecules, and acquiring plant materials, although medication discovery from medicinal plants continues to be a major source of innovative therapeutic leads. The review article discusses recent interdisciplinary collaborations on studying natural resources, focusing on potential therapeutic avenues similar to health-promoting therapies, and plans to standardize global use of plant-based medicines.

Keywords: Green Medicines, Therapies, Drug Discovery, Bioassays, Traditional treatments

INTRODUCTION

Natural products and traditional treatments are essential for medicinal agents and structural variation, and there is growing interest in their capacity to modify biological functions. The difficulty of finding viable and marketable lead candidates from natural sources makes drug development difficult. The screening procedure for finding new drugs has been revolutionized by new technologies, which present a special chance to revive natural products as a major source for therapeutic development. The process of identifying, evaluating, and employing bioactive substances obtained from natural products as potential medications is referred to as "natural product in drug discovery" in this article. Human life has depended heavily on natural products, and the discovery of herbal medicines frequently depends on an extraordinary natural occurrence [1, 2, 3].

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Since ancient times, therapeutic plants have been used for their special medical properties, which are attributed to their active bioactive compounds. Because they reduce disease, produce bioactive compounds that are less harmful and more effective, and make it possible to transform and extract natural products into potent medications, these plants are essential to the medical system. For instance, dried herbal powders, extracts, or mixes are the main source of plant-based ingredients used

in Ayurvedic medications. With an estimated 75,000 species of higher plants on Earth, ethno botanical plant usage has a long history among many ethnic cultures [4]. Just 1 to 5 percent of these herbs have been scientifically studied and shown to have medicinal potential, and only 10 percent are employed in traditional medicine [5]. This will support the development of superior herbal medications by the pharmaceutical sector and advance world health benefits of traditional remedies [6, 7].

Natural goods have played an important role in medicine research and discovery, with several drugs currently on the market with natural origins [8]. The most common drug, aspirin, is derived from the plant genera Salix spp [9]. and Populous spp. and is associated with salicin. The fungus Penicillium notatum is the source of the antibiotic penicillin, which was unintentionally found in a laboratory. Natural products made from microorganisms and plants have proven valuable and significant in the modern period. One recent example of an important natural substance affecting medicine is paclitaxel, which was initially extracted from the bark of the Pacific yew tree (Taxus brevifolia). Two compounds found in Hypercomperforator, hyperacid and pseudo hypericin, exhibit anti-retrovirus properties, including HIV, by maintaining the structure of the HIV capsid and preventing the release of reverse transcriptase (Figure 1) [10, 11].

In four distinct methods, medicinal plants with strong therapeutic characteristics are beneficial for the current system of herbal and natural medication development.

- Therapeutic and bioactive agents are directly derived from them.
- Bioactive fractions are used as a starting point for the production of more complicated semisynthetic chemical compounds derived from herbs.
- The structures that have been identified from herbal plant species can serve as a guide for the development of novel drugs and herbal compounds.
- Plants can be utilized as bioactive markers for spectroscopy and chromatography, leading to the identification of novel chemicals.

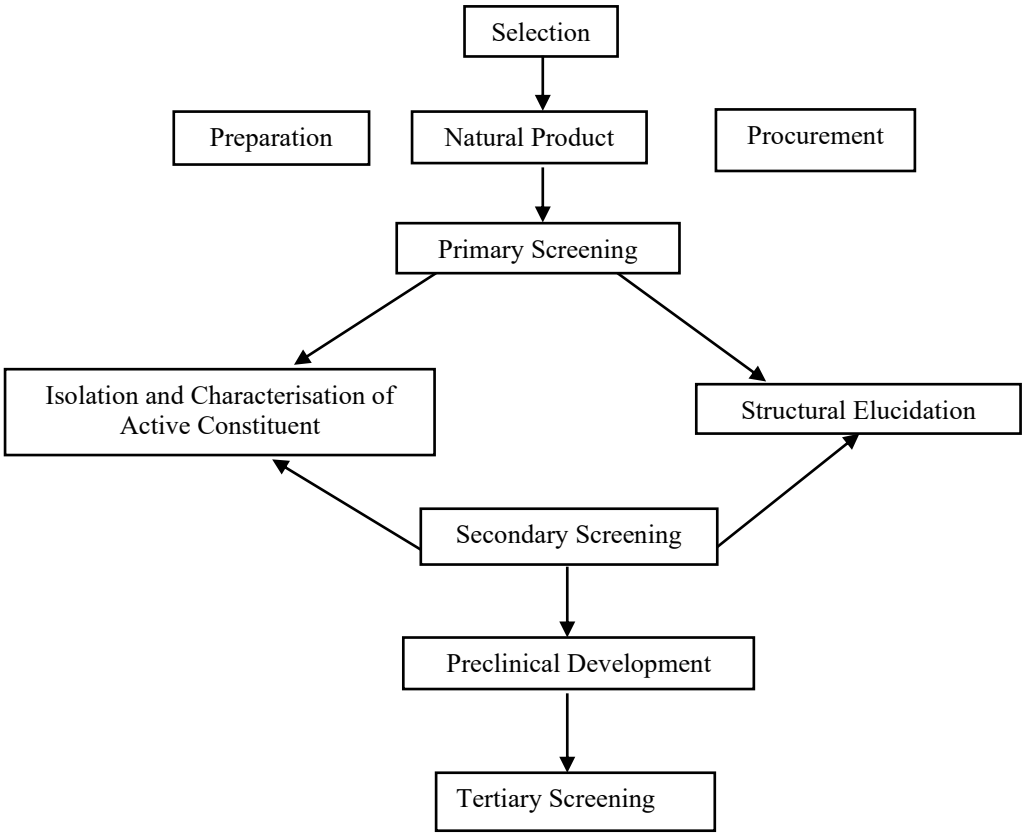

Figure 1. Various strategies for the discovery of drugs from natural resources.

Objectives of Green Medicines in Drug Discovery

- Minimize the use of hazardous and toxic chemicals during drug synthesis.
- Utilize renewable and sustainable raw materials, such as plant-based or bio-derived compounds.
- Develop environmentally friendly and biodegradable drug formulations.
- Improve the efficiency of chemical processes to reduce energy and resource consumption.
- Design synthetic routes that generate minimal waste and by-products.
- Replace harmful solvents with safer, greener alternatives.
- Incorporate green technologies such as biocatalysis and solvent-free synthesis.
- Ensure the safe disposal or degradation of pharmaceuticals to prevent environmental pollution.
- Reduce the overall carbon footprint of drug manufacturing and supply chains.

ADVANTAGES

- Diversity of Bioactive Compounds.
- Lower Risk of Resistance.
- Fewer Side Effects.
- Sustainability and Eco-Friendliness.
- Cost-Effectiveness in Early Drug Discovery.
- Traditional Knowledge and Cultural Relevance.
- Potential for Treating Complex or Chronic Diseases.
- New Mechanisms for Drug Resistance.
- Personalized Medicine [12, 13].

DISADVANTAGES

- Lack of Scientific Evidence and Clinical Trials.
- Variability in Composition.
- Complexity of Isolating Active Compounds.
- Safety Concerns and Toxicity.
- Regulatory and Intellectual Property Challenges.
- Slow Drug Discovery Process.
- Cultural and Ethical Concerns.
- Limited Availability and Sourcing Issues [14, 15].

FACTORS AFFECTING

Bioavailability of Active Compounds

- *Absorption and Metabolism:* The body finds it difficult to absorb and metabolize many bioactive chemicals found in plants or other natural sources because of their low bioavailability. The efficiency of these substances may be limited by factors such their solubility, stability, and permeability through the gastrointestinal tract. For instance, the chemical curcuma, which is present in turmeric, has a relatively low bioavailability because of its quick metabolism and poor absorption [16].

Stability and Shelf Life

- *Chemical Instability:* When exposed to environmental elements like heat, light, and oxygen, many plant-based chemicals become more prone to deterioration and chemical instability. For example, certain polyphenols, flavonoids, and alkaloids may lose their stability, which would decrease their medicinal effectiveness. Their application in medication formulations that need a lengthy shelf life or steady potency may be restricted by this instability [17].

Toxicity and Safety Concerns

- *Drug-Herb Interactions:* Green medicine's natural ingredients may interact with prescription medications, decreasing their efficacy or increasing their toxicity. St. John's Wort, for instance, can

affect how several medications, such as antidepressants, birth control pills, and anticoagulants, are metabolized. Such interactions must be carefully taken into account when developing medication delivery systems that use green medicines [18].

Pharmacokinetic and Pharmacodynamic Considerations

- *Complex Mechanisms of Action:* The study of natural substances' pharmacokinetics and pharmacodynamics might be made more difficult by the fact that they frequently interact with several biological targets. It's possible that the bioactive substances used in green medicine have dose-dependent effects and that their exact modes of action are unclear. Quercetin and other flavonoids, for instance, influence several molecular pathways, which makes it challenging to forecast their precise therapeutic effects.
- *Metabolic Pathways:* Enzymes like cytochrome P450 in the liver break down a variety of natural substances, which might impact their bioavailability and therapeutic benefits. Natural products' effects on these enzymes may cause changes in the way medications are metabolized by the body, which might compromise their efficacy and safety [19].

Cultural and Ethical Factors

- *Cultural Sensitivity:* Traditional and indigenous knowledge are frequently at the core of green medicines. To guarantee that the advantages of green medicine are distributed fairly, ethical plant material procurement and intellectual property rights protection are crucial. Problems with biopiracy, in which businesses use indigenous knowledge without paying people fairly, might impede the advancement and use of green medicine in medication delivery [20].

CLASSIFICATION OF PHYTOCHEMICALS

Due to their great diversity, the precise categorization of phytochemicals found in different plants has not yet been completed. Phytochemicals are classed as major or secondary components based on their involvement in plant metabolism and therapeutic value. Common sugars, proteins, amino acids, purines and pyrimidines of nucleic acids, chlorophylls, etc. are examples of primary components of plants. Alkaloids, terpenes, flavonoids, lignans, saponins, plant steroids, curcumin's, phenolics, flavonoids, and glucosides are examples of secondary components. According to a review of the literature, the most abundant and structurally varied plant phytoconstituents are phenolics (Figure 2).

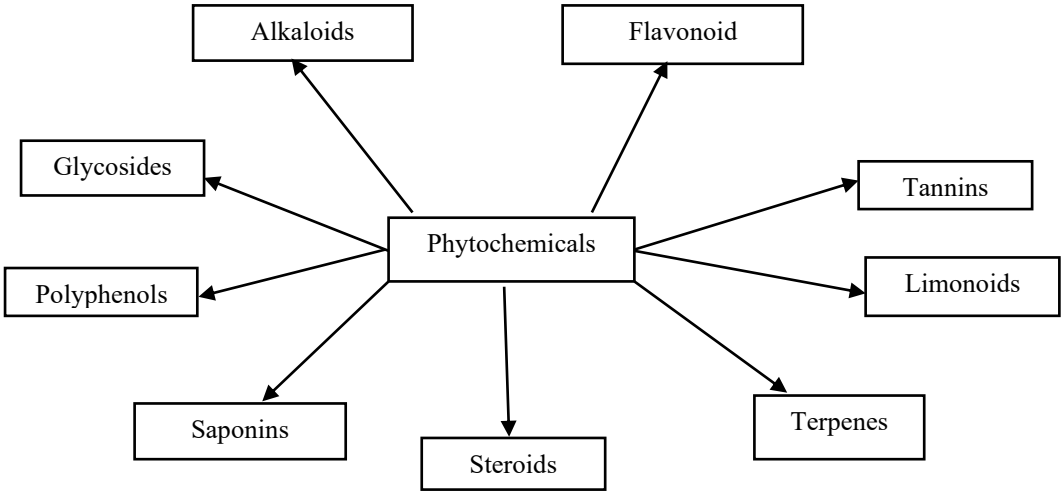

Figure 2. Classification of Phytochemicals.

- *Alkaloids:* Alkaloids are the most structurally varied family of secondary metabolites; they are nitrogenous bases, often heterocyclic. They come in a variety of forms, from basic to intricate, as those of several neurotoxins. Seldom do they contain sulphur, as is the case with the dithiolanes that were separated from Bruguiera species. Their diverse pharmacological properties have long

piqued human curiosity, and certain plant products containing alkaloids have been employed as stimulants, psychedelics, euphoriants, medicine, and poison for hunting, killing, and euthanasia. Numerous examples of basic nitrogen compounds from higher plants are strong in vitro and in vivo inhibitors of different oxidative processes.

- *Flavonoid:* Derivatives of flavonoids and flavanol-lignan are strong triplet oxygen quenchers and suppress lipid peroxidation. Numerous changes to the flavonoid skeleton result in a broad class of chemicals, including chalcones, isoflavones, and isoflavone's. Some of these isoflavones are currently being sold as treatments for menstruation diseases. Polyhydroxylated chalcones, such as those found in Pongamia pinnata, which are metabolic intermediates between cinnamic acids and flavonoids, have significant antioxidant properties. Anthocyanins are pigments that are produced when glycosides (often glucosides) hydrolysed to produce colourful aglycones called anthocyanidins. Rotenone, an isoflavone, is a naturally occurring pesticide. The name "proanthocyanidin" is based only on the experimental finding that these colourless molecules produce anthocyanidins when treated with strong acids; it lacks structural specificity Scalbert, 1991: Stafford, 1988. They have the power to tan leather and have an astringent flavour. In fact, this family of chemicals includes the so-called "condensed tannins." Quinines are a frequent term for "oxidized" phenol compounds [21].
- *Tannins:* Polyphenolic compounds called tannins are found in many higher plants. Their capacity to precipitate proteins like gelatine from solution sets them apart from the majority of other naturally occurring phenol compounds. Their utility in tanning animal skins in the past and today is due to this characteristic, which is frequently referred to as astringency. Tannins are divided into two types based on their structures: proanthocyanidins (condensed tannins) and hydrolysable or water-soluble tannins. This family of natural polymers, which are also known as flavotannins, proanthocyanidins, condensed tannins, or flavolans, has a generic formula where "n" ranges from 2 to 20. When heated with alcoholic hydrochloric acid, they produce colours called anthocyanidins [21].
- *Limonoids, Terpenes, Steroids and Saponins:* Terpenoids, terpenes, or isoprenoids refer to a diverse, widespread, and exceedingly numerous families of natural products made up of five carbon building blocks (isoprenyl carbon skeleton) and containing compounds with C5, C10, C15, C20, and C40 skeletons, with steroids sometimes designated as a separate class. However, the structures of the increasingly found terpenoid compounds deviated from, or "violated," this "isoprene" criterion. Usually present in every portion of higher plants, these substances can also be found in mosses, liverworts, algae, and other plants. Since ancient times, members of this family have been utilized as constituents in oils or extracts to make tastes, preservatives, fragrances, medications, narcotics, soaps, and pigments. Terpenes are classified as monoterpenes (C10 compounds), sesquiterpenes (C15), diterpenes (C20), and triterpenes (C30) based on the number of isoprene units they include in their structures. The most prevalent terpenes in plants are triterpenes, which typically have pentacyclic structures similar to those of amyrin. Tetraterpenes (C40) are most commonly found in the form of carotenoids, which are pigments whose primary function is to serve as photoreceptive "antenna pigments" for photosynthesis. Additionally, some of them serve as defences against oxidative damage. There are terpenes that have been used as remedies since ancient times.
- Steroids, which are just modified triterpenes, are found in numerous microbes as well as in the kingdoms of plants and animals. Saponins have received a lot of attention in recent years due to their diverse biological features, some of which are harmful and many of which are helpful to human health when shaken with water, these plant glycosides have the ability to generate a soapy lather. They are utilized in traditional and modern medicine, food, and agriculture, and are classed as steroidal or triterpenoidal saponins depending on the type of the aglycone. Sapogenin is a substance. A third kind of saponin, called basic steroid saponins, contains nitrogen analogues of steroid sapogenins known as aglycones. The usage of saponins as natural detergents was known to the prehistoric people, and the plants that contain them are utilized to make natural soaps. Fish are poisoned by saponins, which make up the majority of molluscicides derived from plants. Different antibacterial, antimicrobial, anti-inflammatory, hypoglycaemia, haemolytic analgesic, anthelmintic, and cytotoxic properties are displayed by triterpenoidal saponins.

- Plant saponins have been shown to be effective in a liposomal drug delivery method. The many saponins found in the Chinese medication 'ginseng', which is regarded as a panacea and a drug for longevity, are responsible for its intriguing pharmacological effects. As raw materials for the production of steroidal hormones, steroidal saponins are in high demand in the market. Modified triterpenes are called limonoids. They belong to the Rutales plant order and are its most characteristic secondary metabolites. They specifically describe members of the Meliaceae family, which is rich and varied, as well as, to a lesser degree, members of the Rutaceae family. Limonoids have garnered significant interest recently because to their notable antifeedant, insecticidal, antifungal, bactericidal, and antiviral activity, as well as their growth-regulating qualities and a range of therapeutic benefits on both people and animals Flavonones are what give fresh citrus juice its bitterness. It was discovered that limonoids were the cause of the progressive rise in bitterness following expression.
- *Polyphenols:* The most prevalent antioxidants in human diets are secondary plant compounds called polyphenols. One or more hydroxyl moieties are carried by an aromatic ring in the design of these molecules. Based on the quantity of phenol rings and the structural components that hold them together, many groups may be distinguished. Two primary categories of polyphenols, known as flavonoids and nonflavonoids, have historically been used in this context. Flavonones, flavones, dihydroflavonols, flavanols, flavan-3-ols, anthocyanidins, isoflavones, and proanthocyanidins are among the chemicals that make up the flavonoid group. Simple phenols, benzoic acids, hydrolysable tannins, acetophenones and phenylacetic acids, cinnamon acids, coumarins, benzophenones, xanthones, stilbenes, chalcones, lignans, and secoiridoids are the subgroups of the nonflavonoids group, which is categorized based on the number of carbons [21].
- *Glycosides:* A molecule having a sugar attached to another functional group by a glycoside link is called a glycoside. Glycosides have a variety of vital functions in living things. Many plants store compounds as inactive glycosides, which may be activated by hydrolysing the enzyme. This breaks off the sugar portion, making the chemical usable. Many of these plant glycosides have application in medicine. Numerous Helicoids butterfly species are able to use these plant components as a chemical defence mechanism against their predators in both humans and animals, toxins frequently bind to sugar molecules as part of their body's removal processes. The French scientists Antoine Boutron-Charlard and Pierre Sobriquet discovered amygdaline, the first glycoside, in 1830.

CHARACTERIZATION OF GREEN MEDICINE

- *Solubility:* The potential of green medicines as medicinal agents is largely dependent on their solubility in drug development. A compound's solubility affects its absorption, bioavailability, and therapeutic effectiveness. Solubility problems can pose serious problems for green medicines, which are frequently made from natural sources including plants, fungus, and marine creatures [22].
- *Melting Point:* A compound's melting point is a crucial physical characteristic for characterizing green medicines, especially in drug development. It offers information about the stability, purity, and crystallinity of bioactive substances that come from natural sources. The purity of natural chemicals and their potential for therapeutic administration and formulation may be evaluated using the melting point.
- *Ultraviolet:* The ultraviolet (UV) absorption properties of green medications are critical for characterisation in drug development. The chemical structure, functional groups, and purity of bioactive chemicals originating from plants may all be discerned from the UV-visible spectra. One popular method for identifying and measuring natural compounds and their derivatives is UV analysis [23].
- *Infrared Spectroscopy:* Infrared (IR) spectroscopy is a commonly used method for characterizing molecules in drug development, particularly those generated from green medicines (plant-based or natural goods). IR spectroscopy is a crucial method for detecting and characterizing bioactive components in green medicine since it offers information on the functional groups, molecular vibrations, and chemical structures of substances.
- *Nuclear Magnetic Resonance (NMR) Spectroscopy:* NMR spectroscopy is a potent analytical method that offers comprehensive details on a compound's molecular structure, functional groups,

and interactions. NMR is often used in green medicine medication development to identify, characterize, and clarify the structure of bioactive compounds obtained from plants and natural sources. It is regarded as one of the most trustworthy methods for figuring out the molecular makeup of the active ingredients in herbal formulations or extracts [24].

IN VITRO EVALUATION

- *Anti-Oxidant Effect:* Numerous green remedies are abundant in flavonoids, polyphenols, and other antioxidants. By counteracting free radicals, these substances lessen oxidative stress and shield cells from harm. By influencing cellular signalling pathways, the antioxidants may strengthen the body's defensive mechanisms against oxidative damage. Green tea (Camellia sinensis) includes catechins, which function as antioxidants, lowering oxidative stress and inflammation [25].
- *Anti-Inflammatory Effects:* By blocking important enzymes like cyclooxygenase (COX) and lipoxygenase (LOX) or by reducing inflammatory cytokines, a number of green medications lessen inflammation. This can aid in the treatment of long-term illnesses like cardiovascular disease, asthma, and arthritis. Turmeric (Curcumalonga) includes curcumin, which inhibits COX-2 and NF-kB, two inflammatory proteins [26].
- *Antimicrobial and Antiviral Properties:* Some green medications include flavonoids, alkaloids, and essential oils, which give them antibacterial qualities. These chemicals disrupt microbial cell membrane integrity, limit protein synthesis, or prevent viral entrance. Garlic (Alliums sativum) includes allicin, which has antibacterial and antiviral effects [27].
- *Anticancer Properties:* Some green medications include flavonoids, alkaloids, and essential oils, which give them antibacterial qualities. These chemicals disrupt microbial cell membrane integrity, limit protein synthesis, or prevent viral entrance. Garlic (Allium sativum) includes allicin, which has antibacterial and antiviral effects [28].

SYNERGISTIC EFFECTS WITH CONVENTIONAL DRUGS

The synergistic effects of green medicines with conventional treatments relate to how plant-derived medicines (or herbal products) interact with pharmaceutical drugs to improve therapeutic results, minimize adverse effects, or even increase bioavailability. Modification of enzyme activity, changes in drug metabolism, or complementary effects on physiological pathways are some of the ways in which these interactions might take place.

- *Modulation of Cytochrome P450 Enzymes (CYP Enzymes):* Many medications are metabolized in the liver by cytochrome P450 enzymes. Drug effectiveness and toxicity may be impacted by altered drug metabolism caused by the inhibition or induction of certain enzymes by some green treatments. For example, by altering enzyme activity, several herbal supplements might improve the bioavailability of medications or lessen their adverse effects [29].
- *Enhancing Drug Absorption or Bioavailability:* Some green medicines enhance the absorption or bioavailability of conventional pharmaceuticals, resulting in improved therapeutic effects. This is frequently accomplished by making the medication more stable or soluble in the digestive system or by blocking efflux pumps, which stop drugs from being absorbed [30].
- *Reduction of Drug Toxicity:* Green medicines function as protective agents that can lessen the toxicity or adverse effects of conventional medications. This can occur due to antioxidant actions, hepatic protection, or inflammation decrease [31].
- *Complementary Action on Disease Pathways:* Certain green medicines have a more thorough therapeutic impact by acting on illness pathways that are complimentary to those of conventional medications. An herbal remedy, for instance, may have anti-inflammatory properties, but a pharmaceutical medication may target a particular pathogen or underlying pathology that causes disease [32].
- *Potentiating the Anticancer Effects of Chemotherapy:* Green medications have been shown to boost the effectiveness of chemotherapy therapies, increase their cytotoxicity, and protect against chemotherapy-induced adverse effects like nausea and exhaustion. They can operate together to modulate cellular processes implicated in drug resistance, apoptosis, and oxidative stress [33].

THE ROLE OF PHYTOCHEMICALS IN DRUG DISCOVERY

Identification of Lead Compounds

Green medicine lead compound discovery is the process of finding bioactive chemical compounds with potential therapeutic effects that come from natural sources including plants, fungi, and microbes. These substances frequently serve as the foundation for the creation of novel medications or therapies. Alternative or complementary therapies derived from natural sources are referred to as "green medicines."

Screening of Natural Products

- *In Biological Screening:* chemicals from other natural sources or plant extracts are tested for biological activity, such as antibacterial, anti-inflammatory, or anticancer qualities.
- *In Silico Screening:* By simulating how compounds obtained from natural products interact with biological targets, computational techniques are utilized to predict the bioactivity of those compounds. Phytochemical Screening: Plant extracts are examined for chemical components (terpenoids, alkaloids, flavonoids, etc.) that could have medicinal uses [34].

Bioactivity-Guided Isolation

Isolating the active ingredients is the next step once a natural source is shown to have possible medicinal action. This is frequently accomplished by chromatographically isolating the chemicals and then evaluating their activity in a variety of bioassays [35].

Preclinical and Clinical Studies

Preclinical research is carried out in animal models to assess the safety and effectiveness of a lead molecule once it has been identified. Positive outcomes might result in human clinical trials. Artemisinin, produced from Artemisia annua, was discovered to have antimalarial properties and has since become a popular malaria therapy [36].

Structure-Activity Relationship (SAR)

The relationship between the pharmacological activity of bioactive chemicals found in plant-derived medications and their chemical structure is known as the Structure-Activity Relationship (SAR) of green medicines. SAR studies shed light on how a molecule's structure affects its toxicity, potency, and selectivity as well as other biological impacts. This information helps create herbal medications or chemicals that are more effective.

- *Curcumin (From Turmeric -Curcuma Longa):* The structure of curcumin is essential for its anti-inflammatory, antioxidant, and anticancer properties. The hydroxyl groups and β-diketone functionality contribute significantly to its ability to scavenge free radicals and chelate metal ions, which are critical for its antioxidant and anti-inflammatory effects. The conjugation between the phenolic rings increases the stability of the molecule and enhances its biological activity [37].
- *Quercetin (Flavonoids Found in Various Plants):* By stabilizing free radicals and giving electrons, quercetin's aromatic rings' hydroxylation pattern improves its antioxidant properties. The catechol group (3', 4’-dihydroxy group) is essential to its capacity to chelate metal ions, which amplifies its anti-inflammatory and antioxidant properties [38].
- *Epigallocatechin Gallate (EGCG) From Green Tea (Camellia Sinensis):* The galloyl group at position 3 improves EGCG's accessibility to receptors and enzymes involved in apoptosis and cell signalling. The hydroxyl groups at positions 3' and 4', which make up the catechol structure, help explain EGCG's antioxidant qualities. The phenolic nature and hydroxyl groups are vital for scavenging free radicals, and the galloyl group adds to its capacity to control enzyme activity (e.g., inhibiting matrix metalloproteinases and cyclooxygenase enzymes [39].

EXAMPLE OF PHYTOCHEMICALS LEADING TO FDA APPROVED DRUGS

- *Paclitaxel (Taxol):* Approved in 1992 to treat non-small cell lung cancer, breast cancer, and ovarian cancer [40].

- *Artemisinin (Coartem):* In 2009, the FDA approved Coartem, a combination medication based on artemisinin, to treat malaria [41].
- *Resveratrol:* Although resveratrol is not yet a licensed medication, several clinical trials have examined its potential to treat diabetes, cardiovascular disease, and neurodegenerative disorders. As a dietary supplement, it is often advertised [42].
- *Morphine:* Currently approved and extensively used for severe pain, morphine has been utilized for pain treatment since the early 19th century [43].

ADVANTAGES OVER SYNTHETIC COMPOUND

- *Sustainability and Environmental Impact:* Natural materials, which are frequently more sustainable than synthetic chemicals that need lengthy industrial procedures and may contribute to pollution and environmental damage, are used in green medicine. Compounds generated from plants are replenish able and often extracted without seriously damaging ecosystems, particularly when they are produced utilizing sustainable farming methods [44].
- *Lower Toxicity and Side Effects:* Numerous bioactive substances, many of which work in concert to maximize therapeutic effectiveness while reducing toxicity, are frequently found in green medicine. In comparison, manufactured medications may be more harmful because of their strength and absence of these natural balance chemicals. In contrast to synthetic drugs, which frequently act on a single target, natural plant-based compounds usually target multiple biological pathways in a holistic manner, potentially resulting in fewer side effects [45].
- *Lower Risk of Resistance:* Plant-based chemicals have frequently developed over millions of years to combat viruses, fungus, and diseases in their natural habitat. Unlike synthetic drugs that may target a single pathogen or enzyme, these compounds tend to target multiple pathways or act in a more broad-spectrum manner, which decreases the likelihood of resistance developing [46].
- *Multifunctional Properties:* Many phytochemicals possess multifunctional properties, meaning they can address a variety of health conditions. Plants contain flavonoids, terpenes, and alkaloids, for instance, which can combine to provide anti-inflammatory, antiviral, antioxidant, and anticancer properties. This contrasts with synthetic drugs, which are often designed to target a single condition or mechanism of action, potentially requiring a combination of medications to treat multiple symptoms or diseases [47].

ADVANCES IN EXTRACTION AND OPTIMIZATION TECHNIQUES

Modern Extraction Methods

- *Supercritical Fluid Extraction (SFE):* Supercritical fluid extraction, typically using CO_2 as the solvent, has become a popular method for extracting bioactive compounds. In its supercritical state, CO_2 can penetrate plant material efficiently, extracting essential oils, alkaloids, flavonoids, and terpenes, while maintaining the integrity of the compounds [48].
- *Microwave-Assisted Extraction (MAE):* MAE speeds up the extraction of bioactive chemicals from plant sources by heating liquids using microwave radiation. This method shortens the extraction time while increasing extraction efficiency [49].
- *Ultrasound-Assisted Extraction (UAE):* High-frequency sound waves are used in ultrasound-assisted extraction to produce cavitation bubbles in the solvent, which makes it easier for plant cells to release bioactive chemicals [50].
- *Enzyme-Assisted Extraction (EAE):* In order to more effectively release bioactive chemicals from plant cell walls, enzymes such as cellulase and pectinase are used in enzyme-assisted extraction. This approach is thought to be a more environmentally friendly substitute for conventional extraction techniques [51].
- *Green Solvent-Based Extraction:* For extraction, green solvents including ethanol, glycerol, and water are utilized in place of traditional organic solvents. These solvents have little effect on the environment, are biodegradable, and are non-toxic [52].
- *Solid-Phase Micro-extraction (SPME):* With SPME, volatile chemicals are extracted from plant material using a fibre covered in an absorbent substance. It has become more well-liked for separating perfumes and essential oils [53].

- *Pressurized Liquid Extraction (PLE):* PLE increases the effectiveness of bioactive component extraction from plant matrices by applying high pressure. It can be carried out at higher temperatures to increase a compound's solubility [54].

Nanotechnology Based Delivery of Phytochemicals

Phytochemical delivery systems based on nanotechnology have become a viable approach to improve the stability, bioavailability, and therapeutic effectiveness of plant-derived substances in green medicine. Alkaloids, flavonoids, terpenes, and polyphenols are examples of phytochemicals whose quick metabolism, restricted bioavailability, and poor solubility limit their potential for medicinal use. By encapsulating these substances in nanoscale carriers, nanotechnology improves their efficacy and delivery, overcoming these difficulties.

- *Nanoparticles For Phytochemical Delivery:* Phytochemicals are frequently encapsulated in nanoparticles, such as lipid-based nanoparticles (liposomes, solid lipid nanoparticles), polymeric nanoparticles, and inorganic nanoparticles. These nanoparticles can increase the solubility, prevent degradation, and enable controlled release of sensitive chemicals [55].
- *Phytochemical Encapsulation with Liposomes:* Liposomes are spherical vesicles made of lipid bilayers that have the ability to encapsulate phytochemicals that are hydrophilic or hydrophobic. They are very helpful in delivering bioactive compounds such as polyphenols and essential oils. Liposomes provide regulated release and enhance the stability of delicate phytochemicals [56].
- *Solid Lipid Nanoparticles (SLNs):* SLNs are lipid-based nanocarriers that are utilized to deliver phytochemicals that are lipophilic. They are made of solid lipids that, when heated to body temperature, generate stable nanoparticles that provide regulated release of the active components [57].
- *Polymeric Nanoparticles:* Made from synthetic or natural polymers, polymeric nanoparticles provide an additional delivery system for phytochemicals. These carriers offer targeted delivery, enhanced pharmacokinetics, and controlled release for a range of bioactive substances [58].
- *Nanostructures Lipid Carriers (NLCs):* NLCs are a novel type of lipid nanoparticle that combines the benefits of liposomes and SLNs. They provide improved stability, solubility, and controlled release when utilized to encapsulate hydrophilic and hydrophobic phytochemicals [59].

Bioavailable Enhancement Strategies

Improved absorption, distribution, metabolism, and excretion (ADME) of bioactive chemicals sourced from natural sources such as plants, herbs, and other traditional medicine is the goal of bioavailability improvement efforts in green medicine. Since many phytochemicals have low bioavailability—that is, they are not effectively absorbed or used by the body—these tactics are essential. These chemicals' bioavailability may be improved using a variety of methods, which will boost their medicinal effectiveness.

- *Nanotechnology-Based Delivery Systems:* To increase the solubility and absorption of phytochemicals, nanotechnology-based systems are used, including dendrimers, liposomes, solid lipid nanoparticles (SLNs), and nanoparticles. By encapsulating bioactive substances, these systems can improve their stability and prevent degradation, increasing their bioavailability [55].
- *Cyclodextrin Complexation:* Cyclodextrins are cyclic oligosaccharides that have the capacity to combine with hydrophobic substances to create inclusion complexes that increase the solubility and stability of those molecules. This is especially helpful for substances that frequently have limited water solubility, such as polyphenols, flavonoids, and alkaloids [60].
- *Solid Lipid Nanoparticles (SLNs) And Nanostructured Lipid Carriers (NLCs):* These lipid-based carriers can be employed to transport phytochemicals that are lipophilic. They promote stability, prolonged administration, and controlled release, all of which increase bioavailability [61].
- *Additional Bioenhancers, Including Piperine:* One of the most researched bioenhancers is piperine, a substance presenting black pepper. By preventing the enzymes that are in charge of their metabolism and improving their absorption, it raises the bioavailability of several phytochemicals, including resveratrol, curcumin, and quercetin [62, 63].

- *Liposomes, Micelles, And Nano-emulsions:* Lipid-based delivery methods, including as liposomes and micelles, are frequently employed to increase the bioavailability and solubility of lipophilic substances. By encasing phytochemicals, these methods improve their absorption and water solubility [64].

PRECLINICAL AND CLINICAL TRIALS

- *Importance:* The importance of preclinical and clinical trials in the development of green medicines (plant-based or natural product-derived drugs) cannot be overstated. These trials play a critical role in ensuring that potential drug candidates are safe, effective, and suitable for human use. The growing interest in green medicines has sparked increased research into their pharmacological properties, and understanding how these compounds behave in the body is essential for translating traditional knowledge into modern therapeutic applications [65].

Clinical Trial Phases for Green Medicines

The four main phases of clinical trials for green medicines are Phase I, II, III, and IV, and they are structured similarly to those for synthetic medications. Every stage has distinct goals and protocols.

Phase I: Safety and Dosage (Human Trials)

The first phase involves testing the medication on human volunteers. Assessing the green medicine's pharmacokinetics, safety, and tolerability is the main objective.

Phase I Procedures

- *Healthy Volunteers:* To track the medication's effects on people, a small sample of healthy people (20–100) are often involved in this phase.
- *Dose Escalation Studies:* To ascertain the maximum tolerated dose (MTD) and track any negative effects, volunteers receive escalating dosages of the green medication.
- *Pharmacokinetic Profiling:* Scientists evaluate the drug's absorption, distribution, metabolism, and excretion inside the human body. This aids in comprehending the active chemicals' bioavailability.
- *Side Effects Monitoring:* Careful attention is paid to any negative side effects or toxicity (such as allergic responses or organ damage).

Phase II: Efficacy and Side Effects

In phase II studies, 100–300 people with the ailment the medication is intended to treat make up the larger participant pool. Evaluating the green medicine's effectiveness and adverse effects is the main goal.

Phase II Procedures

- *Patient Groups:* Individuals with the targeted illness, such as diabetes, hypertension, or cancer, are enrolled.
- *Efficacy Evaluation:* Clinical goals like symptom relief or biomarker alterations are used to assess the green medicine's therapeutic efficacy in treating the illness.
- *Optimal Dose Determination:* By evaluating the balance between efficacy and adverse effects and comparing various doses, the study determines the ideal dose.
- *Safety Monitoring:* Because of the greater scope, any negative effects that were missed in Phase I are now more likely to be larger patients sample size detected [65].

Phase III: Confirmatory Trials and Comparison with Existing Treatments

Phase III trials are extensive research projects designed to offer more solid proof of the green medicine's safety and effectiveness. These studies can run anywhere from a few months to years and usually involve hundreds to thousands of people.

Phase III Procedures

- *Randomized Controlled Trials (RCTs):* Participants are randomized to receive the green medicine as part of the treatment group or a placebo or an already-approved medication as part of the control group.

- *Comparative Effectiveness:* Current conventional medicines or placebos are used to compare the green medicine's effectiveness. This is done to make sure the new green medication works just as well as the current therapies, if not better.
- *Long-Term Safety:* Over an extended length of time, the green medicine's long-term safety and adverse effects are meticulously observed. This aids in locating any uncommon adverse effects that might not have been noticeable in previous stages.
- *Data Analysis:* To ascertain if the green medicine may be suggested for general use, the trial's data is examined for statistical significance.

Phase IV: Post-Marketing Surveillance

Phase IV studies, also known as post-marketing monitoring, are carried out following the green medicine's approval and release onto the market. The purpose of these studies is to track the medication's efficacy and long-term effects in the general population.

Phase IV Procedures

- *Long-Term Safety Monitoring:* Following a prescription for the green medicine, patients are watched for any negative responses or fresh side effects that might not have manifested during the clinical trial stages.
- *Real-World Effectiveness:* Unlike clinical trials, assessments of the efficacy of green medicine are conducted in real-world settings, frequently with a more varied patient group.
- *Regulatory Feedback:* If significant side effects are found, this stage may result in additional regulatory measures, such as revised dosage guidelines, more warnings, or even a product's removal from the market [66, 67].

CHALLENGES AND LIMITATIONS

Certain plant species may be threatened if they are over extracted for their medicinal components, which might deplete natural resources. Additionally, resource extraction that is not sustainable may result in habitat degradation, which can disrupt ecosystems and endanger biodiversity. In order to maintain the environment and the native communities that depend on these resources, these issues highlight the necessity of sustainable and responsible procurement practices as well as the preservation of medicinal plant species. It might be challenging to guarantee the consistent efficacy and purity of compounds obtained from plants. The chemical composition of natural products may be influenced by harvesting methods, environmental conditions, and plant genetics [68]. It may be necessary to enhance the standardization of plant extracts, which is an essential component in guaranteeing the reliable reproduction of therapeutic effects. To guarantee the efficacy and safety of products made from natural sources, strict quality control measures must be put in place, including extensive testing and the establishment of exact quality standards. The reliability and safety of herbal treatments are impacted by variations in the concentration of bioactive components or contaminants. Significant variation exists in the pharmacokinetics of compounds originating from plants, which affects the body's absorption, distribution, metabolism, and excretion of these chemicals [69]. Pharmacological medications' chemical stability, absorption rates, and interactions with other substances can all affect how effective they are. To produce drugs with predictable and consistent therapeutic effects, it is crucial to understand and improve the pharmacokinetic properties of plant compounds [70]. To improve the effectiveness of these compounds in therapeutic settings, this may entail introducing chemical changes, employing formulation techniques, or developing drug delivery systems. Drugs generated from plants may be subject to complicated regulations that differ between countries and geographical areas. Strict safety and efficacy testing is frequently required by regulatory agencies, which adds time and costs to the development process [71]. Additionally, the commercialization of plant resources and traditional knowledge may raise intellectual property issues, leading to debates regarding fair compensation for indigenous people and the preservation of their cultural heritage. Some botanical materials come from different regions and might not be affordable or readily available to everyone [72]. Fair access to these medications' advantages may be hampered by their limited availability, especially for people living in

underserved or economically disadvantaged areas. Adopting a multidisciplinary approach that includes conservation efforts, sustainable harvesting practices, tight quality control standards, regulatory harmonization, and ethical considerations is required to address these challenges and limitations. There are several advantages to using compounds originating from plants in medication development. However, in order to maximize advantages and minimize negative consequences on the environment, society, and healthcare, it is imperative that these problems be approached appropriately.

FUTURE PERSPECTIVES

- *Renewed Interest in Natural Products:* Natural product drug development is booming as researchers look for novel medications in plants and their bioactive chemicals. Alkaloids, flavonoids, terpenoids, and phenolic compounds are examples of phytochemicals that have demonstrated promise in the treatment of a variety of illnesses, including infections, diabetes, cancer, and cardiovascular conditions. There will probably be more phytochemicals entering the clinical pipeline in the future due to the rising desire for natural medicines.
- *Advanced Methods of Analysis:* Phytochemicals research is being advanced by the use of advanced analytical methods including high-performance liquid chromatography (HPLC), mass spectrometry, and NMR (Nuclear Magnetic Resonance) spectroscopy. These instruments make it possible to precisely identify and separate bioactive substances from intricate plant matrices. Drug discovery is accelerated as a result of researchers' increased ability to quickly and accurately identify relevant phytochemicals.
- *Integration with Modern Pharmaceutical Research:* Although phytochemicals are frequently researched separately, there is a rising movement to combine them with biotechnology, pharmacogenomics, and synthetic biology to produce novel hybrid substances that outperform their natural equivalents. It is possible to tailor phytochemicals to improve their stability, effectiveness, and bioavailability.
- *Targeting Complex Diseases:* In the treatment of neurological illnesses (such as Parkinson's and Alzheimer's), autoimmune disorders, and chronic diseases like cancer, phytochemicals are shown growing potential. In disorders where single-target medications are less successful, for example, some plant components may have numerous modes of action (e.g., antioxidant, anti-inflammatory, apoptotic).
- *Ethnobotanical Knowledge:* Ethnobotany and traditional knowledge from indigenous cultures are crucial in pointing researchers toward plants that could have medicinal value. In order to find novel plant species and phytochemicals that may be investigated for drug development, this historical knowledge is being integrated with contemporary research [73, 74].

OPPORTUNITIES

New Anticancer Agents: Numerous phytochemicals have demonstrated great promise in the treatment of different forms of cancer.

- Turmeric's key ingredient, curcumin, has shown anticancer effects by focusing on many signalling pathways implicated in the growth, metastasis, and apoptosis of cancer cells.
- One of the most well-known phytochemical-based medications used in cancer therapy, namely for the treatment of lung, ovarian, and breast cancers, is Taxol (Paclitaxel), which is extracted from the bark of the Pacific yew tree.
- *The opportunity:* More plant-derived chemicals that target certain cancer types may be discovered as a result of ongoing research, and current medications' formulations and delivery systems may be improved.

Anti-Microbial and Antiviral Drugs: New families of antibiotics and antivirals are desperately needed in light of the growth in antimicrobial resistance (AMR). The use of phytochemicals as organic antimicrobials is becoming more popular. Extracts from echinacea and elderberries, for instance, are used to treat viral illnesses like the common cold and flu. Berberine, a substance present in plants like Berberis vulgaris, has been demonstrated to have antibacterial and antifungal qualities.

- *The Opportunity:* The identification of new antimicrobial substances derived from plants presents a chance to address drug-resistant infections, a serious problem for world health.

Anti-Inflammatory and Immune Modulator Drugs: Numerous illnesses, such as diabetes, heart disease, arthritis, and neurological disorders, are associated with chronic inflammation. The use of phytochemicals with anti-inflammatory qualities to treat various ailments is becoming more and more popular. For example, omega-3 fatty acids (found in flaxseeds and fish oil) have potent anti-inflammatory effects and are being researched for their role in autoimmune diseases and cardiovascular health. Resveratrol, found in grapes and red wine, is a well-known anti-inflammatory compound that may offer protection against diseases such as Alzheimer's and Parkinson's.

- *The Opportunity:* As the population ages, there will be a greater need for immunomodulators and anti-inflammatory medications, opening up a sizable market for plant-based substitutes.

Neuroprotective Agents: Additionally, phytochemicals are shown promise as neuroprotective agents; compounds are being investigated for their potential to treat multiple sclerosis, Parkinson's disease, and Alzheimer's disease.

- Ginkgo biloba, recognized for its memory-enhancing characteristics, is being examined for its role in preventing cognitive decline.
- Cannabinoids from Cannabis saliva have neuroprotective benefits, notably for epilepsy and Parkinson's disease.
- *The Opportunity:* Phytochemicals have an increasing chance to help prevent or treat these crippling disorders as the market for neurodegenerative diseases grows.

Chronic Disease Management: The potential of phytochemicals derived from plants such as ginger, garlic, and ginseng to treat hypertension, diabetes, and hyperlipidemia is being investigated.Ginseng has been demonstrated to help diabetics become more insulin sensitive.

- Research has been done on the potential of garlic components, such as allicin, to reduce cholesterol and blood pressure.
- *The Opportunity:* Phytochemicals may be developed as supplemental or alternative treatments for the management of chronic illnesses, such as diabetes and heart disease, which are becoming more prevalent.

Cosmeceuticals: Cosmeceuticals, which blend cosmetics and medications, have emerged as a result of the rising desire for natural skincare products. Green tea extracts, hyaluronic acid, and vitamin C are examples of phytochemicals that are utilized in skin-repair and anti-aging products.

- *The Opportunity:* Phytochemicals have a chance to be created and promoted as active components in skincare and cosmetic formulations thanks to the growing worldwide market for natural beauty products [75].

CONCLUSIONS

Plant-based natural chemicals have long been and will be extremely important sources of therapeutic agents and models for the design, semi synthesis, and synthesis of different medications for the treatment of human and animal diseases. Opportunities are increasing to research the biological and therapeutic properties of previously untested natural products, as interest in developing herbal medicines with minimal side effects continues to grow. Plant phytochemicals are tailored to provide potential analogs with the necessary efficacy and safety in plant-derived drug development and discovery studies. A number of novel methods and technical advancements have been developed for the selection, identification, isolation, characterization, and biological screening of natural components as a result of medicinal chemists' growing interest in natural substance drug development. These creative methods might lessen the technological drawbacks of developing natural products and get around the challenges of finding and creating new natural medicines because of their complex behaviour. It is anticipated that plants will continue to produce unidentified biomolecules, which will

enable the development of novel, distinctive treatments for microbial infections and illnesses. Their existence is also threatened by the growing demand for medicinal plants in drug research and traditional medicine. In order for future generations to be able to manage and use these species more effectively and wisely, it is imperative that genetic resources that are endangered, fragile, and overexploited be preserved to the greatest extent possible.

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