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Chemical Pharmacognosy in natural drug discovery-bridging folk wisdom and modern medicine

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Abstract
"Chemical Pharmacognosy" explores natural drug discovery, traversing from traditional remedies to modern therapeutics. This interdisciplinary approach aids biodiversity exploration, supports conservation, and validates Traditional, Complementary and Alternative Medicine. The significance extends to drug formulation, quality control, and combating drug resistance. Symbolizing a holistic journey, it bridges traditional wisdom with scientific innovation, playing a pivotal role in harnessing nature's chemical diversity for human health and guiding drug development.

Keywords: Medicinal plants, biodiversity exploration, complementary and alternative medicine, drug resistance, combination therapies, quality control, regulatory compliance, synergy

1. Introduction
Chemical Pharmacognosy (CP) combines two words: “Chemical” and “Pharmacognosy”. It is the first and most significant phase for natural drug discovery as it is the foundational phase in natural drug discovery, providing the necessary knowledge and compounds for further investigation in pharmacology, medicinal chemistry, and drug development. The basis of CP revolves around the systematic study of natural products to identify and understand their chemical composition, bioactivity, and potential applications in drug discovery and development. Natural products have historically been a rich source of lead compounds for drug development. CP helps identify and isolate bioactive compounds from natural sources (plants, animals, minerals or microorganisms), which can serve as starting points (lead compounds) for developing new drugs. Natural products often possess complex and diverse chemical structures. So, extraction, separation and identification of the bioactive compound responsible for the desired therapeutic effect are necessary. These unique scaffolds can be challenging to create synthetically, making them valuable for drug development. Novel drug scaffolds can lead to innovative drugs with different mechanisms of action, addressing unmet medical needs. CP combines principles from various scientific fields, including chemistry, pharmacology, botany, and biochemistry [1]. The objectives of CP are as follows.

2. Role of Chemical Pharmacognosy
2.1 Traditional, Complementary and Alternative Medicine (TCAM)
Herbal medicine and other natural remedies are still widely used as complementary and alternative treatments. CP helps validate the efficacy and safety of these natural products through scientific analysis, leading to evidence-based integration of TCAM into mainstream healthcare. This allows practitioners to make informed decisions about using TCAM therapies in patient care [2, 3]. Here's how CP is helpful in TCAM.

2.1.1 Traditional Medicine Validation
Traditional medicine systems worldwide have long relied on the therapeutic properties of natural products. CP bridges the gap between traditional knowledge and modern science. It is crucial to validate traditional medicine by scientifically identifying and characterizing the active compounds responsible for the therapeutic effects. By analyzing the chemical composition and biological activities of these natural products, CP provides a rational basis for using traditional medicine in modern healthcare [4]. Here are a few examples of how CP has been used to validate traditional medicines.

2.1.1.1 Story of Quinine

In 1620, the Spanish Jesuit missionary (Bernabe Cobo) observed that Indians of South America used drinks made from the powdered bark of *Cinchona officinalis* to cure malaria. In 1632, Cobo took Cinchona bark to Europe. The tree is named after the Countess of Chinchon from Peru. In 1630, she was very sick with malaria and had a high fever. Her doctor gave her a drink from Cinchona, and she improved. She introduced Quinine to Europe in 1638, and in 1742, botanist Carl Linnaeus called the tree "Cinchona" in her honour. In 1820, by the joint effort of a French Pharmacist (Joseph Bienaime Caventou) and a French chemist (Pierre Joseph Pelletier), Quinine was extracted, isolated and purified from *Cinchona officinalis* bark. During the 1866-1868 clinical trial, Quinine was proved to be a practical anti-malarial alkaloid present in the bark of *Cinchona officinalis* [5].

2.1.1.2 Story of Strychnine

In 1803, French botanist Jean-Baptiste Leschenault de La Tour noted indigenous people in the jungles of Assam, Burma, Malaysia, and Java using *Strychnos nux vomica* bark, while Indians in South America used *Strychnos toxifera* bark as arrow poison for hunting. The resulting black resinous liquid from these plants caused fatal convulsions upon contact. This French botanist gave that black gummy liquid to his friend Antoine-Laurent de Jussieu, the other French botanist, who had identified that arrow poison source as *Strychnos* spp. He also gave the same liquid to his other friend, Alire Raffeneau Delile, who injected the same in a hen and rabbit. As a response to that injection, violent convulsions lead to death after 5 minutes. In 1808, by the joint effort of a French Pharmacist (Joseph-Bienaimé Caventou) and a French chemist (Pierre Joseph Pelletier), strychnine was isolated from *Strychnos nux vomica* (bark). Later on, the clinical trials proved that strychnine is responsible for violent convulsions leading to death [6, 7].

2.1.1.3 Story of d-tubocurarine

In 1813-1878, Claude Bernard (French physiologist) observed that South Africans were using curare (resinous brown sticky mess) as an arrow poison and blowpipe poison obtained from *Chondrodendron tomentosum* (bark). After hitting the prey, it causes death after muscular paralysis. He further observed that Indians orally used the same sticky mass to improve their digestion. He injected the same curare into a frog's leg, interrupting the blood circulation from the injection point to the whole body. He observed that these frogs remain alive. He concluded that when curare is directly injected with blood and allowed to circulate in the entire body, it causes death. But when it is taken orally, it improves digestion. In 1936, an analytical chemist in London (Harold King) isolated d-tubocurarine from *Chondrodendron tomentosum* (bark). In 1942, a Canadian doctor, Dr Harold Griffith, used the same d-tubocurarine as a muscular relaxant during surgery to cause general anaesthesia [8, 9].

2.1.1.4 Story of Artemisinin

Artemisia annua (Sweet Wormwood) has been used in traditional Chinese medicine for centuries to treat fever and various febrile conditions. In 1971, there was an isolation of artemisinin from sweet wormwood. CP studies identified the active compound artemisinin as the principal bioactive constituent responsible for the antimalarial properties of *Artemisia annua*. The isolation and characterization of artemisinin from the plant validated its traditional use. They led to the development of artemisinin-based combination therapies, now widely used as first-line treatments for malaria. In 1972-75, there was a synthesis of artemether and artesunate. In 1989, Paluther (artemether IM) was launched by Rhone-Poulenc Rorer [10].

2.1.1.5 Story of Salicin

The bark of *Salix alba*, commonly known as White Willow, has been used in traditional medicine for centuries to alleviate pain and reduce fever. CP investigations identified salicin as the active compound in White Willow bark responsible for its analgesic and antipyretic effects. Salicin is a natural precursor to salicylic acid, eventually leading to acetylsalicylic acid (aspirin) synthesis. The discovery of salicin and its transformation into aspirin validated the traditional use of White Willow bark and revolutionized pain management and fever reduction in modern medicine [11].

2.1.2 Evidence-Based TCAM Practices

CP provides a scientific foundation for Evidence-Based TCAM Practices by validating traditional remedies, identifying bioactive compounds, elucidating mechanisms of action, and ensuring quality control and standardization in the formulation of herbal medicines. Increased recognition of TCAM practices by regulatory bodies may lead to more structured clinical trials, with CP guiding the selection and standardization of herbal interventions to establish the efficacy and safety [12].

2.2 Biodiversity Exploration

Earth's biodiversity represents a vast reservoir of potential medicinal compounds. CP allows researchers to explore and study the chemical diversity in different organisms, leading to biodiversity conservation and uncovering unique and valuable compounds that may not be found through synthetic chemistry. Biodiversity exploration aims to understand and catalogue the vast array of species and their unique characteristics, including the chemical compounds they produce [13]. Here's how CP is helpful in biodiversity exploration.

2.2.1 Conservation and Sustainable Use

CP encourages the conservation of diverse ecosystems and their unique species. By documenting the chemical diversity of various organisms, researchers highlight the potential benefits of conserving these species for future generations [14].

2.2.2 Natural Product Libraries

These libraries are collections of crude extracts, natural product fractions and pure bioactive compounds derived from various natural sources. These libraries serve as valuable resources for screening potential new treatment options and overcoming drug resistance [15].

2.2.3 Drug Discovery, Development and Commercialization

Many modern drugs have origins in natural sources, and biodiversity exploration remains a valuable source of potential new drug candidates. The most promising bioactive compounds identified through CP are further optimized for improved pharmacokinetic properties, reduced toxicity, and enhanced efficacy. Medicinal chemistry techniques are used to modify the chemical structures of lead compounds. If a

compound passes preclinical evaluations, it progresses to clinical trials in humans. Clinical trials assess the compound's safety and efficacy in patients and provide the data necessary for regulatory approval and market authorization. Upon successful completion of clinical trials and regulatory approval, the compound becomes a new drug available for medical use. Pharmaceutical companies manufacture, market, and distribute the drug to patients worldwide [16-18]. Table 1 depicts some examples of modern medicine of natural origin, and Figure 1 shows Natural drug discovery and development.

Table 1: Some modern drugs of natural origin

Modern drugs	Natural origin	Indications of disease	Year of Discovery
Morphine	*Papaver somniferum* (Opium Poppy)	Severe pain, post-surgery, palliative care	1804 [19, 20]
Quinine	*Cinchona officinalis* (Cinchona Tree Bark)	Malaria treatment and prevention	1820 [5]
Aspirin	*Salix alba* (White Willow bark)	Pain relief, fever, inflammation, blood clot prevention	1897 [21]
Vinblastine	*Catharanthus roseus* (Madagascar Periwinkle)	Cancer, particularly lymphomas and leukemias	1958 [22]
Camptothecin	*Camptotheca acuminata* (Happy Tree bark)	Anticancer agent	1966 [23, 24]
Taxol (Paclitaxel)	*Taxus brevifolia* (Pacific Yew Tree)	Breast, ovarian, and lung cancer treatment	1967 [23, 24]
Artemisinin	*Artemisia annua* (Sweet Wormwood)	Malaria treatment	1972 [25]

2.2.4 Exploring Alternative Reservoirs for Previously Reported Plant Chemical Compounds

CP facilitates the identification of alternative botanical reservoirs for known chemical compounds, contributing to the sustainable sourcing of valuable natural products. This involves systematically studying the chemical constituents present in various plant species to identify and isolate specific compounds reported in earlier studies. The process involves extracting and isolating bioactive compounds, followed by detailed chemical analysis and structural elucidation. CP validates and verifies said chemical compounds by ensuring their presence in different plant sources. This expands our understanding of the distribution of these compounds in nature and provides alternative and potentially more abundant sources (Table 2) [26].

Table 2: Bioactive compounds, their original source and alternative reservoirs

Bioactive Compounds	Original Source	Alternative Reservoirs
Berberine	*Berberis vulgaris* (Barberry)	*Berberis* spp. *Caulophyllum thalictroides*, *Coptis chinensis*, *Jeffersonia diphylla*, *Mahonia aquifolium*, *Rollinia mucosa*, *Xylopia polycarpa* [27]
Curcumin	*Curcuma longa* (Turmeric)	*Curcuma amada*, *Curcuma zedoaria*, *Curcuma aromatica*, and *Curcuma raktakanta* [28]
Quercetin	*Allium cepa* (Red onions)	*Allium fistulosum*, *Apium graveolens*, *Asparagus officinalis*, *Brassica oleracea* var. *italica* (Broccoli), *Calamus scipionum*, *Camellia sinensis*, *Capparis spinosa*, *Centella asiatica*, *Coriandrum sativum*, *Hypericum hircinum*, *Hypericum perforatum*, *Malus domestica*, *Moringa oleifera*, *Morus alba*, *Nasturtium officinale*, *Prunus avium*, *Prunus domestica*, *Solanum lycopersicum*, and *Vaccinium oxycoccos* [29]
Resveratrol	*Vitis vinifera* (Red grapes)	*Vaccinium macrocarpon* (cranberries), *Arachis hypogaea* (peanuts), *Morus notabilis* (Mulberry) [30]

2.3 Understanding Mechanisms of Action of Bioactive Compounds

CP aims to understand how bioactive compounds interact with biological systems and elucidate their mechanisms of action. When investigating the pharmacological effects of natural compounds, it is essential to comprehend how these compounds interact with biological targets to produce their therapeutic effects. It allows researchers to optimize and design more effective and selective drugs, improving their therapeutic outcomes and reducing potential side effects. Isolation and structural elucidation of bioactive compounds make it easier to determine which compound is responsible for the observed pharmacological activity, provide insights into the compound's functional groups, and help identify potential interaction sites with biological targets. Here's how CP contributes to the understanding of drug mechanisms of action.

2.3.1 Systematic Isolation of Active Compounds through Bioassay-Guided Fractionation

Screening natural products for various biological activities involves testing the compounds against specific biological targets or disease models to identify their effects on living organisms, providing insights into their ecological and medicinal significance. In bioassay-guided fractionation, the active components of a natural product are isolated and purified based on their bioactivity. The process involves extracting compounds with solvents, using chromatographic separation for fractionating the crude extract. Each fraction undergoes bioactivity and toxicity screening iteratively until a purified, active molecule is obtained. Validate its biological activity via bioassays, ensuring its responsibility for observed effects. Scale up isolation for ample bioactive compound production, securing result reproducibility. Characterize the compound for purity, stability, and physicochemical properties. Document the process for future reference. Conduct additional studies, including formulation development, to assess its potential as a therapeutic agent [31, 32]. Figure 2 shows a general scheme for Bio-assay guided fractionation and discovery of bioactive compounds

In vitro studies expose cultured cells to natural product extracts or compounds to observe their therapeutic effects and toxicity. Cell viability, proliferation, and apoptosis assays can provide insights into the cytotoxic or anti-proliferative properties [33]. Receptor Binding Studies helps researchers understand the mechanisms through which compounds interact with receptors and modulate their function. Binding assays and radioligand binding studies investigate bioactive

compounds' binding affinity and selectivity for specific biological targets [34]. Enzyme Inhibition Studies explore the inhibitory effects of natural compounds on particular enzymes. This information is essential for drugs targeting enzyme-related diseases like cancer or inflammation [35]. In preclinical research, *in vivo* models are employed to examine the pharmacological impacts of bioactive compounds. Utilizing animal studies offers crucial insights into the effects of these compounds on living organisms, aiding the comprehension of their mechanisms of action. This involves administering natural products to animals to evaluate their physiological and pharmacological effects, encompassing toxicity, pharmacokinetics, and efficacy investigations. The selection of appropriate animal models is tailored to the specific claimed biological activity, such as employing models of inflammation for anti-inflammatory properties [36].

2.3.2 *In Silico* Evaluation

Structure-activity relationship (SAR) studies shed light on the molecular requirements for effective drug-receptor interactions. Researchers can establish structure-activity relationships by correlating the structure of the bioactive compounds with their observed biological activities. SAR studies help identify the essential structural features required for a compound to exhibit a specific therapeutic effect. Researchers can locate specific structural features necessary for the compound's activity by synthesizing analogues and derivatives of the bioactive compound. Molecular docking determines potential biological targets, such as receptors, enzymes, or ion channels. It can predict how natural product compounds interact with specific molecular targets, providing insights into potential mechanisms of action [37].

2.3.3 Comprehensive Omics Strategies - Metabolomics and Proteomics

Metabolomics and proteomics are omics sciences that study the metabolites and proteins within biological systems. Metabolomics and proteomics can comprehensively understand the metabolic and protein expression changes natural products induce. The application of computational methods in CP, such as *in silico* modeling, aids in predicting the interactions between natural compounds and metabolites or proteins. This contributes to the efficiency of drug discovery and development processes [38]. CP is crucial in metabolomics and proteomics, contributing to a comprehensive understanding of natural products' chemical composition and biological activities. Understanding the chemical composition of natural products allows for identifying biomarkers and assists in identifying specific protein targets within biological systems. These biomarkers can indicate specific physiological or pathological conditions. This knowledge is crucial for elucidating the pathways and processes influenced by these compounds [39].

2.4 Drug Formulation and dosage optimization

CP is significant in formulating and standardizing natural medicines. Compound Selection is the crucial ingredient in the formulation relevant to the therapeutic use. Pharmacokinetic Considerations aid in designing formulations that optimize their absorption, distribution, metabolism, and excretion in the body. Dosage Form Development by guiding the choice of appropriate excipients and formulation techniques to create stable and effective dosage forms. Examples of dosage forms include tablets, capsules, ointments, creams, syrups, and extracts [40, 41].

2.5 Quality control and standardization

CP plays a role in establishing standardized protocols for the analysis and quality control of natural products. It ensures the correct chemical substance is present in the right amount (within the defined limits) in a crude drug for the desired therapeutic effect (safety, quality and efficacy) and helps in regulatory compliance [42].

2.5.1 Development of Reference Standards

The reference standards of known quantities of specific active compounds enable precise and reliable quality control. Identification of chemical compounds and Comparison with Reference Standards distinguishes authentic products from adulterated ones. It compares the chemical composition of the test samples with established reference standards.

2.5.2 Chromatographic and Spectroscopic Fingerprints of Natural Extracts or Formulations

It serves as a unique chemical profile that can be used to assess the authenticity and consistency of products. Chromatographic techniques in CP separate and analyze the components, and spectroscopic techniques determine the chemical structure and composition of bioactive compounds derived from natural resources and the degraded chemical compounds with time. These techniques aid in verifying the presence of characteristic compounds in the authentic product and identifying any unexpected or foreign substances indicating adulteration or the presence of contaminants [43-45]. Combining these advanced analytical tools with the vast knowledge of natural product chemistry enables researchers to unlock the therapeutic potential of nature's chemical diversity [46, 47].

2.5.3 Quality Control Testing

It evaluates the presence and quantity of specific compounds, ensuring that the product meets predefined quality parameters. CP contributes to establishing a baseline for product stability by quantifying the concentration of particular active compounds. Deviations from these baseline concentrations can indicate potential issues affecting the product's quality.

2.5.4 Stability Assessment and Shelf Life

CP plays a significant role in the stability assessment and determination of shelf life for natural products. The stability of these products is crucial to ensure their efficacy, safety, and quality throughout their intended shelf life. By understanding how environmental factors such as temperature, humidity, and light factors influence the chemical composition, recommendations for optimal storage conditions can be established.

2.5.5 Safety Assessment

It helps identify and quantify potential contaminants or toxic compounds in natural products. CP is crucial in detecting drug adulteration, especially in natural products. Adulteration refers to the intentional or unintentional addition of inferior or inappropriate substances to a genuine product. Natural products involve adding other plant materials, synthetic drugs, or contaminants, which can compromise the product's quality, safety, and efficacy.

2.5.6 Regulatory Compliance
It ensures that herbal medicines and natural products meet safety and efficacy standards set by health authorities. Authorities often mandate stability data to ensure that herbal medicines and natural products meet specified standards throughout their shelf life.

2.6 Synergy and Combination Therapies for Improved Efficacy and Reduce Drug Resistance
Drug synergy is the enhanced therapeutic effect achieved when two or more drugs are used together, resulting in a more significant impact than the sum of their effects. Synergistic effects obtained through combination therapies can enhance therapeutic outcomes, reduce drug resistance, and improve patient outcomes in various diseases [48-50].
CP provides insights into the compatibility and stability of different bioactive compounds in combination therapy. When used together, this helps formulate the drugs to ensure their efficacy and safety. Combination therapies are particularly effective in combating drug resistance as they simultaneously target multiple pathways or molecular mechanisms. These therapies must consider potential drug-drug interactions and cumulative toxicity [51-53]. Drug resistance in bacteria often involves efflux pumps that expel drugs from the bacterial cell, reducing their effectiveness. CP has identified compounds that can inhibit these efflux pumps, making the drugs more effective in combating drug-resistant bacteria. Anticancer, antibacterial and antiviral agents derived from natural products may offer alternative treatment options for cancerous cells, bacterial and viral infections that have developed resistance to conventional drugs [54, 55].

3. Limitations
CP has various applications in various fields, contributing to the understanding, developing, and utilizing natural products for diverse purposes. While CP plays a crucial role in drug discovery, certain limitations or weaknesses are associated with the discipline. Some of these include:

3.1 Complexity of Natural Products
Natural products, which are the focus of CP, are often complex mixtures of compounds. Isolating, characterizing, and studying these complex mixtures can be challenging, leading to difficulty in pinpointing the active components responsible for therapeutic effects. Understanding the mechanisms of action of natural products within complex biological systems can be challenging. Biological interactions may involve multiple targets and pathways, making elucidating the exact mode of action difficult.

3.2 Limited Supply
Some bioactive compounds found in nature may have limited availability due to the scarcity of the source organism or environmental factors. This limitation can hinder the large-scale production and commercialization of drugs derived from these compounds.

3.3 Standardization Issues
Ensuring the consistency and standardization of natural products poses a challenge. The composition of plant extracts or other natural sources can vary due to geographic location, climate, and harvesting methods. This variability can impact the reproducibility of results in drug development.

3.4 Lack of Intellectual Property Protection and Validation Challenges
Natural products may not be easily patentable, unlike synthetic compounds, as they are part of the public domain. This lack of intellectual property protection can reduce pharmaceutical companies' incentives to invest in developing natural product-based drugs. Bridging the gap between traditional knowledge and modern validation standards can be challenging and may involve cultural, ethical, and methodological considerations.

3.5 Side Effects and Toxicity
Natural products, despite their origin, can exhibit side effects or toxicity. The complex mixture of compounds may include substances that are not therapeutically beneficial or may have adverse effects, necessitating thorough toxicity studies.

3.6 High Cost of Drug Development
Discovering, isolating, and characterizing bioactive compounds from natural sources can be time-consuming. In contrast to the rapid pace of synthetic drug development, the natural product-based approach often requires substantial time and resources. The overall cost of drug development from natural products can be high. Extensive research, extraction, purification, and clinical trials contribute to elevated expenses, making the process economically challenging compared to synthetic drug development.
Despite these weaknesses, CP remains a valuable approach to drug discovery. Addressing these challenges requires ongoing research, technological advancements, and interdisciplinary collaboration to harness the potential benefits of natural products for therapeutic purposes.

4. Future prospects
The future of CP in drug discovery is portrayed as optimistic, dynamic, and integral to addressing the evolving needs of healthcare. The discipline is expected to grow through innovation and integration, contributing substantially to creating safer and more effective drugs to benefit global health. Future endeavors may involve increased collaboration among researchers globally, facilitating knowledge exchange and traditional wisdom. This collective effort could accelerate the validation of TCAM practices through CP on a broader scale. Technological and scientific methods and interdisciplinary collaboration will drive the evolution of chemical pharmacology.

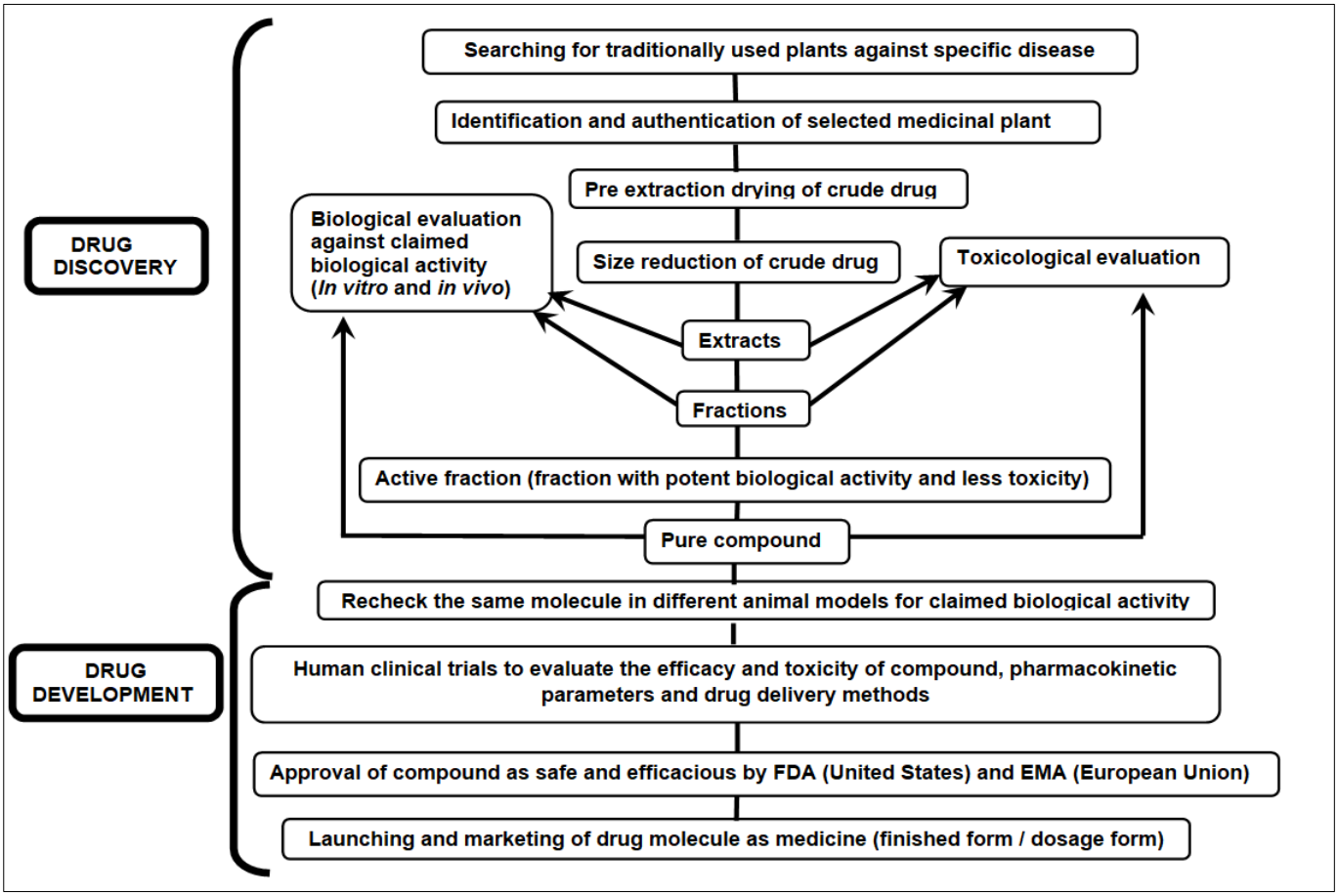

Fig 1: Natural drug discovery and development

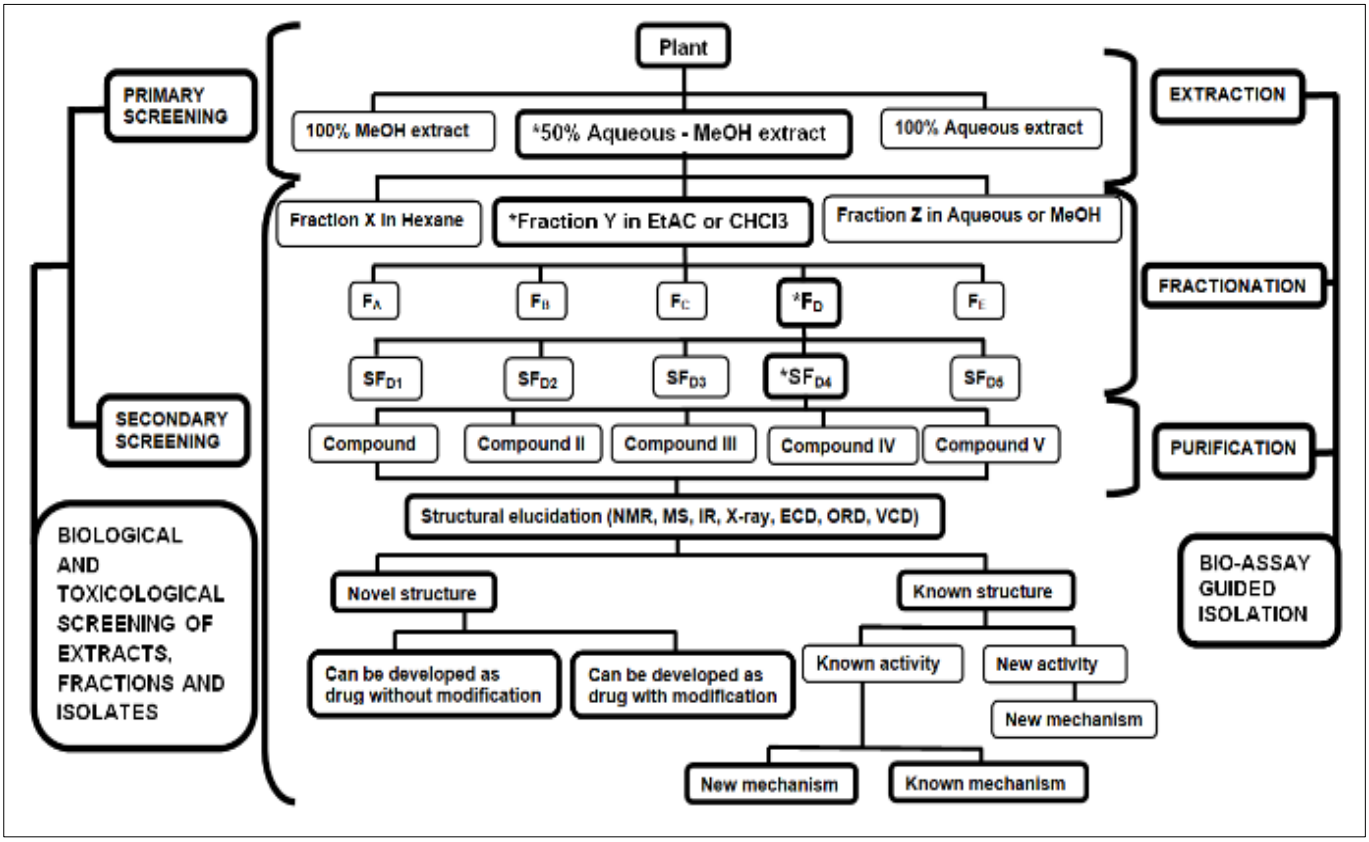

Fig 2: A general scheme for Bio-assay guided fractionation and discovery of bioactive compounds [56, 57]. Where * shows potent bioactivity with less or no toxicity, MeOH = methanol, EtAC = ethylacetate, CHCl3 = chloroform, F = fraction, SF = subfraction; structural elucidation is carried out by spectroscopy NMR = Nuclear magnetic resonance gives basic skeleton, molecular vibrations, spin interactions, degree of unsaturation, MS = Mass Spectrometry gives mass fragmentation and molecular formula, IR = Infrared gives functional groups; X-ray crystallography provides detailed atomic-level information, ECD (Electronic Circular Dichroism), ORD (Optical Rotation Dichroism) and VCD (Vibrational Circular Dichroism) studying the stereochemistry and chiral properties of molecules in solution or when crystallization is challenging

5. Conclusion

CP plays a vital role in modern drug discovery by tapping into the vast chemical diversity of natural products. By combining traditional knowledge with modern scientific methods, researchers can unlock the therapeutic potential of nature's enormous chemical diversity and contribute to developing safer and more effective medicines for various health conditions.

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