International Journal of Pharmacognosy and Pharmaceutical Sciences

ISSN Print: 2706-7009
ISSN Online: 2706-7017
IJPPS 2025; 7(1): 33-40
www.pharmacognosyjournal.net
Received: 03-02-2025
Accepted: 05-03-2025

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Traditional therapeutic plants adopting biotechnological approaches: An overview

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DOI: https://dx.doi.org/10.33545/27067009.2025.v7.i1a.165

Abstract
The kingdom Plantae harbour's an immense number of potential drugs, and the significance of traditional medicines is increasingly acknowledged. The primary origin of herbal supplements, which have been utilized in traditional medical systems since antiquity, is the vast array of plant species found worldwide. Prior to the advancement of medicine, human beings often utilized plants as basic remedies. The advent of novel technology has fundamentally transformed the process of screening natural items for the purpose of developing new pharmaceuticals. By employing those tools, researchers conduct studies to screen novel compounds utilizing software and databases, thereby establishing natural products as a significant reservoir for drug discovery. In order to benefit both the scientific community and society at large, the review sought to outline the significance of traditional medicinal plants and the adoption of diverse contemporary biotechnological approaches.

Keywords: Traditional plant, biotechnology, techniques, *in vitro* assay, molecular docking

Introduction
Multiple segments of medicinal plants, compassing more than 80,000 species, have been employed as traditional remedies in various Indian medical systems to treat a wide range of diseases [1]. The presence of various phytochemicals in plants is determined by several factors, such as genotype, size and maturity of the plants, soil conditions, irrigation practices, pesticide usage, presence of disease and pests, geographical location, and prevailing climate conditions [2, 3]. Plants are recognized for their ability to produce secondary metabolites that possess antioxidant effects. Numerous investigations have demonstrated a strong association between inflammation and hyperlipidemia, which is a major risk for the development of atherosclerosis and other cardiovascular diseases [4, 5]. By anticipating molecular interactions, improving compound design, and hastening the identification of potential drugs with particular activity against disease-related targets, molecular docking contributions to the quick development of natural product-based treatments for cancer and diabetes which have several important benefits.
The utilization of *in vitro* screening approaches might furnish the necessary initial studies required to pinpoint crude extracts that are really beneficial for further chemical and pharmacological assessments [6]. The review main focus is on the value of traditional medicinal plants implementing innovative biotechnological techniques.

Traditional medicine
Traditional herbal therapy has an extensive historical lineage dating back at least 60,000 years. Chinense medicine, Ayurveda, Kampo, traditional Korean medicine, and Unani employ natural substances and provide a great repository of human wisdom. Traditional plants possess a broad range of active chemicals that contribute to their defensive characteristics [7, 8]. Traditional medicine has relied on the usage of medicinal plants for several centuries, making them globally recognized [9]. It has been emphasized that most development nations or less developed nations rely on traditional treatments and medicinal plants as the basis for maintaining good health. Traditional treatments consist of either a single plant, specific portions of plants, or a combination of different plant parts. The potential of these plants relies on the existing knowledge of plant taxonomy, plant parts, and biological properties of medicinal plants, which in turn is influenced by the existence of

primary and secondary metabolites. In most instances, conventional medicine is employed to treat ailments. A wide range of plant components, such as roots, leaves, barks, seeds, fruits, and flowers, are commonly used in traditional medicine throughout many countries with over 80% utilizing this approach [10]. Consequently, when plants are utilized appropriately, they have the potential to preserve lives.

Globally, the prevalence of infectious diseases caused by bacteria, viruses, fungi, or parasites had led to a substantial rise in both illness and death rates. The nation is well-acquainted with the conventional methodology of healthcare, which is especially prevalent in rural regions. With the increasing popularity of herbal drugs, it is crucial to consistently assess any possible pharmacognostic, and optimizing their use. Biologically active chemicals present in medicinal plants have been utilized for ages in traditional medicine to address a range of ailments [11]. The scientific foundation of medicinal plants consistently confirmed the authenticity of the important ethnobotanical medical knowledge. Consequently, rather than relying on existing pharmaceutical drugs that can lead to substantial issues with antibiotic resistance, scientists consistently show a strong inclination towards exploring natural sources such as medicinal plants for the treatment of infectious diseases. The widespread accessibility, affordability, and few adverse effects of plant-based preparations establish them as the primary plants offer a plentiful supply of bioactive compounds that are devoid of unwanted side effects and exhibit potent pharmacological effects [12, 13, 14, 15, 16, 17].

Approaches to drug discovery inspired by traditional medicine

The emergence of microbial resistance is a worldwide problem, despite the pharmaceutical industry's endeavours to create novel antibiotics for the management of many diseases. Developing novel drugs leads through the use of natural resources presents a formidable challenge in the field of drug discovery. It encompasses a broad spectrum of scientific fields, such as biology, chemistry, and pharmacology.

While synthetic drugs and antibiotics have greatly transformed the treatment of different ailments, plants continue to be essential sources of raw ingredients for some vital medications. These plants are gathered and processed before being used. Natural ingredients are extensively found in several natural sources, such as plants, microbes, and invertebrates. A significant proportion of the medications being used in clinical settings are derived from plants. The combination of active chemicals in pharmaceuticals or medications, along with diverse plant components, can synergistically work together to provide the desired effect. This is a valuable advantage of using a whole plant. The increasing expenses associated with prescription pharmaceuticals for personalized healthcare and the exploration of new plant-based drugs have generated interest in medicinal plants as a resurging and for health and well-being.

Infectious illnesses can be transmitted between individuals by direct or indirect means and are caused by harmful microorganisms, such as bacteria, parasites, viruses, or fungi. The prevalence of various infectious agents has increased in recent decades due to rapid population growth, poverty, urban migration, international travel, and environmental changes. Due to the limited assessment of the world's biodiversity for possible biological activity, there are still numerous untapped natural lead compounds with valuable properties that remain to be discovered [18]. Modern medical professionals are actively exploring more effective methods to prevent such unfortunate incidents related to the usage of modern medications. They have decided that utilizing medication produced from traditional and folklore plant-based drugs is the most optimal approach. The secondary metabolites derived from medicinal plants, whether in their pure form or as a combination of compounds, have been found to contribute to various biological functions [19]. Prolonged utilization of antibiotics or chemicals has resulted in the emergence of bacteria with resistant strains [20].

Globalization hinders the transmission of diseases. Disease prevention at a worldwide level is affected by the boundaries set by different jurisdictions, while microorganisms have unrestricted movement around the globe [21]. One prominent instance thus far is the production of anti-inflammatory drug acetylsalicylic acid (aspirin), which is generated from salicin and extracted from the bark of the willow tree *Salix alba* L. Additional instances include morphine, codeine, digitoxin, quinine, as well as the anticancer agent's paclitaxel, vincristine, and vinblastine, among numerous more medications. Moreover, the synthesis of antibiotics by microorganisms was a significant milestone in the field of pharmaceutical exploration during the twentieth century. Nevertheless, the intricate nature of natural molecules necessitates a collaborative endeavour involving several academic disciplines and advanced analytical and technical skills to extract, isolate, identify, and transform them potentially valuable discoveries [18].

Phytochemical

The natural world is rich in secondary metabolites that consist of natural compounds, many of which possess diverse pharmacological properties. Similarly, the exist distinct flora such as plants, trees, herbs, shrubs, and species that possess pharmacological properties and medicinal benefits [22]. The composition of phytochemicals in plants are greatly influenced by several internal and external elements, such as genetic characteristics, the specific plant parts utilized, and the conditions during growth, drying, and storage. Phytochemicals collected can be influenced by stress factors, such as unfavorable climatic conditions and plant diseases.

Phytochemical ingredients are classified into two distinct categories: primary metabolites and secondary metabolites. The initial set of chemicals consists of a crucial metabolite that is essential for the vital processes of plants, whereas the second set primarily serves a supportive function in relation to the external environment [23]. Secondary metabolites are categorized into many classes based on their chemical structures, including phenolics, alkaloids, saponins, and terpenes. Subsequently, groups can be further categorized into many classes and subclasses. Phenolics consists of many compounds such as simple phenolics, tannins, coumarins, flavonoids, chromones and xanthones, stilbenes, and lignans. Terpenes are categorized into six groups: hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, and triterpenes. Additionally, the primary metabolites of lipid category encompass fixed oils, waxes, and essential oils. Carbohydrates can be classified into four

categories: monosaccharides, disaccharides, oligosaccharides, and polysaccharides [22]. The chemical derived from natural sources have yielded several therapeutic agents possessing antibacterial, antiviral, antioxidant, antiulcer, anti-inflammatory, and anticancer properties.

Antioxidant

Antioxidants has the power to eliminate free radicals, which have the potential to harm proteins and DNA, resulting in genetic instability and the development of cancer. The presence of natural antioxidants in the human body can shield it from the harmful effects of free radicals and slow down the advancement of various chronic illnesses. Additionally, these antioxidants can also prevent lipid oxidative rancidity in food products [24]. A crucial focus of current nutrition research involves the exploration of substances that can diminish the generation or responsiveness of reactive oxygen species (ROS). Free radicals can act as either oxidants or reductants, by either donating or accepting an electron from biological molecules [25]. The radicals mentioned are hydroxyl radical, superoxide, hydrogen peroxide, oxygen singlet, and nitric oxide [26]. Antioxidant activity can be assessed using many techniques, both in laboratory settings (*in vitro*) and in living organisms (*in vivo*). The DPPH-based approach is widely used by *in vitro* tests because of its simplicity, rapidity, and affordability [27]. DPPH, also known as 1,1-diphenyl-2-picrylhydrazyl, is an enduring radical that can undergo reduction through the transfer of a hydrogen atom from other molecules. Conversely, *in vivo* tests enable study in circumstances that mimic the natural environment but necessitate the utilization of animal models, particularly mammals, which can be costly and time-intensive. The antioxidant action of plants is attributed to the presence of flavones, isoflavones, flavonoids, anthocyanin, coumarin, lignans, catechins, and isocatechins [28]. Flavonoids, anthocyanins, tannins, phenols, and other plant compounds have the potential to act as antioxidants [29]. Food that are high in antioxidants are crucial in preventing various diseases. Numerous studies have shown that oxidative stress, which can lead to the production of free radicals, plays a significant role in the development of conditions such as diabetes, cancer, neurodegenerative disorders, cardiovascular diseases, inflammation, and age-related problems affecting cells and the skin [30, 31, 32].

Antibacterial

Pathogenic microorganisms, including bacteria, viruses, fungi, and parasites, have resulted in substantial illness and death among populations globally [33, 34]. Over the past two decades, numerous plant species have been assessed for their antibacterial properties. Consequently, the effectiveness of various medicinal plants in treating numerous diseases has been examined in multiple laboratories [35, 36]. Bacterial infections are the primary cause of death and illness on global scale, and the rise of antibiotic-resistant bacteria is currently a significant worldwide issue. Therapies developed from medicinal plants have shown great potential as an effective treatment for stubborn bacterial infections, serving as an alternative to synthetic medications now in use. The majority of infections are linked to oxidative stress caused by free radicals, which are crucial components of aerobic life and metabolism [37]. Plants that contain flavonoid and tannin compounds have effective antimicrobial properties. Tannins are responsible for deactivating the adhesions, enzymes, and cell-enveloped proteins of microbes. Flavonoids, specifically flavones and flavanones, are able to bind to the extracellular and soluble proteins as well as the cell wall of microbes [38, 39]. α-amyrin, betulinic acid, oleanolic acid, and ursolic acid, which are triterpenoids, have been documented for their antibacterial properties [40]. The conventional treatment of diseases with antifungal and antibacterial drugs becomes ineffective in curing patients due to the development of resistance in microorganisms. Numerous researchers have investigated the antibacterial properties of plants in quest of novel substances that could potentially be efficacious in pharmaceutical treatment.

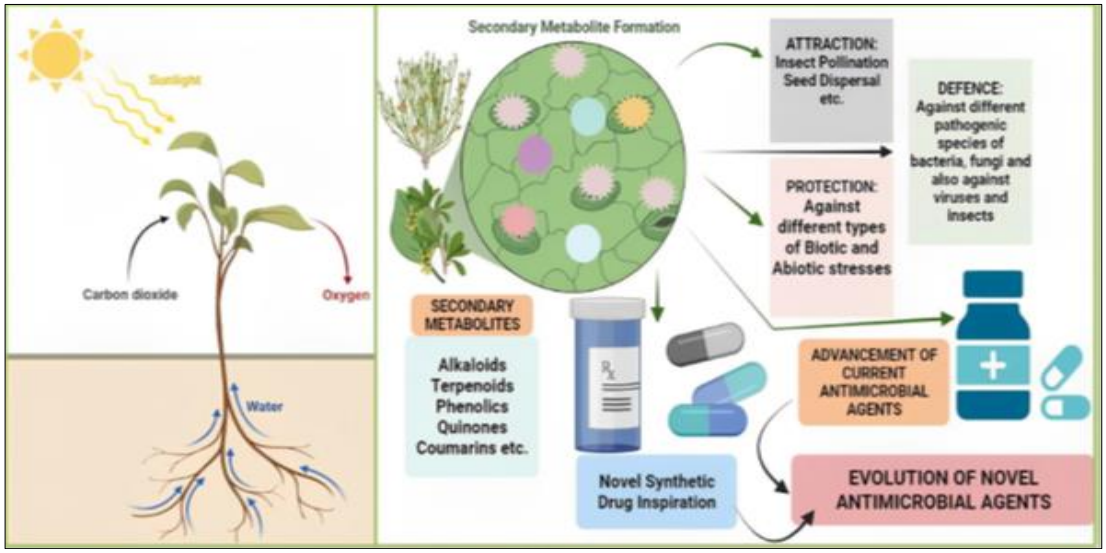

Fig 1: Illustration depicting the process of creating new antibacterial substances derived from several medicinal plants [41]

According to the National Institute of Health (NIH), biofilm formation is linked to more than 60% of all bacterial infections and 80% of chronic bacterial illnesses [42]. Infectious diseases rank as the second most common cause of mortality globally [43]. *Staphylococcus aureus*, a gram-positive bacterium, can cause a range of infections,

including minor skin and soft tissue infections such as impetigo, folliculitis, and cutaneous abscesses, as well as severe and life-threatening diseases such as sepsis, infective endocarditis, toxic shock syndrome, respiratory tract infections, and bloodstream infections [44, 45]. In addition, *S. aureus* has the ability to generate a range of toxins, such as enterotoxins associated with food poisoning, toxic shock syndrome toxin, hemolysin, leucocidin, and exfoliative toxins. These can lead to a variety of diseases, spanning from skin infections to severe, life-threatening systemic conditions [46, 47]. Methicillin-resistant *Staphylococcus aureus* (MRSA) poses significant challenges in terms of treatment efficacy [48]. The development of biofilms during chronic infections is a strategy employed by staphylococci that leads to the ineffectiveness of antibacterial treatment, hence escalating costs and prolonging the patient's recuperation [49]. The ability of *S. aureus* to create biofilms and persisters is a significant factor contributing to the to the development of stubborn infection that are challenging to manage [50]. Recent research has extensively investigated the antibacterial properties of plant extracts, specifically phenols and flavonoids [51]. Gallic acid, a molecule containing ellagic acid found in *Polygonum chinense* L., has the ability to interact with many targets inside the bacterial cell wall. This interaction leads to the disruption of the cell wall structure and hampers the efficiency of the cell wall production process [52, 53]. Antibiotics, which are synthetic antimicrobial agents, are commonly employed for treating infections. However, their excessive and unselective application leads to the development of antimicrobial drug resistance. Consequently, medicinal plants are being explored as alternative therapeutic agents.

Anti-lipidemic

Hyperlipidemia is a prevalent metabolic syndrome that is characterized by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C). These lipid abnormalities contribute to endothelial dysfunction and the development of atherosclerosis, which is the primary risk factor for cardiovascular disease. Elevated lipid levels pose a risk factor for hypertension, coronary heart disease, and cerebrovascular damage. The presence of GST-α was predominantly observed in the centrilobular cells of the liver, indicating a significant concentration in this metabolic region. Consequently, this specific area of the liver exhibited higher susceptibility to injury [54]. TNF-α is commonly observed in animal models of hepatic damage and inflammation. TNF-α, a pro-inflammatory cytokine, plays a key role in inducing apoptosis and necrotic liver damage [55]. HMG-CoAR is a crucial enzyme involved in the synthesis and control of various vital chemicals. Auranofin (AuRF), an anticancer drug, has been demonstrated to inhibit HMG-CoAR, similar to statins, at micro molar levels of half maximal inhibitory concentrations. Statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin cholesterol levels, notably in the treatment of hyperlipidemia. The majority of cases demonstrated that these drugs are well tolerated and possess a finite and generally safe side effect profile. Statins are projected to remain the primary recommended medication for treating hypercholesterolemia in the next years [56]. They inhibit the actions of 3-hydroxy-3-methtlglutaryl-CoA reductase (HMGR), which hinders the production of mevalonic acid. This acid is crucial in the synthesis of cholesterol and acts as a limiting factor. However, this treatment often leads to negative side effects such as gastrointestinal problems, myopathy, and hepatotoxicity and myotoxicity, rendering their utilization unfavorable in certain patients. Consequently, there is a pressing need to explore the usage of medicinal plants as alternative therapeutic agents. Multiple studies have demonstrated a strong correlation between hyperlipidemia and inflammation, which have a substantial role in the development of specific cardiovascular conditions such atherosclerosis [57, 58].

Anti-inflammatory

Inflammation is an immune system response that promotes survival in the face of infection and tissue damage. The body's protective response to physical trauma, harmful chemicals, or microbiological pathogens are important for maintaining tissue homeostasis. Uncontrolled inflammation can result in tissue and cellular damage, chronic inflammation, chronic illnesses, and neoplastic transformation [59]. The conventional indicators of inflammation encompass edoema, erythema, discomfort, and pyrexia [60, 61]. The initial stage of inflammation is a result of the secretion of histamine and serotonin, whereas the later stage is triggered by the secretion of bradykinin, protease, prostaglandin, and lysosome [62]. Ginwala *et al*., have reported that flavonoid-containing compounds can restore normal cellular activity in inflammation-related cells [63]. Saponins have also been documented to reduce the expression of tumor necrosis factor (TNF-α), interleukin-1B, IL-6, and pro-inflammatory cytokines [64]. Inflammation can be categorized as either acute or chronic. Chronic inflammation leads to the excessive synthesis of many substances, including reactive oxygen (ROS), nitrogen species (RNS), cyclooxygenase (COX), and cytokines [65]. Inflammatory cell activation results in an upsurge in intracellular signaling via cascades that involve tyrosine kinases and inhibitor of κB kinase (IKK). This activation subsequently triggers the nuclear transcription factor (NF)-κB and promotes the expression of different inflammatory genes, including inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) [66, 67, 68, 69]. Consequently, a variety of substances that cause inflammation, such as nitric oxide (NO) and prostaglandin E2 (PGE2), as well as pro-inflammatory proteins, are released. These substances attract other inflammatory cells, triggering the production of enzymes that break down molecules and toxic substances [70].

Oxidative stress is a pivotal factor in the progression of numerous chronic diseases associated with ageing [71]. Moreover, there is a strong correlation between oxidative stress and inflammation, as they are interconnected pathophysiological mechanisms [72, 73]. Phytochemicals extracted from plants exhibit several biological actions, one of which is their anti-inflammatory function [74]. Research has indicated that naturally occurring chemicals may influence inflammation processes by regulating the biology of macrophages [75]. Inflammation is closely associated with a variety of conditions, such as diabetes, cardiovascular diseases, chronic respiratory diseases, arthritis, cancer, and obesity [76]. In the present era, the majority of inflammatory illnesses are managed using standard anti-inflammatory

medications, such as steroidal and non-steroidal anti-inflammatory agents. Nevertheless, prolonged usage of these medications can result in a range of negative effects associated with pharmaceuticals, such as gastrointestinal diseases, immunodeficiency, and abnormalities in humoral functions [77]. Numerous endeavors have been made worldwide to develop synthetic drugs. However, many of these drugs have been found to exhibit various side effects. In contrast, the analysis of plant-derived medicinal products has revealed their remarkable ability to either have no side effects or very minimal ones, which is unparallelly compared to the side effects exhibited by synthetic drugs [78, 79]. Although there have been significant advancements in medicines for cancer, hyperlipidemia, and inflammation, none of these diseases have a permanent cure. Hence, it is essential to investigate and discover novel potential drug derived from a range of natural sources [80,81].

Molecular docking

Molecular docking is a computational technique used to predict the binding affinity and orientation of a small molecule (ligand) to a target protein or receptor. The process of drug development is arduous and time-consuming, encompassing several stages such as target identification, validation, lead optimization, preclinical trials, clinical trials, and post-marketing surveillance for medication safety.

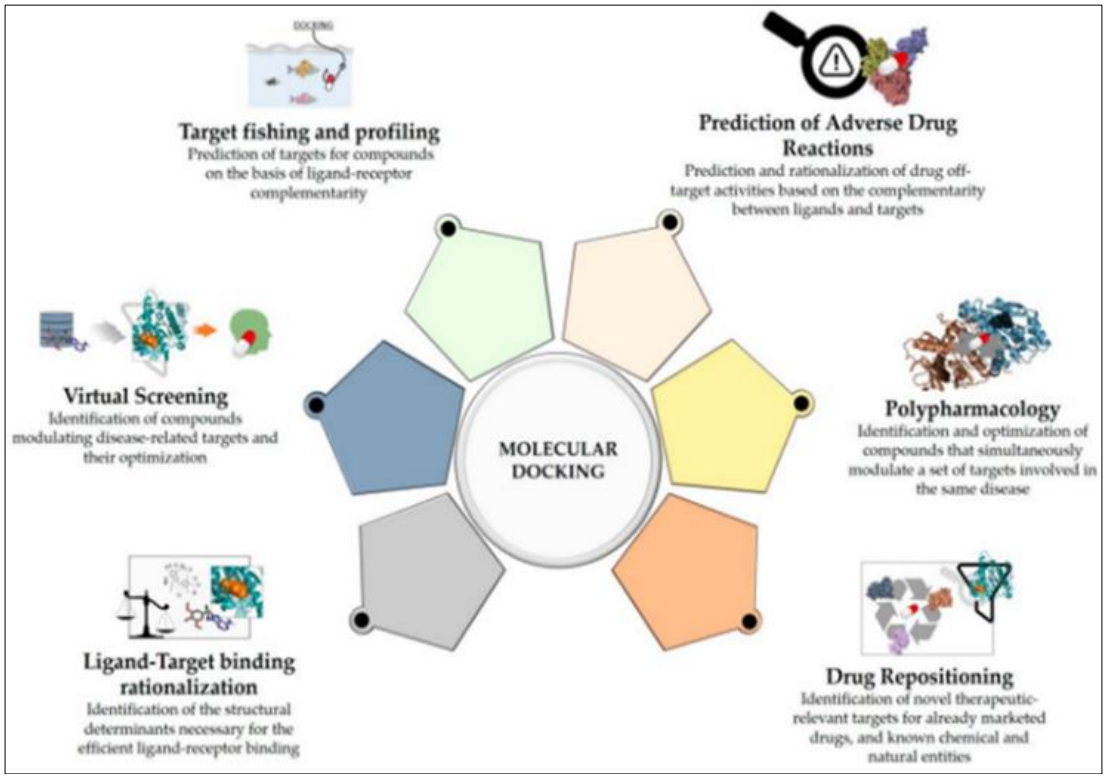

Fig 2: Illustrated the primary uses of molecular docking in contemporary drug development [82]

Molecular docking is a computer approach that allows us to virtually screen compounds, providing us with an initial assessment of the ligand's activity potential against biological targets. According to an estimate, the overall mean expense of producing a novel medication is within the range of $2 billion to $3 billion. Additionally, it requires a minimum of 13-15 years to complete the process of bringing a drug to the market, starting from the original discovery phase until it receives approval. The utilization of computer aided drug designing (CADD) is an essential method for creating secure and efficient medications. It is commonly employed to decrease expenses, save time, and accelerate the first phase of developing novel physiologically active compounds [83].

CADD methods, such as pharmacophores modelling, molecular docking, inverse docking, chemical similarities (CS), quantitative structure activity relationship (QSAR), virtual screening (VS), and molecular dynamics stimulations, have been highly effective in predicting the therapeutic effects of potential drugs or compounds and saving valuable time. Originally designed for studying molecular recognition large and small molecules, this technique has now become effectively employed in various aspects of drug discovery programmers. These include hit identification and optimizations, drug repositioning, target identification, multi-target ligand design and repositioning (Figure 2). CADD is a valuable and necessary approach for developing medications that are helpful in treating human ailments [84]. Pharmacophores searches, protein-ligand interaction fingerprinting, or protein docking can be employed. These strategies are only applicable to targets that have clearly defined structures. Various internet servers, such as TarFisDock, INVDOCK, and idTarget, have been created specifically for this objective. Nonetheless, the reliability of these methods that rely on docking is contingent upon the effectiveness of the scoring algorithms used and the accessibility of high-performance supercomputers [85]. Furthermore, CADD plays a crucial role in forecasting the absorption, distribution, metabolism, excretion, and toxicity of drugs [86].

Conclusion

Traditional medical methods have been extensively employed throughout, including in India. Natural products serve as a primary reservoir for the exploration and identification of new drugs. The wide range of secondary

metabolites found in medicinal plants accounts for their various pharmacological effects, leading to the utilization of numerous species from this family in traditional medicine. Subsequently, the application of computationally methods has resulted in the identification of numerous pharmaceuticals that have successfully undergone preclinical testing, subsequently emerging as innovative therapies for a wide range of medical conditions. In addition to providing relevant information about its significance for the advancement of biotechnological approaches, the current study also discusses the preservation and application of natural medicinal herbs.

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