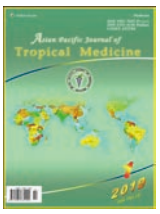

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Perspectives and challenges of tropical medicinal herbs and modern drug discovery in the current scenario

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ABSTRACT

Tropical diseases such as malaria, tuberculosis, trypanosomiasis, and leishmaniasis, account for a large number of deaths annually. Herbs are an excellent source of tropical medicines. Many advancements and discoveries have taken place in the field of drug discovery but still, a major population of tropical diseases relies on herbal traditional medicine. There are some challenges related to policy implementation, efficacy, resistance and toxicity of tropical medicines. There are many tropical diseases such as such as schistosomiasis, leishmaniasis, African sleeping sickness, filariasis and chagas disease which are neglected because very few pharmaceutical companies have shown their interest in developing therapeutics against these diseases of poor people. There are many benefits associated with herbal medicine such as the cost of production, patient tolerance, large scale availability, efficacy, safety, potency, recyclability, and environment friendly. A large number of natural extracts such as curcumin, artemisinin, morphine, reserpine, and hypericin, are in use for treatment of different tropical diseases for a long time. The current review is to discuss the overview of tropical medicinal herbs, its scope and limitations in the modern drug discovery process.

1. Introduction

1.1. Study of herbal drugs in the light of modern drug discovery

Natural products extracts are of paramount importance because of their therapeutic relevance and structural and chemical diversity. Literature survey shows that there are approximately 130 life-saving drugs which are phytochemicals isolated from different medicinal plants. Such life-saving drugs have been found in about 6% of the total available medicinal plants. Undoubtedly the vast world of global fauna and flora are to be explored for finding the core molecules based on which the probable cure can be found for several deadly diseases like cancer, AIDS and diabetes *etc*[1].

The study conducted by Cravotto *et al.* in 2010 surveyed commonly available 1 000 plant-derived products marketed in western countries and revealed that only 156 out of these products could succeed for clinical trial publications. Overall fifty products were reported for preclinical studies, and the remaining 12% of the products were found to be of no substantial importance for the study of their properties. The pieces of evidence suggested that five compounds out of the total obtained products were highly toxic and their use is forbidden. However, nine plants were found to be of clinical importance for use as therapeutics[2]. According to World Health Organization, about 75% of the world population rely on the use of such traditional medicinal system and plant-derived products are used prominently[3,4]. Till date, many drugs with clinical importance having worst side effects are given in Table 1. The optimization of such drugs can be possible with the help of modern drug discovery approach to design their potential analogues/derivatives with lesser toxic/side effects.

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Table 1
Potential drugs with their clinically known toxic/side effects[5-13].

Types of medications	Name of drugs	Toxic/side effects
Psychiatric medications	Olanzapine (zyprexa), quetiapine (seroquel), haloperidol (haldol), zolpidem (ambien), eszopiclone (lunesta), clonazepam (klonopin), lorazepam (ativan), ropinirole (requip)	Hallucination[5,6]
Antidepressants	Trazodone (desyrel), clozapine (clozaril), hydroxyzine (atarax), chlorpromazine (thorazine), prazosin (minipress), sertraline (zoloft), fluoxetine (prozac), paroxetine (paxil)	Memory loss, priapism (an unwanted, painful, persistent erection that is not caused by sexual stimulation)[7]
	montelukast (singulair), isotretinoin (claravis), varenicline (chantix), mefloquine (lariam)	Suicidal behavior[8]
Anti-Parkinson's disease and restless legs syndrome	Requip, carbidopa-levodopa (sinemet), aripiprazole (abilify)	Compulsive behaviors[9]
Antihyperuricemic	Allopurinol (zyloprim), acetaminophen (tylenol), barbiturates	Stevens-johnson syndrome[10]
Anticoagulant and immune system suppressant	Warfarin, divalproex (depakote), paxil, topiramate (topamax), methotrexate (rheumatrex)	Birth defects[11]
Antidiabetic	Pioglitazone (actos)	Increased risk of bladder cancer[12]
Antipsychotic	Seroquel, zyprexa, sotalol (betapace), amiodarone (cordarone), procainamide (procanbid), morphine, adderall	Death (sudden cardiac arrest)[13]

1.2. History of traditional medicine

Drug is a medicine or a substance which has a physiological effect when introduced into the human body. Medicine improves or restores health from illness through prevention, mitigation or complete treatment. Since ancient times, all the human societies have firm beliefs in the medicinal system that provides explanations for birth, diseases and their treatment and death[14]. Early records on ancient medicinal systems have incorporated plants (herbalism), animal parts and minerals to treat various diseases worldwide. Herbs are substances derived from natural plant resources, that were used for the treatment of various diseases and its history is as old as human civilization. From the previously documented literature, it has been clearly described that most of the medicinally active substances were identified in Egypt, Greece, China, and India. In China, the plant products were used in the form of crude extract since 5000 B.C. The oldest known script (Pen ts'ao) was written in around 2 700 BC by an emperor Shen-Nung which contained 365 drugs, one for each day of the year[3].

Ancient Indians worked meticulously on herbs which they came across and classified these into classes known as Gunas. Today the large population of India depends on Ayurveda 'an ancient science of life'[15]. Ayurveda is based on two textbooks, Charaka Samhita, dealing with etiology, symptomatology, pathology, prognosis, and medical management of disease, and Sushruta Samhita dealing with surgical procedures (1000 years B.C.)[16].

In 1 800 AD, Fredrick Surterner first isolated morphine from opium plants and this gave the idea about natural product chemistry. In the modern times, many other similar developments took place *viz.* the use of cinchona bark extract (*Cinchona officinalis*) in the 17th century for the treatment of enteric fever; digitalis for the treatment cardiac problems and the use of coca tree leaves by Andean cultures to name a few. Later in 1860, cocaine was isolated as a chemical responsible for the local anesthetic activity. Traditionally pineapple juice was used by American Indians to reduce inflammation in wounds and other skin injuries. However, it was followed later on, by isolation of an enzyme from the fresh juice of pineapple that broke down proteins (bromelain) and was found to break down blood clots in 1891 *etc.* Several phytochemicals used previously in traditional medicine are now being recognized in modern clinical practice[17,18]. Today a plethora of knowledge about therapeutics of medicinal plant products and its application has accumulated through either experiences or knowledge evolved and passed from generation to generation among tribal people. The crude extracts of plant products can be a starting material for the extraction, isolation or synthesis of conventional drugs. The introduction of first synthetic pharmaceutical product aspirin in 1897, a derivative of acetylsalicylic acid a plant-based drug used for the treatment for pain, inflammation, and fever, compelled human beings to believe in the natural wonders and their diverse floristic wealth[3,19-22]. For metabolic processes in plants, a large number of chemical compounds known as phytochemicals are formed which are further divided into three classes[23]: (1) Primary metabolites: sugars, lipids, and fats *etc.*; (2) Secondary metabolites: these are compounds frequently formed for defense or other specific purposes. Alkaloids, terpenoids, glycosides and natural phenolic compounds *etc.*; (3) Some secondary metabolites are toxins, pigments, and pheromones which can be modified to make useful drugs. Traditional Knowledge Digital Library established in 2001 contains a few lakh medicinal formulations.

1.3. Limitations of traditional herbal medicine

It is estimated that about 7 500 plants are used traditionally in local health care system, mostly in rural and tribal villages of India, out of these, approximately 4 000 plants are either little known or unknown to the majority of the population. Classical and indigenous systems of medicine in India such as Ayurveda, Siddha, Tibetan, and Unani have till today information of only approximately 1 200 plants[19,23,24].

The preparation of a medicine in these above-mentioned systems is mostly based on plant extracts containing diverse types of chemical substances which act synergistically or in other words these crude drugs are complex mixtures of a large number of biologically active substances that are integrated to make crude drug function as a single agent. For the purpose of proper use of plant extract as a crude drug, the isolation of biologically active principles and the determination of their individual functional structures and pharmacological investigation have to be carried out[25].

In Ayurveda generally, crude plant extracts are used, which despite their potency have no scientific backing. Systemic scientific studies

can dispel these apprehensions. Detailed toxicity studies in the light of modern findings can make these herbal preparations more acceptable to the western world. However, Ayurveda is not only restricted to herbalism but has wider applications. In Ayurveda heavy metals such as arsenic, mercury and lead are sometimes employed in extremely lower doses since these have more precise targets in the human system. Some such preparations exported from India to the U.S. have been shown to contain these metals beyond the permissible limits[26]. Due to several stringent restrictions imposed by U.S. Food and Drug Administration, there is a ban on the import of certain Ayurvedic preparations during the last few years[27].

In case the popular doubts prevalent regarding herbal drugs are dispelled by modern researches, these problems can be solved. Certain confusions like same popular names for herbal products from different origin, subtle differences in structures of products isolated from plants growing under different environmental conditions, variations in the methods of collection, extraction, processing and storage and lack of information regarding the toxicity of the products, have to be clarified through modern tools and techniques.

Modern drug discovery approaches reduce the risk of failure and toxicity and help in identification of compounds with the high rate of success during clinical trials. Advances in the methods of compound screening and lead optimization have sped up the process of drug discovery because both to identify the compounds with high affinity for the target as well to know the site and strategy of modification are very important.

2. Computer aided drug designing (CADD)

The current scenario with the cracking of human genome sequence at the beginning of the present century opens up a new era in drug development processes and furnishing new gene products or pathways as new targets that were previously not discovered[27,28]. The modern computer-aided drug discovery is one of the robust and money-saving approaches for the designing of novel drugs. In contrast, previous methods for the development of new drugs took a large number of human resources, money and also lots of time. It is very common to do high throughput screening of a large number of small molecule library against selected biological targets to get a potential lead for further modification accordingly by doing testing against cell lines and then *in vivo* testing for its efficacy[29]. Due to the involvement of many computation techniques researchers have been able to know the involvement of atoms of a ligand with the atoms of a receptor for its interactions and that can be used for the designing of future drugs.

In modern approach for drug discovery the identification of lead is done after virtual screening, lead optimization to increase the affinity, selectivity, efficacy/potency, oral bioavailability and, metabolic stability (to increase the half-life). The leads which fulfill the above-mentioned criteria are used further in drug development process and then finally go to clinical trials (Figure 1). Currently, the pharmaceutical industry is changing rapidly as new diseases and targets are discovered, giving rise to the necessity of finding more specific drugs. Scientists are trying to go beyond all this as for personalized medicine. There is always need to develop novel potent drugs against many deadly diseases due to resistance development of pathogens[30-32]. Previously finding a drug candidate against particular disease was based on hit and trial methods and a large proportion of such drugs failed at the final phase of clinical trials, so the total cost to launch one drug for public use was about the 4 to 8 hundred million US dollars. But due to advancement and application of computers in our daily life, the process of drug designing is optimized with respect to time, cost, and human resources. The current cost is about the 2 to 4 hundred million US dollars to launch one drug in the U. S. The computational based drug designing and discovery techniques are aimed at the systematic study of the effect of small/drug like molecules on different targets and attempts to optimize their potency[33].

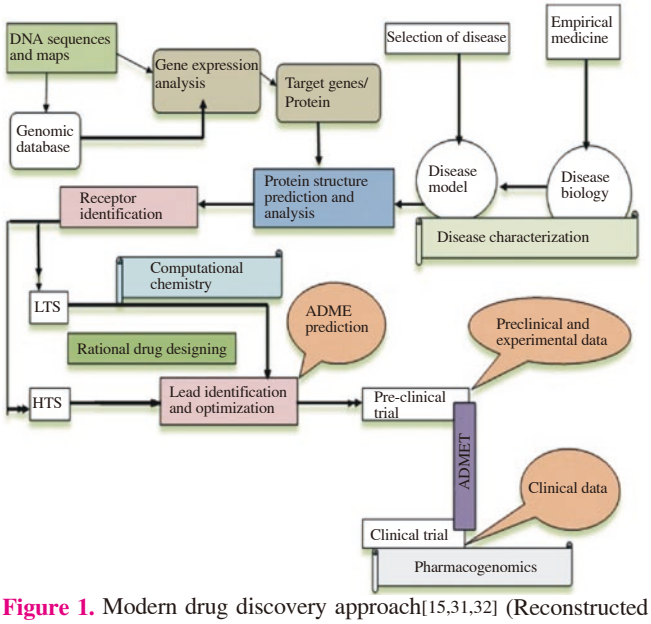

Figure 1. Modern drug discovery approach[15,31,32] (Reconstructed and modified).

2.1. Drug designing process

Till date many computational methods have been discovered and applied all over the world very efficiently. These methods include the use of different biologically important databases (PDB, ZINC *etc*), virtual screening *via* docking simulation, molecular modeling, quantitative structural activity relationship (QSAR), ADMET filtering, similarity searching, data mining, molecular dynamics, pharmacophore study, use of visualization tools, network analysis tools etc. to predict biological activity of new derivatives without wet lab testing[34]. The generation of data *via in silico* study is very large. The importance of QSAR was understood during 1960's. This resulted in the emergence of CADD. Lead molecules from different plants, animals or microorganisms, known for their medicinal properties by experience over the ages form the basis of such studies. Some anticancer drugs like paclitaxol, vincristine and vinblastine are such examples. Some drugs like sildenafil were a well-designed drug for clinical trials of cardiovascular diseases. Most of the drugs have been discovered by SAR. Rationale designing of drugs started only in 1980's and systematic screening was initiated in 1990's (Figure 2).

In CADD, also known as computer-assisted molecular design, drugs can be designed computationally by using the following two strategies.

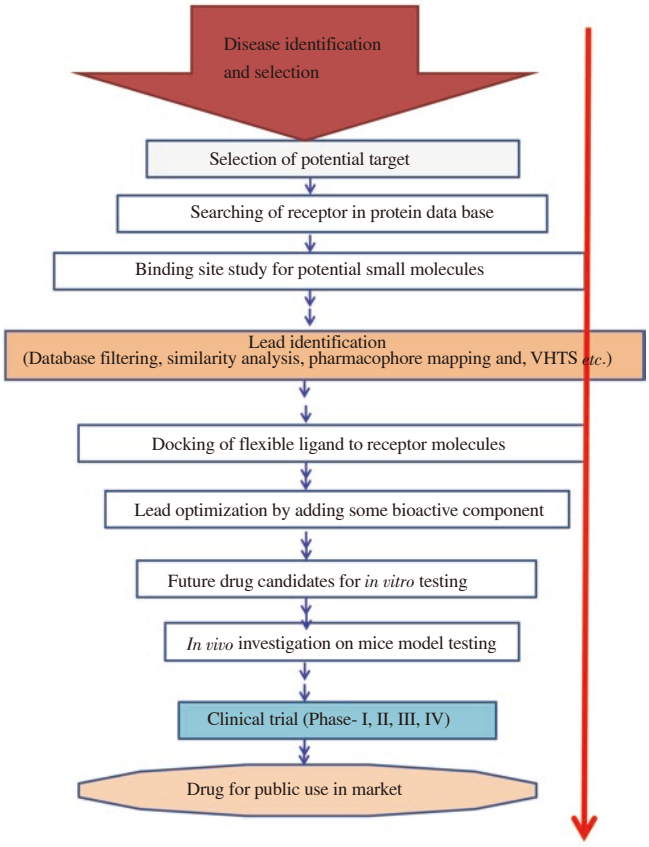

Figure 2. Flow diagram of CADD[32,34] (reconstructed and modified).

2.2. Ligand based drug designing

There are only two known bio-physical methods so far for structural determination of proteins, *viz.*, nuclear magnetic resonance and X-ray crystallography. The structures of most of the target proteins specifically membrane proteins is unknown due to the limitation in getting their X-ray crystallographic structures. In such cases, the homology modeling approach is adopted and studies are carried out using the probable model. A lead molecule or active ligand is found, which guides the drug design process. This approach is based on analysis using sets of biologically active ligands. Pharmacophore designing guides the approach. Phamacophoremodelisa set of points in space with certain specific properties and distances between them, which are responsible for binding of given set of ligands with the target. The classical concept of QSAR is helpful to a very great extent for designing analogs of known ligands. However, the 3D-QSAR has an additional advantage of considering the 3-D stereo structures of compounds and therefore is an improved method for predicting the pharmacological activity of different chemical compounds with greater precision[35].

2.3. Structure based drug designing (SBDD)

This approach uses multiple procedures prevalent in the rational drug design and pharmaceutical research. The main aim of SBDD is to identify active small molecules specifically peptides which are capable of site-specific binding at key positions of biologically relevant targets, *eg.* enzymes or receptors. The necessary condition is that the three-dimensional structures (3-D structures) of these moieties should be known[36]. The 3D structures of receptors/targets are downloaded from the protein database. Complete information regarding the 3-D structural configuration of these macromolecules is available in these databases since it is derived from X-ray crystallography or nuclear magnetic resonance spectra. Where such structural information is not available, homology modeling is resorted to[37].

2.4. Success story of CADD

The beginning of the present century started with cracking of the human genome which opened a pandora box for identification of molecular targets for various diseases which resulted in tremendous progress in the field of drug designing. The increasing number of successful applications of drug design has led to the discovery of new therapeutics. There are an enormous amount of ligand based drug designing and SBDD approaches that have been already in practice to derive more potent drug molecules. The first pioneer and unequivocal example of the application of structure-based drug design resulting in an approved drug are, dorzolamide the carbonic anhydrase inhibitor, which was approved in 1995[36-38]. Another very important case study in the area of rational drug design is imatinib, a tyrosine kinase inhibitor which was designed specifically for the bcr-abl fusion protein and is substantially efficacious. Imatinib targets only cancerous cells by differentiating between normal and tumor cells which makes it better than other known drugs targeting all the dividing cells. Additional examples include atypical antipsychotics cimetidine, the prototype H_2-receptor antagonist from which the later other members of the class were developed. Selective COX-2 inhibitor nonsteroidal anti-inflammatory drugs that reduce pain; enfuvirtide, a peptide HIV entry inhibitor; antiviral drug such as zanamivir, and, HIV Integrase inhibitor *eg.* isentress[39] are some more important examples.

2.5. Limitations of CADD

Computer-aided drug designing uses computational approaches for searching, analyzing, screening and optimizing the activity of compounds. The predictive accuracy of these approaches and tools depends on the significance of parameters used in predictions. In recent years, many new parameters related to ADMET and other problems came into existence and they should be incorporated in the tool to increase the accuracy of prediction. Improvement in software used for 3D structure visualization is also required for better understanding of receptor-ligand interaction which may further guide the desired changes in the ligand in order to achieve the goal of drug discovery. There also exists a possibility to include some other physiological parameters in molecular dynamics simulation for better understanding and dynamic mapping of changes occurring during the receptor-ligand interaction.

3. Current status and future perspective

Neglected tropical diseases (NTD) are a group of 17 diseases transmitted by virus, protozoa, helminths and bacteria[40]. The drugs available are toxic, less efficacious and there are reports of

resistance. Medicinal chemistry approaches such as molecular modelling, synthesis of novel series of molecules, biological activity evaluation and structure-activity relationships tools can guide us to design potential drug. NTD such as schistosomiasis, leishmaniasis, African sleeping sickness filariasis and Chagas disease, devastate the lives of poor people's living in Africa, Asia and the Americas. Treatments for these diseases are not very effective and often highly toxic. Pharmaceutical companies have a limited commercial interest in developing therapeutics for these poor patient populations. The Sandler Centre for Drug Discovery at the University of California, San Francisco grant funding for designing of new therapeutics for treatment of several of NTDs. Cathepsin-like cysteine proteases that play a critical role in parasite biology of NTDs[41]. In *Trypanosoma cruzi* (Chagas disease), the cysteine protease cruzain, a close homolog of human cathepsin L, expressed in all lifecycle stages and play important role in nutrient processing, immune evasion and differentiation. There is need to investigate new targets that are specific to the parasite or to the host–parasite interaction.

Major tropical infectious diseases, namely, malaria, tuberculosis, trypanosomiasis, and leishmaniasis, account for more than 2.2 million deaths annually[42]. The application of computational technologies in drug discovery at the hit identification, hit-to-lead, and lead optimization stages can speed up the process of discovery and also reduces the risk of drug failure. Most drug discovery strategies rely on high-throughput screening of synthetic chemical libraries using phenotypic and target-based approaches[43]. Combinatorial chemistry libraries lack the structural diversity required to find entirely novel structure. Natural products have a unique chemical diversity that can serve as excellent templates for the synthesis of novel, biologically active molecules. Frequent appearance of chemo-resistance for tropical diseases is a big challenge which suggest the need of new drugs against these diseases. Metal compounds can serve as a new leads against malaria, leishmaniasis and trypanosomiasis[44]. A few metal-based drugs are available in this therapeutic area, and others are in process of development. Identification of molecular targets for the disease can guide us in developing mechanism-based metallodrugs. The use of metal complexes as drug against tropical diseases appears as a very attractive treatment alternative[45]. A number of potential metal-based drugs are available for the treatment of tropical diseases such as trypanosomiasis, malaria, and leishmaniasis. New vectors (micro and nano-particles, mesoporous materials) can cross host or parasite natural barriers and can deliver the drug to the target site with a minimum dosage and less side effects[46].

The modern drug discovery process is mainly based on the exploration and selection of naturally occurring lead molecules on the basis of their well known medicinal applications and safety. Among the different herbal compounds 'curcumin', the yellow pigment of turmeric alone has been selected as a lead molecule based on its prolific therapeutic activity reported in literature against cancer and plethora of other illnesses[47].

From literature search it has been found that more than sixty-five hundred publications is available in PubMed, and approximately fourteen thousand articles have been documented in google scholar in last five years on curcumin, a molecule surpassing all others herbal molecules. The enormous amount of literature available on cancer alone in PubMed shows its importance and attention of the scientific community. Among the most prevalent cancers, the literature of breast cancer is highest compared to other diseases like AIDS and TB *etc.* This shows how it affects the women population worldwide (although reported in men also) and appeared as a major cause of women mortality. Breast cancer is a very lethal disease because of its heterogeneity in terms of morphology, biological features, clinical characteristics and different types of prognostic and therapeutic implications[48,49].

Highly advanced and meticulous research works are going worldwide on various therapeutic applications of curcumin in multiple myeloma, lowering of blood cholesterol, cervical cancer, pancreatic cancer, prevention of low-density lipoprotein oxidation, myelodysplastic syndromes, suppression of symptoms associated with type Ⅱ diabetes, colon cancer, psoriasis, HIV, protection from pulmonary toxicity, fibrosis and Alzheimer's disease[50-52]. The role of different herbs, their composition and applications are given in Table 2.

Table 2

Composition and applications of herbal products[57,58].

S. No.	Product name	Plant/Composition	Applications
1.	OraMagic Rx	*Aloe vera*	Cold sores, psoriasis[53]
2.	Ellura	Berry fruit (North America)	Urinary tract infection[54]
3.	Valerian	Root of Valerian	Insomnia[55]
4.	Azo-Cranberry	Berry fruit (North America)	Bladder infection, pain[56]
5.	5-HTP	Seeds of *Griffonia simplicifolia* (African plant)	Depression, fibromyalgia[57]
6.	EGb 761	Extract of *Ginkgo biloba* leaves	Antioxidant, cancer, diabetes[58]
7.	VP-PRECIP	Flaxseed oil, evening primrose oil and bilberry extract	Dry eye syndrome, blepharitis[59]
8.	Vitadirect Turmeric Plus	*Turmeric curcumin*, curcuminoids	Anti-inflammatory[60]
9.	Hofels ginger one a day	Ginger root	Motion sickness, nausea/vomiting[55]
10.	Aloven	*Aloe vera*	Skin inflammation, radiation dermatitis[61]
11.	Forever living Aloe vera gel	*Aloe vera*	Healthy digestive system[62]
12.	Chenopodium album Linn	Chenopodium oil (seed, leaves)	Anthelmintic, diuretic, nutritive[63]
13.	LG Asafoetida-Hing Powder	*Ferula asafoetida* (Hing)	Stomach disorder, skin problems, cough and asthama[64]
14.	Adelphane	Reserpine, dihydralazine sulphate	Antihypertensive and antipsychotic[65]
15.	MS-IR	Morphine	Analgesics[66]
16.	Garlic	*Allium sativum*	Anti-inflammatory, immunity, cardiovascular diseases[67]
17.	Minvital	Ginseng, vitamins and minerals	Digestion, inflammation and infection of intestine and colon[68]
18.	Jarrow formulas milk thistle	Milk thistle from *Silybum marianum*	Liver diseases[69]
19.	Medisys-Saw Palmetto	Saw palmetto from *Serenoa repens*	Prostate gland problems[70]
20.	St. John's wort	Hypericin from St. John's wort (*Hypericum perforatum*)	Depression, menopause and wound healing[70]

Apart from these clinical studies, it is also suggested that curcumin has antioxidant, amyloidal, anti-inflammatory, antiarthritic, antimalarial, and various other therapeutic properties[70,71]. Curcumin having a number of different targets, however, it lacks optimal pharmacokinetic profile which is a very big drawback for considering it as a drug so far[72].

The natural herbs are the excellent source of lead for drug discovery. Many metabolites from different parts of the herbal plant have not been screened for their biological activity. The use of computational methods has reduced the cost, time, labor and risk of failure in drug discovery. But, still, the possibility for the improvements in the accuracy of prediction and analysis tools exists. In future, new approaches for drug discovery from the herbal substance may come into existence, which may be boon for the people suffering from the complex and incurable diseases.

Conflict of interest statement

The authors declare that they have no conflicts of interest

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