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Natural Products in Drug Discovery: Approaches and Development

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Authors' contributions

This work was carried out in collaboration among all authors. All authors made substantial contributions to conception and design, acquisition of data and interpretation of data, took part in drafting the article and agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Historically, natural products (NP's) have played a significant role in drug discovery, not only in cancer and infectious diseases, but also in other therapeutic areas including cardiovascular diseases and multiple sclerosis. Profit and loss, Partnerships and averages, natural products also present certain challenges for drug discovery, such as technical obstacles to screening, isolation, characterization and optimization, which added to decline in their search by the pharmaceutical industry from the 1990s onwards. In recent days the applications of molecular biological techniques have increased the availability of novel compounds that can be conveniently produced in bacteria or yeast or plant sources. In addition to this, combinational chemistry approaches are being based on natural product scaffolds to create screening libraries that closely resemble drug-like compounds. Employing these technologies gives us a chance to execute research in screening

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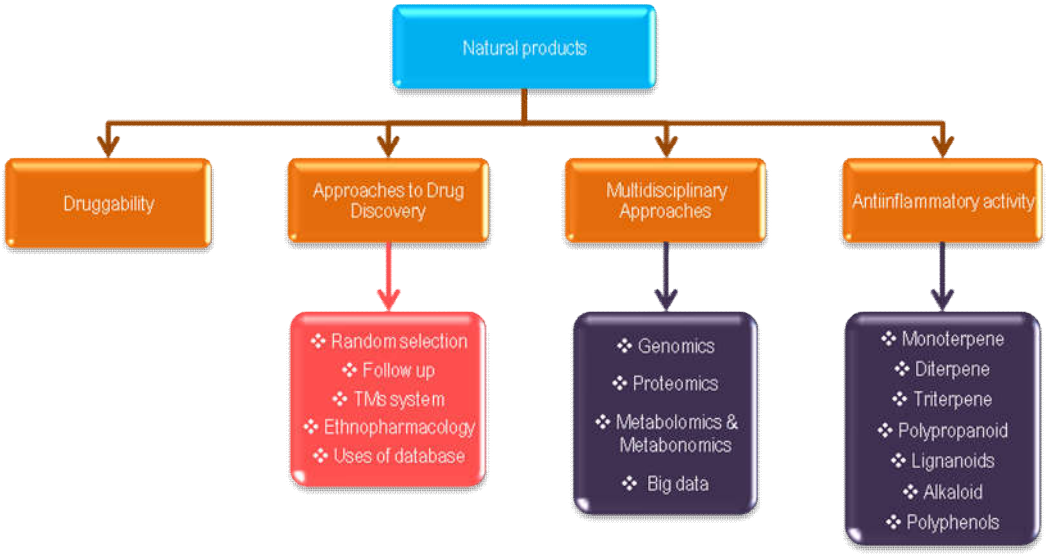
new molecules by means of a software and data base to ascertain natural products as a major source for drug discovery. It lastly directs to lead structure discovery. This review discusses plant based natural product drug discovery and how innovative technologies play a role in next generation drug discovery and highlights from the published literature on plants as sources of antiinflammatory agents.

GRAPHICAL ABSTRACT



Keywords: Drug discovery; natural products; traditional medicine; antiinflammatory.

1. INTRODUCTION

The practice of plants as medicine goes backside to the period of early humans. Fossil proceedings date back human use of plants as medicines as a minimum to the middle Paleolithic age. Confirmation of this an early association have been originated in the grave of a Neanderthal man buried 60000 years ago. The earliest recognized medical document is a 4000 year old Sumerian clay tablet that traced plant remedies for a multiplicity of illnesses. By the time of the ancient Egyptian civilization, an immense wealth of information previously existed on medicinal plants. For nearly 3500 years, this information, along with the hundred of other remedies, has been preserved in the *Ebers papyrus* [1,2,3].

The growth of systematic pharmacopoeias dates back to 3000 BC, when the Chinese were previously making use of more than 350 herbal remedies. China has established the best use of conservative medicine in providing health care. Ayurveda, a system of herbal medicines were extensively practiced in India. Sri Lanka and Southeast Asia has more than 8000 plant remedies and was nearly 35,000 to 70,000 plant species [4].

Among the very old civilization, India has been known to be the richest granary of medicinal plants. On the subject of 8000 herbal medication have been codified in Ayurveda. The **Rigveda** (5000 BC) has recorded 67 medicinal plants, the **Yajurveda** 81 species, the **Atharvaveda** (4500-

2500 BC) 290 species and the **Charaka Samhita** (700 BC) and **Sushruta Samhita** (200 BC) have described properties and makes use of 1100 and 1270 species, respectively, to compound the drugs and use. They are still used in the traditional formulation of medicine in the Ayurvedic system of medicine [4]. Snakeroot or *Rauwolfia serpentina,* which has been in use for centuries together for its sedative effects is one useful plant from Ayurveda knowledge. Today the active components in snakeroot are widely used in Western medicine too be effectively treat high blood pressure [1]

The number of higher plant species (angiosperms and gymnosperms) on this planet is estimated as 2,50,000 with a lower level at 215,000 and an upper level as high as 500,000 (5,6,7,8,9]. Of these, only about 6% have been screened for biological activity, and a reported 15% have been evaluated phytochemically [10].

Before the initiation a high throughput screening and the post genomic era, more than 80% of drug materials were solely natural products or were inspired by the molecule obtained from natural sources (including semi-synthetic analogs). An examination into the sources of new drugs from 1981 to 2007 discloses that since 1994 were based on natural products almost half of the drugs were agreed. For occurrence, plants, microorganisms and animals produce small molecules, which have played a chief role in drug discovery. Among 69 small molecule new drugs recommended from 2005 to 2007 worldwide, 13 were natural products or created from natural products, which underlines the consequence of such products in drug research and growth (11,12].

There are a choice of examples of growth of new drugs from the plant sources. Morphine was isolated from opium manufactured from cut seed pods of the poppy plant (*Papaver somniferum*) roughly 200 years ago. Pharmaceutical research advanced after the Second World War to include huge screening of microorganisms for new antibiotics, stimulated by the detection of penicillin. Few drugs developed from natural sources have certainly revolutionized medicine like antibiotics (eg. penicillin, tetracycline, erythromycin), antiparasitics (eg. avermectin), antimalarials (eg. quinine, artemisinin), lipid control agents (eg. Lovastatin, analogs), immune-suppressants for organ transfers (eg. cyclosporine, rapamycins), and anticancer drugs (eg. paclitaxel, irinotecan) [13].

Over the past 50 years, there has been a great variety of new drugs expanded using high-throughput screening techniques and combinatorial chemistry; nonetheless, natural products and their resultant compounds have continued to be highly-important constituents in pharmacopoeias. Of the reckoned 250,000-500,000 existing plant species, only a minute proportion has been systematically researched for bioactivities [12]. Chemical trials are ongoing on more than 100 natural manufactured goods derived drugs and at least 100 molecules/compounds are in preclinical stage [13]. Most of these molecules in the developmental pipeline are derivated from leads from plants and microbial resources. There are six classes of sources for innovative chemical entities in common. The four classes are the following: botanical sources, fungi, bacteria and marine sources. Besides these four classes, modern pharmaceutical chemistry added two categories of man-made substances. They are synthetic chemistry and combinatorial chemistry. Of these natural sources, botanical sources are of obvious importance in the background of this review. The botanical sources are known to provide the subsequent classes of new chemical entities for drug discovery processes.

a) to separate bioactive compounds for straight use of drugs e.g., digoxin, taxol, vinblastine, digitoxin, morphine, reserpine, vincristine.

b) to make bioactive compounds of new or known structures as lead compounds for semisynthesis to mark patentable entities of high activity and/or lower toxicity for instance, nabilone, metformin, oxycodone (and extra narcotic analgesics), taxotere, teniposide, verapamil and amiodarone, which are based respectively, on galegine, Δ^9 –tetrahydrocannabinol, taxol, morphine, podophyllotoxin and khellin.

c) to practice agents as pharmacologic tools eg., lysergic acid diethylamide, mescaline, yohimbine and

d) to customize the entire plant or part of it as a herbal remedy for example, cranberry, echinacea, feverfew, garlic, *Ginkgo biloba*, St. john's wort, *Mucuna pruriens* saw palmetto.

2. DRUGGABILITY OF ISOLATED PHYTOCHEMICAL COMPOUNDS

Disputes in the new drug development are chiefly encountered from two categories: the current paradigm for drug discovery in big pharmaceutical industries and technical restrictions in identifying few compounds with striking activity. Koehn and Carter ([14] have listed the subsequent distinctive features of the compounds separated from natural products.

- Greater number of chiral centers
- Increased steric complexity
- Higher number of oxygen atoms
- Lesser ratio of aromatic ring atoms to whole heavy atoms
- High number of solvated hydrogen bond donors as well as acceptors
- Great molecular rigidity
- Broad distribution of molecular properties like molecular mass, octanol water partition coefficient as well as diversity of ring systems.

These special features of chemical entities of natural origin create a string of challenges for medicinal chemists as they begin working upon expansion of analogs, either to get improved absorption or to reduce toxicity and recover upon efficacy which is often attained by addition or deletion of chosen functional groups. As per a review by Ehrman *et al*. [15] diverse bioactive plant compounds was isolated in China from 1911 to 2000 like alkaloid, steroid, triterpene, limonoid, diterpene, sesquiterpene, monoterpene, tannin, isoflavonoid, flavonoid, polycyclic aromatic, lignan, coumarin, simple phenolic, aliphatic etc. Alkaloid may be distributed as 20% flavonoids as 15%, triterpenes and simple phenolics around 10% and enduring others below that, with limonoid being the least.

It can be carefully presumed that large number of natural products, apart from being biologically active and having first-class ADMET profile (absorption, metabolism, distribution, excretion and toxicity), do not gratify the criteria “drug likeness”. The challenge is of building a physio-chemical tuned natural products library in line with the direct generation to encourage natural products to their full potential. Lipinski [16] spread simple set of calculated property called “rule of five” for the drug candidates reaching phase II clinical trials. This rule is an algorithm consisting of four rules in which many of the cutoff members are five or multiples of five, thus originating the rule’s name. To be drug-like, a candidate ought to have:

- less than five hydrogen bond donors
- less than 10 hydrogen bond acceptors
- molecular weight of less than 500 Da; and
- partition coefficient log p of less than 5.

The aim of the ‘role of five’ is to focus possible bioavailability problems if two or more properties are violated. Had Lipinski’s rule been followed, paclitaxel would by no means have become a drug. For the reason it does not comply with “rule of five”, to find substitute druggability criteria for the compounds of natural source is a chief challenge.

As a result the biggest challenge is to find additional druggability criteria for the compounds of natural source.

3. APPROACHES TO DRUG DISCOVERY USING HIGHER PLANTS

Several reviews pertaining to approaches for selecting plants as candidates for drug discovery programs have been published [17,18,19,20,3,21]; however, most-concern screening plants for anticancer or anti HIV activity. Early listing of the candidate species for screening of biological activity is a major task of definite importance in itself. Fabricant and Farnsworth [22] and Katiyar *et al*. [21] have computed the following approaches being used so far by researchers for this purpose.

3.1 Random Selection Followed by Chemical Screening

These supposed phytochemical screening approaches (i.e., for the presence of triterpenes, flavonoids, isothiocyanates, alkaloids, iridoids etc. have been used in the past and are at present followed largely in the developing countries. The tests are easy to perform, but false-positive and false negative tests frequently render results hard to assess. More vital, it is usually impossible to relate one class of phytochemicals to detailed biologic targets; for case, the alkaloids or flavonoids create a huge array of biologic effects that are frequently not predictable in advance.

3.2 Random Selection Followed by One or More Biologic Assay

Plant extracts were assessed mainly in experimental animals, chiefly mice and rats in the past. The most expensive of these programs were sponsored by the National cancer Institute (NCI) in the United States and the Central Drug Research Institute (CDRI) in India. More than 35,000 species were screened *in vitro* and later*in vivo* at NCI from 1960 to 1981. Taxol and camptothecin [23] were discovered in this program as well as several other plant derived compounds that were unsuccessful in human studies. In 1986 the NCI program discarded this approach and continued to collect and screen plants employing a battery of 60 human tumour cell lines. It also commenced a screening of plants for anti-HV activity *in vitro*. Calanolide A, currently in Phase I clinical trials, was developed from this program [24,25]. CDRI, followed this approach about three decades ago. They screened around 2000 plants for biological efficacy. Nonetheless, the screening did not give any new drug. If target based bioassays are used, e.g. screening against protein-tyrosine phosphatase 1B (PTP1B), chances of success would probably be more. This method, nevertheless, needs a vast library of extracts, but very few organizations in the world are having.

3.3 Follow-up of Biologic Activity Reports

These reports portrayed that the plant extracts had increasing biologic activity, but the extracts were not studied for their active principles. The literature from the 1930s through the 1970s contains these types of reports.

3.4 Follow-up of Ethnomedicinal (Traditional Medicine) Uses of Plants

Numerous types of ethnomedicinal information are available.

3.5 Plant Used in Organized Traditional Medical (TM) Systems

Countries like India and China have a thriving heritage of well-documented traditional system of medicine in trend. Though these codified systems of medicine employ mostly botanical sources as medicines, still these stand apart from ethnomedicine principally on three accounts.

- The ethnomedicinal practice is based on empirical experience. Equally, these codified systems built up the observed practices on strong conceptual foundations of human physiology in addition to of pharmacology.
- The pharmaceutical procedures have been more advanced against the use of crudely extracted juices and decoctions in ethnomedicinal methods. Due to this phenomenon, the idea of standardization was identified to the system.
- They are well documented and extensively institutionalized. Conversely, the ethnomedicinal practices are localized and may be mainly controlled by few families in each of the community.

Yet in expressions of historicity, ethnomedicinal practices might be older than codified systems of medicine.

Detection of artemisinin from guggulsterones from *Commiphora mukul* (for hyperlipidemia), *Artemesia alba* for malaria, boswellic acids from *Boswellia serrata* (anti-inflammatory) and bacosides from *Bacopa monnieri* (no tropic and memory development) was foundation on the leads from these codified schemes of medicine existing in China and India. Nevertheless, it can be stated that this approach for selecting candidates in drug discovery programs has not been followed much so far. However, the approach has a district promise in conditions of hit rates. But the different example for this approach has been the detection of reserpine from *Rauwolfia serpentina*, which was based on the performance of unani medicine.

3.6 Ethnopharmacology Approach

The method of ethnopharmacology fundamentally depends on empirical experiences related to the use of botanical drugs for the detection of biologically active new chemical entities. This process involves the observation, description and experimental investigation of indigenous drugs, and is based on botany, chemistry, biochemistry, pharmacology, history and linguistics [26]. This method based on ethnomedicinal usage history has been some success of *Andrographis paniculata* was used for dysentery in ethnomedicine and the compounds responsible for the activity were isolated as andrographolide. Morphine from *Papavar somniferum* and berberine from *Berberis aristata*

are some examples of this approach. Some of the plants which are not selected on the basis of ethnomedicinal use also had some success stories, like L-Dopa from *Mucuna pruriens* and pacilitaxel from *Taxus brevifolia*.

3.7 Modernization: A Threat

The most severe threat to existing knowledge and practice on traditional medicinal plants comprise cultural change, chiefly the influence of modernization and less interest shown by the younger generations. These were the most important problems reported by the informants all through the field survey [27]. Hence, the proper documentation of the use of traditional medicinal plants as phytotherapeutic agents and the related indigenous knowledge held by the tribal community is inevitably required to preserve our traditional knowledge.

People who use traditional remedies may not understand the scientific rationale behind their medicines, but they from personal experience that some medicinal plants can be highly effective if used at therapeutic doses. Since we have a better understanding today of how the body functions, we are in a better position to understand the healing powers of plants and their potential as multifunctional chemical entities for treating complicated health conditions. Medicinal plants typically contain mixture of different chemical compounds that may act individually, additively or in synergy to improve health [28].

3.8 Use of Database

The NAPRALERT is a relational database that was proposed to evaluate the natural products literature for the principle of identifying new sources of commercially important or clinically helpful drugs. Started in 1975, NAPRALERT contains data on upward of 60,000 species, including more than 200000 distinct chemical compounds of natural origins, extracted from over 200000 scientific articles and reviews from nearly 10,000 scientific journals, representing organisms from all countries of the world. NAPRALERT encompasses of data on medicinal folklore, geography, taxonomy, chemistry and biological actions of natural products, which embraces clinical trials, of their extracts and isolates and by itself symbolizes a single tool for the discovery of novel bioactive compounds [29].

4. MULTIDISCIPLINARY APPROACH

Innovative drug discovery from natural products requires a multidisciplinary approach utilizing available and innovative technologies to package such natural product compounds for medical practice and drug development. The successful use of such an approach will allow the development of next generation drugs to combat the over-increasing health challenges of today and the future, a system biology approach coupled with appliance of available technologies like proteomics, metabolomics/metabonomics, genomics, transcriptomics, automation and computational strategies will surely pave the way for inventive drug design leading to better drug candidates. Molecular libraries of lead compounds from natural products R & D will be used as sources of lead compounds/herbal tinctures for inventive drugs. In the presentation of original technologies combined with systems biology, the focus must not be a reductionist method of trying to source a single active compound although to consider the synergistic results of compounds. It is significant to emphasis that innovative drug discovery from natural products will require a non-reductionist strategy to understand their complex mechanisms of action at the molecular level.

4.1 Identification of Genomics and Biomarker in Plant Based Natural Products

The practice of a diverse or wrong plant species will possibly affect the therapeutic properties due to different compounds and quantities that will be present in the species. Genomic methods are important in establishing an accurate identification method for plants and natural product species [30]. Genomic techniques such as DNA barcoding are established techniques that rely on sequence diversity in short, standard DNA regions (400-800bp) for species-level identification [31]. DNA barcoding utilizing genomics will provide a more robust and precise identification compared to traditional methods of morphological identification and local traditional names [32]. In biodiversity inventories, DNA barcoding of natural products has been applied [33] and authentication of herbal products ([34,35,36] DNA barcoding was employed in an integrative approach for recognition of plant species like *Amaranthus hybridus* and crude drugs traced in the Japanese pharmacopoeia by

means of ITS2 or psbA-trnH sequence application [32,37] Genomic based techniques represent an actual platform for natural product identification but different parts of the same plant with similar sequences may have different qualities, clinical utilities and indications owing to the diverse conditions under which they develop.

Marker development from species through genomic techniques can be incorporated into DNA chips to provide an effective, high-throughput tool for genotyping and also plant species authentication [30,38]. An innovative transcriptomic technology that allows a fast and effective analysis of many transcripts is Gene expression using micro assay analysis [30,39,40]. This transcriptomic investigation makes it possible to concurrently assess variations in multiple gene [41]. This symbolizes a robust tool for elucidating the molecular mechanisms of therapeutic natural products and biological networks important for their pharmacological actions.

4.2 Proteomics in Natural Products Validation and Biomarker Identification

Proteomic methods to innovative drug discovery from natural manufactured goods have the potential to clarify the protein function, protein expression, metabolic and biosynthetic pathways found on therapeutic effects translating to consistency in quality and profile of the product [42,43]. In identifying species in Chinese herbal medicine, *Panax ginseng* versus *Panax quinquefolius*, Proteomics application has been successfully used [44,45].The therapeutic results of natural products can be elucidated by making use of proteomics and imaging techniques to productively study the metabolism of natural goods and their compounds [46,47]. Proteomics is an efficient way to elucidate multi-target effects of complex natural product groundworks as well as the discovery of multiple compounds and fractions, categorization of natural products and ultimately a molecular diagnostic platform [30,48].

For natural products to be used as drugs it is crucial that their target proteins be identified – several methods comprising affinity chromatography have been in use to identity target proteins with relative success. Of late, several methods have been able to identity target proteins using label free natural products such as Drug affinity responsive target stability (DARTS) is one of the direct methods used to identity target proteins using label free natural products [49]. Stability of proteins from rates of oxidation (SPROX) is another method that takes advantage of ligand – induced changes to target proteins [49,50,51]. Modification of the SPROX method, named stable isotope labelling with amino acids in cell culture (SILAC)- based SPROX is an improvement of the original method and has the advantage to covering more target protein [52-54] This technique is bounded to only recognizing of methionine containing proteins. Cellular thermal shift assay (CETSA) is a recently introduced method based on stabilization of a target protein by binding to its ligand [55-57]. Thermal proteome profiling (TPP) is a progressed modification of the CETSA technique. This process identifies target proteins displaying thermal stability at elevated temperature induced by ligand binding and the usage of mass spectrometry to determine ligand – target protein interaction of cellular level [58-60].

These new and improved methods measure the responses of natural product – target protein complex to proteomic and thermal treatment [61-63]. It is possible to identify several target proteins for an individual natural product using proteomic analysis, using this new approach [64,56].

4.3 Metabolomics and Metabonomics Approach to Natural Product Drug Discovery

Untargeted metabolomics and metabonomics approaches of discovering compounds of therapeutic interest from natural product have the potential to lead to innovative drugs for global health. Metabolomic profiling of natural products seeks to identify and quantify the complete set of its characteristic metabolites [65,66]. while metabonomics broadly aims to evaluate the global and dynamic metabolic response of living systems to biological stimuli or genetic manipulation [67-70] Drug discovery has conventionally focused on metabolomics to categorize metabolites but of late, the term metabonomics has been assessed to incorporate a systems biology guided technique to study the functions and perturbations of biological system following a pharmacological effect. This explains a complete biological mechanism of both the natural products and its effect on a living system.

Metabolomic profiling of natural manufactured goods using technologies like Ultra-performance high performance liquid chromatography – quadruple TOF MS (UPLC-MS) has facilitated identification of compounds that present therapeutic goods on herbs such as *Newbouldia laevis, Cassia abbreviata, Hyptis suaveolens* and *Panax* herbs [71-73]. As a quality control measure and to show consistency in species usage, metabolomics has been worked in identification of processed *Panax* species (*Panax ginseng* and *Panax quinquefolius*) using Nuclear Magnetic Resonance (NMR) based metabolomics, UPLC-QTOFMS and multivariable statistical scrutiny [74]. Metabonomics method to profiling natural products for drug discovery has been called as a critical phenotyping tool. The systems biology method of this method positions the profiling of natural products in an all-comprehensive manner in terms of metabolite and biology schemes effect. Metabolomic and metabonomics profiling using NMR, MS and UPLC can elucidate the pharmacokinetic, pharmacodynamic and toxicological value of natural products.

4.4 Big Data in Drug Development for Natural Product

Omics analysis, like genomics, metabolomics, transcriptomics, proteomics and metabonomics effects in a generation of a complex multivariable dataset that required computational and chemometric tools for interpretation. The procedure of computational platforms like bioinformatics and multivariable statistical tools will permit the application of omics multidata to clarify pathophysiological effects, mark specificity and molecular effects, as well as clarify the pharmacodynamic, pharmacokinetic and toxicological depiction of natural products and their compounds. Applications used during the drug discovery procedure like docking and virtual screening might make use of novel machine learning algorithms like deep learning. Machine learning methods can be used for virtual screening of thousands of compounds allowing the utilization of data from high throughput screening [75,76].

Creating a lot of data can have the outcome of losing the ability to recognize its meaning. Big data must be useful and put into accomplishment. For big data to be beneficial during drug discovery it must be summarised into a little actionable information [77-79]. There are numerous data sources utilized for drug identification. These include ChemBank, PubChem, ChEMBL, DrugBank, UniPort, STLTCH and the NIH Small Molecule Repository [80-83]. Connectivity map (CMap) is a bioinformatic application that allows the study of disease at the molecular level with the help of computers [84-56]. The CMap also permits associations to be made in between diseases and drugs. For natural products, gene expression and diseases, the similar pattern – matching analysis can be used [87-90].

A confront to scientists using big data to update drug expansion and testing is how to put together a lot of information into a momentous and manageable unit. For 'omics' data to be significant and to develop clinical medicine, clinical phenotype data has to be incorporated with transcriptomic, genomic, proteomic and epigenomic data [91-93].

The usage of, and research into, natural products are far from acceptable. A number of problems need to be addressed in the prospect for example, synergistic effects may be among the compounds that are seen in natural products; on the other hand, the modes and mechanisms of action are seldom very obvious. It is, therefore, essential to make full use of such synergetic effects in the direction of improving the effectiveness of drugs. Equally, it is also requisite that any unpleasant effects of natural products be correctly reduced to meet safety standards.

With the riches of recent technology, such seen in synthesis, pharmacology, pharmacodynamics, fermentation along with biological diversity, chemodiversity and great breakthroughs in evolutionary techniques or concepts combined with a wealth of knowledge about natural products, it will be probable to establish a huge compound library for drug screening [94]. This will improve the possibilities for individual action and prevention of disease. Humankind need to realize more from natural products and conventional medicines.

Humans have to face up to many difficulties and challenges, in order to further advance the development of new medical research on natural products. Precious information on natural products and TMs (Traditional Medicines) is mixed in a bulky number of documents, data, and worthless rumors. Also, one plant or formula of natural products and TMs contains a huge

number of chemical constituents, together with active, invalid, and probable synergistic components. Hence, great effort should be made at first to remove the dross and take the essence-precious experience of natural products and TMs. Also, in many cases, the function of single compound from natural products and TMs is given much attention to. Conversely, as a matter of fact, one advantage of TM's restoratives is the "synergism", that is, habitually multiple components in TMs plays a synergistic function which is superior than that of the individual drug. In the meantime, the "I disease, 1 target, 1 drug" mode cannot care for some complex diseases successfully, such as cardiovascular disease and diabetes. As a result, the treatment has seen a transfer to the "multi-drugs and multi-targets" mode for combination therapies. Henceforth, in the future, multidisciplinary collaborative research, directly cooperated with new ideas, like network pharmacology and big data, will be probable to explain the synergism and other mechanisms of natural products and TMs from which more and superior new drugs and treatment will be noticed and inspired.

5. ANTIINFLAMMATORY ACTIVITY OF NATURAL PRODUCTS

In recent years, a great quantity of natural products, especially form plants, have been reported to exhibit obvious antiinflammatory effects both *in vitro* and *in vivo* [95]. In the light of molecular structure type, natural products form plants with antiinflammation effects mainly include monoterpene, diterpene, titerpene, phenylpropanoid, lignanoid, coumarin, flavonoid, anthraquinone, alkaloid and polyphenol. These natural products exert momentous antiinflammatory effects via acting on different drug targets and cells signaling pathway.

Monoterpene and diterpene such as peoniflorin, ginkolide B, andrographolide, triptolide and ligustilide (Fig. 1) are found in major bioactive compounds in plants such as *Paeonia lactiflora, Ginkgo biloba, Andrograhis paniculata, Tripterygium wilfordii* and *Ligusticum wallichii* respectively. These compounds apply antiinflammatory activity via several inflammation associated signal transduction pathway.

Triterpene such as celastrol, ginsenoside Rb1, asiaticoside and ursolic acid (Fig. 2) are found in an active compounds in plants such as *Tripterygium wilfordii*, *Panax ginseng, Centella asiatica* and *Uncaria tomentosa* respectively. These compounds possess antiinflammatory effects.

Phenylpropanoid, lignanoids, coumarin and anthraquinons such as *salvianic acid* A and B, obvatol, schisandrin B and shikonin (Fig. 3) are found in main bioactive compounds in plants such as *Salvia miltiorrhiza, Magnolia liliflora, Schisandra chinensis* and *Radix lithospermi* respectively. These compounds exhibited antiinflammatory activity.
Flavonoid, alkaloid and polyphenols like quercetin, luteolin, matrine, oxymatrine, sinomenine, berberine, epigallocatechin-3-gallate (EGCG) and resveratrol (Fig. 4) were found to have antiinflammatory results [96].

Curcumin (polyphenol), parthenolide (sesquiterpene lactone), cucurbitacins (triterpene), 1,8-cineole (monoterpene oxide) and pseudopterosins A (diterpene glycosides) (Fig. 5) were isolated from dissimilar plants which possess antiinflammatory activity [97].

Some biological active compounds were extracted from each of *Phellinus linetus, Ganoderma lucidum, pleurotus pulmonarius* and *Grifolia frondosa* mushrooms. For example, eight different triterpenoidganoderic acids were isolated from *G. lecidum*, but only four of them exerted antiinflammatory activity. From *G. frondosa* an ergosterol oxidation product active as an antiinflammatory agent was isolated (Fig. 6) [98].

Azab *et al*. [98] stated that terpenoids are the biggest group of antiinflammatory compounds in mushrooms and offered some seven-membered, structurally attractive examples of these compounds like cyathins and related compounds (Fig. 7)

There are many antiinflammatory natural products from marine sponge. Eight four antiinflammatory compounds dominated by isoprenoid originated metabolites, especially sesterterpenes have been isolated from marine sponges [99]. Manoalide (Fig. 8) is perhaps the most well known of all antiinflammatory products from sponge and well originally isolated by de Silva and Scheuer [100] in from the sponge *Luffariella variabilis*. Manoalide's antiinflammatory property has been studied broadly.

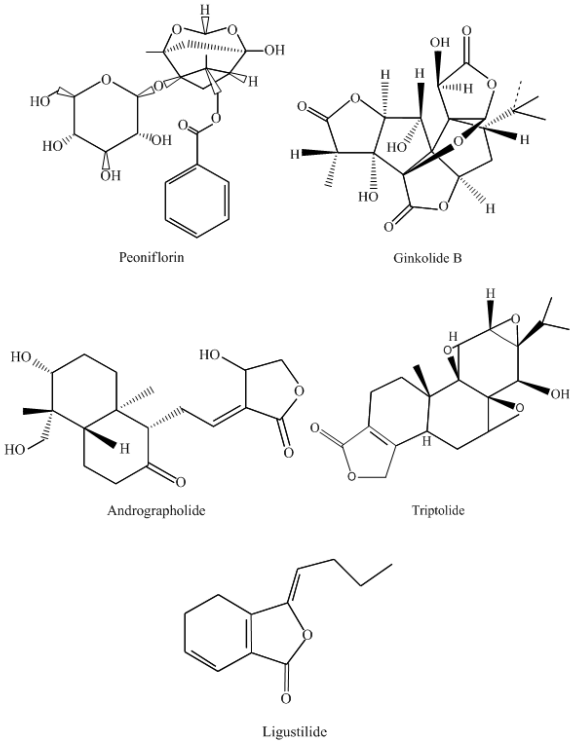


Fig. 1. Structure of certain monoterpene and diterpene

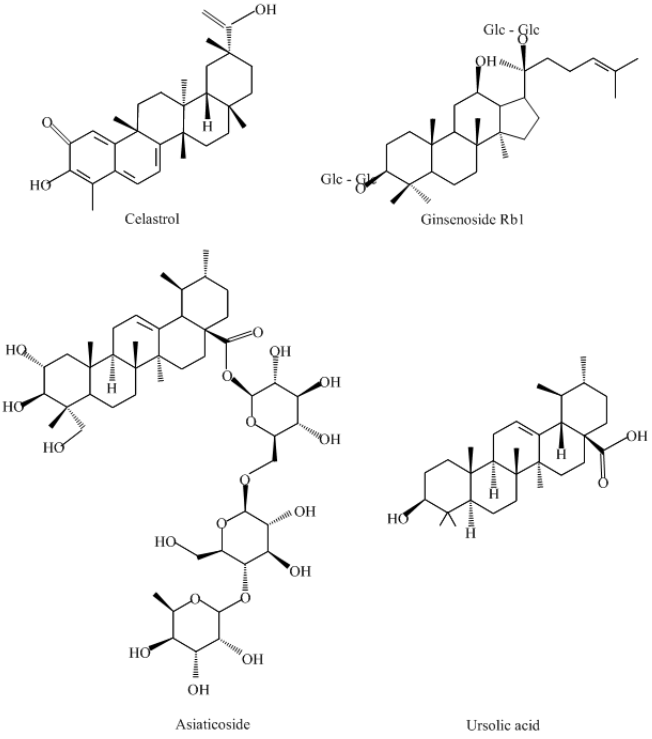


Fig. 2. Structure of triterpene

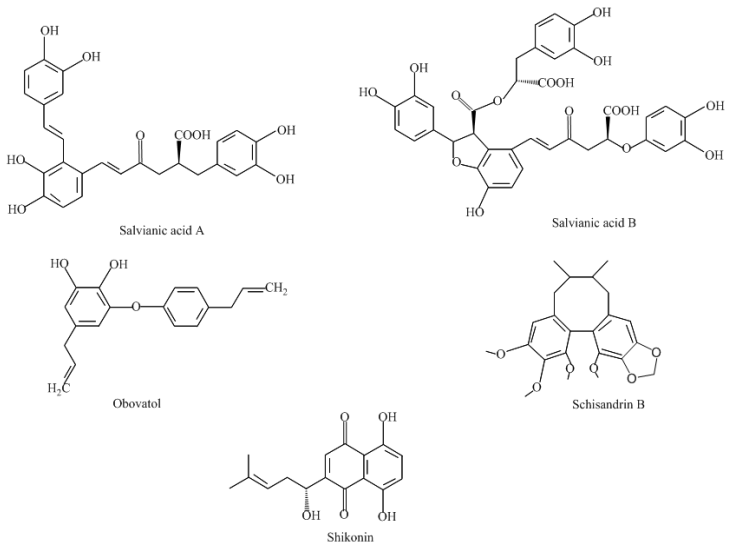


Fig. 3. Structure of salvianic acid A, salvianic acid B, obovatol, schisandrinB and shikonin

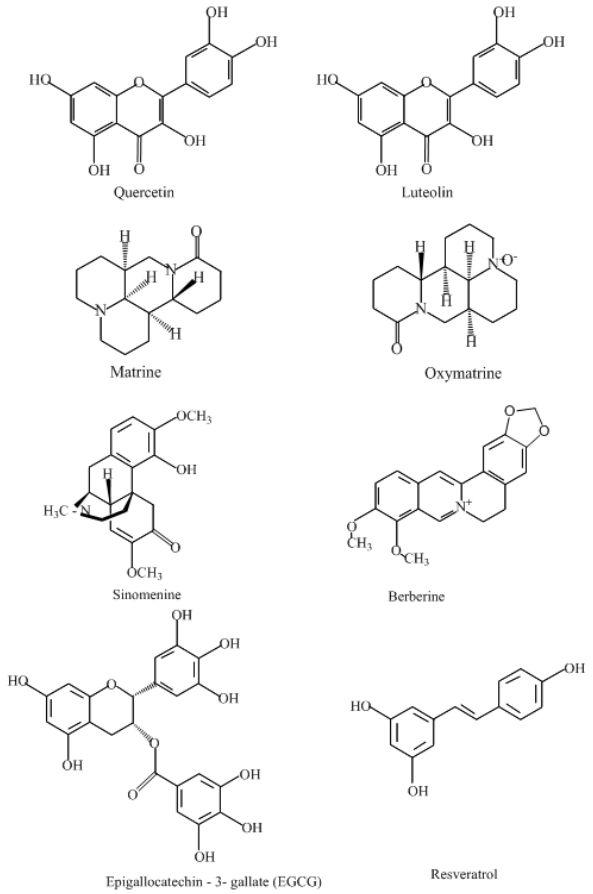


Fig. 4. Structure of quercetin, luteolin, matrine, oxymatrine, sinomenine, berberine, epigallocatechin-3-gallate and resveratrol

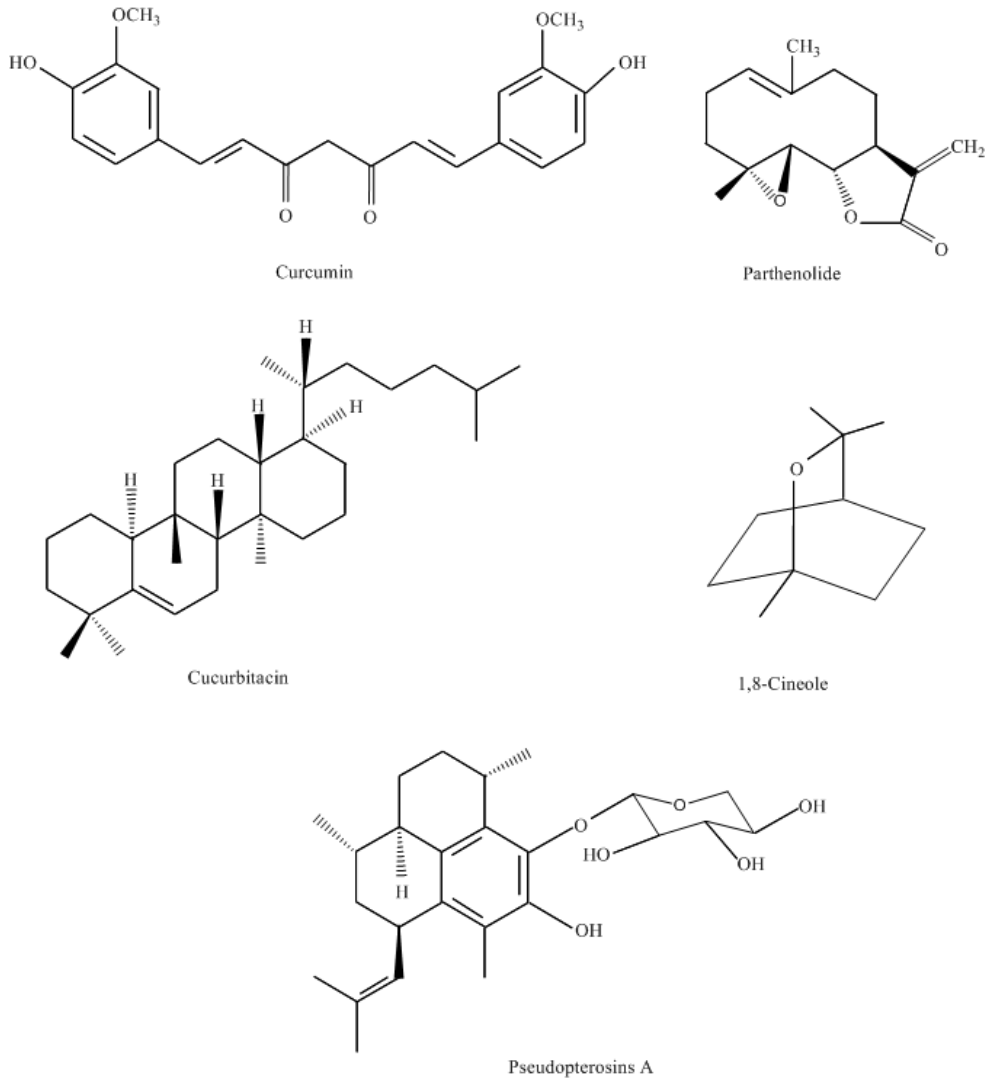


Fig. 5. Structure of curcumin, parthenolide, cucurbitacins, 1,8-cineole and pseudopterosins A

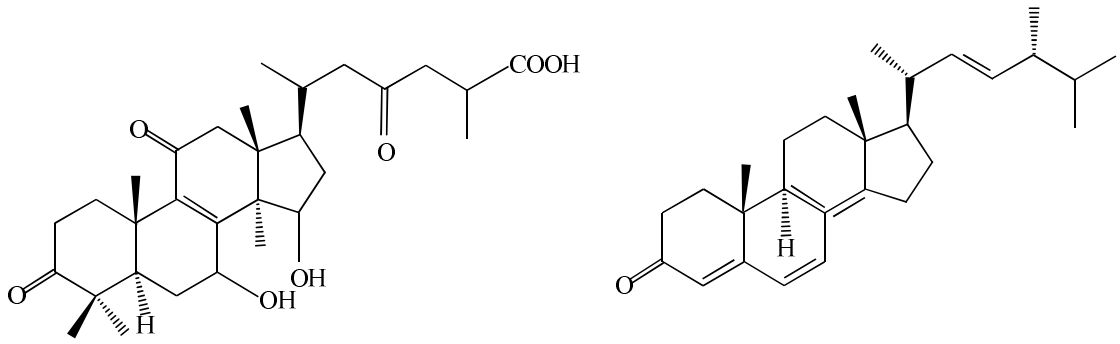


Fig. 6. Strucutre of ganoderic acid and ergosta-4-6-8(14), 22-tetraen-3-one

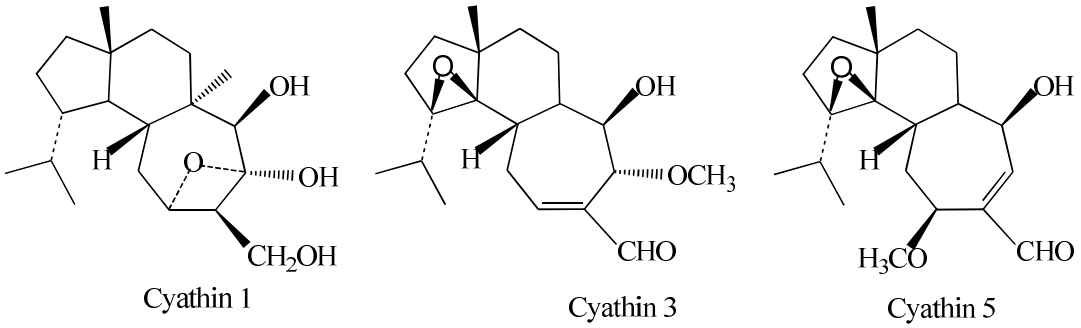


Fig. 7. Structure of some cyathins isolated from mushrooms

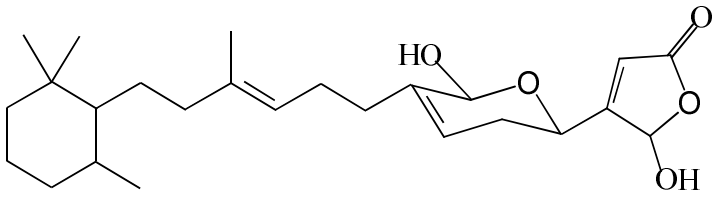


Fig. 8. Structure of manoalide

6. CONCLUSION

There is an important need to renew scientific keenness toward natural products for enclosure in drug discovery program. One of the vital concerns related to natural products has been the preventability of hit rate during various phases of drug growth such predictability is predictable to be lower in case of random selection of candidate species in view of the overall complexity of botanical sources for original chemical entities. Strategic selection and shortlisting of candidate species is essential in order to improve the predictability. Recognized clinical experience with botanical medicines as codified in conventional systems of medicine may simplify the issues associated with deprived predictability. New functional leads picked up from the traditional awareness and experimental database may help to decrease time, money and toxicity which are the three specific hurdles in the drug growth. The collaborative efforts of ethnobotanists, pharmacists and physicians could be a workable strategy to evaluate and validate the usage custom of traditional medicinal plants with the existing modern scientific methods and innovative techniques. An integrative technique by combining the different discovery tools and the new discipline of combined biology will provide the solution for success in natural product drug discovery and development.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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