IBEROAMERICAN JOURNAL OF MEDICINE
iberoamericanjm
Journal homepage: www.iberoamericanjm.tk

Review

Medicinal plants: Prospective drug candidates against the dreaded Coronavirus

Emmanuel Onah Ojah[a,*]

[a]*Phytochemistry Research Group, Organic Chemistry Unit, Department of Chemistry, University of Ibadan, Ibadan, Nigeria*

ARTICLE INFO

Article history:
Received 18 May 2020
Received in revised form 02 June 2020
Accepted 03 June 2020

Keywords:
Medicinal plants
Coronavirus
Diseases
Health
Traditional medicine

ABSTRACT

Introduction: Medicinal plants have been the most productive source of leads for the development of drugs from ancient times. Current research in drug discovery involves a multifaceted approach combining botanical, biological, and molecular techniques. Medicinal plant based drug discovery continues to provide novel and important leads against several diseases.
Methods: Relevant articles relating to the concept were identified using a combination of manual library search as well as journal publication on the subject and critically reviewed.
Results: Drug discovery from medicinal plants continues to provide an important source of new drug leads however; numerous challenges are encountered including the procurement of plant materials and implementation of appropriate high-throughput screening bioassays. Medicinal plants have great prospect in the ultimate search for the cure against the dreaded coronavirus.
Conclusion: It is hoped that the more efficient and effective application of medicinal plants would improve the drug discovery process against the dreaded coronavirus.

1. INTRODUCTION

Plants have been utilized as medicines for thousands of years. These medicines initially took the form of crude drugs and other herbal formulations [1, 2]. The specific plant to be used and the methods of application for particular ailments were passed down through oral history. Eventually information regarding medicinal plants was recorded in herbals. In more recent history, the use of plants as medicines has involved the isolation of active compounds, beginning with the isolation of morphine from opium in the early 19th century [2, 3]. Drug discovery from medicinal plants led to the isolation of early drugs such as cocaine, codeine, digitoxin, and quinine, in addition to morphine, of which some are still in use [4]. Isolation and characterization of pharmacologically active compounds from medicinal plants is in progress. More recently, drug discovery techniques have been applied to the standardization of herbal medicines, to elucidate analytical marker compounds [5].

Drug discovery from medicinal plants has evolved to include numerous fields of inquiry and various methods of analysis. The process typically begins with a botanist, ethnobotanist, ethno-pharmacologist, or plant ecologist who collects and identifies the plant of interest. Collection may involve species with known biological activity for which active compound(s) have not been isolated (e.g.,

* *Corresponding author.*
E-mail address: eojah7403@stu.ui.edu.ng

http://doi.org/10.5281/zenodo.3881344

traditionally used herbal remedies) or may involve taxa collected randomly for a large screening program [6]. Phytochemists also known as natural product chemists prepare extracts from plant materials, subject these extracts to biological screening in pharmacologically relevant assays, and commence the process of isolation and characterization of the active ingredient through bioassay-guided fractionation. Molecular biology has become pivotal to medicinal plant drug discovery through the determination and implementation of appropriate screening assays directed towards physiologically relevant molecular targets [6].

Medicinal plants have been explored from time immemorial due to their efficacy in the prevention and treatment of various disease conditions such as diabetes, oxidative stress, malaria, thiphoid fever, schistosomiasis, onchocerciasis, lymphatic filariasis, African dengue and trypanosomiasis [7-9]. Plants occupy a strategic place in the socio-cultural, spiritual and economic definition of societies [10]. This knowledge was transferred from generation to generation either orally or mystically, and effective plants have been selected by mere trial and error [11]. The traditional medicinal system based on herbal therapies has always played a pivotal role in the health systems of many emerging and under developed countries. The significance of the traditional medicine has also gained cognizance in advanced countries of the World [12]. Herbal medicine is spreading widely today because of its biomedical benefits [13]. The plant parts utilized, mode of preparation and administration vary significantly from one country to the other [14, 15]. The therapeutic effect of some secondary metabolites isolated from medicinal plants with several pharmacological properties such as flavonoids, steroids, alkaloids, terpenes, tannins and lignans has been the subject of incessant phytochemical investigations involving the prospection of new drugs [16, 17]. These substances are found as bio-constituents of plant extracts, possessing great activity for different medicinal purposes [18, 19].

Medicinal plants have been known as successful wellsprings of new and remedially effective medicine. Numerous productive medicines currently in use were initially synthesized to copy the activity of molecules found in them. They are the most reliably successful source of medicine leads [20]. They are utilized for the most part in traditional prescription to treat different infections or ailments. Traditional medication has not exclusively had vital impact in giving therapeutic aids. However, it has been supportive in the finding of most pharmaceutically active substances which are being used in the production of newly synthesized drugs [21, 22]. During the twentieth century, the enthusiasm of the pharmaceutical industry moved from the utilization of these natural-based items (for the production of new drugs without side effects) to the synthetic method. This trend has commanded research and improvements in the industry during the period. In this way, natural extracts have replaced synthetic molecules which are not associated with natural products. Although the use of synthetic drugs has helped to treat, forestall and spare numerous lives throughout the years, such medications come with side effects. This shortcoming in the use of synthesized drugs has stirred enthusiasm for the utilization of plant based natural products particularly medicinal plants as a source of pharmaceutical operators. The joined activity of these substances will increase the activity of the main medicinal constituent by accelerating or inhibiting its coordination in the body. Most biologically active natural products are secondary metabolites with complex structures. These optional metabolites, for example, alkaloids, glycosides, terpenoids, phenols and saponins are used by men as prescriptions [23]. For instance, a solitary plant may contain different secondary metabolites with diverse medicinal properties such as antimicrobial, anti-inflammatory, and diuretics [24].

Drug discovery from medicinal plants has evolved to include numerous fields of inquiry and various methods of analysis. The process typically begins with a botanist, ethnobotanist, ethno-pharmacologist, or plant ecologist who collects and identifies the plant of interest. Collection may involve species with known biological activity for which active compound(s) have not been isolated (e.g., traditionally used herbal remedies) or may involve taxa collected randomly for a large screening program [6]. Phytochemists also known as natural product chemists prepare extracts from plant materials, subject these extracts to biological screening in pharmacologically relevant assays, and commence the process of isolation and characterization of the active ingredient through bioassay-guided fractionation. Molecular biology has become pivotal to medicinal plant drug discovery through the determination and implementation of appropriate screening assays directed towards physiologically relevant molecular targets [6].

Medicinal plants have been explored from time immemorial due to their efficacy in the prevention and treatment of various disease conditions such as diabetes, oxidative stress, malaria, thiphoid fever, schistosomiasis, onchocerciasis, lymphatic filariasis, African dengue and trypanosomiasis [7-9]. Plants occupy a strategic place in the socio-cultural, spiritual and economic definition of societies [10]. This knowledge was transferred from generation to generation either orally or mystically, and effective plants have been selected by mere trial and error [11]. The traditional medicinal system based on herbal therapies has always played a pivotal role in the health systems of many emerging and under developed countries. The significance of the traditional medicine has also gained cognizance in advanced countries of the World [12]. Herbal medicine is spreading widely today because of its biomedical benefits [13]. The plant parts utilized, mode of preparation and administration vary significantly from one country to the other [14, 15]. The therapeutic effect of some secondary metabolites isolated from medicinal plants with several pharmacological properties such as flavonoids, steroids, alkaloids, terpenes, tannins and lignans has been the subject of incessant phytochemical

investigations involving the prospection of new drugs [16, 17]. These substances are found as bio-constituents of plant extracts, possessing great activity for different medicinal purposes [18, 19].

Medicinal plants have been known as successful wellsprings of new and remedially effective medicine. Numerous productive medicines currently in use were initially synthesized to copy the activity of molecules found in them. They are the most reliably successful source of medicine leads [20]. They are utilized for the most part in traditional prescription to treat different infections or ailments. Traditional medication has not exclusively had vital impact in giving therapeutic aids. However, it has been supportive in the finding of most pharmaceutically active substances which are being used in the production of newly synthesized drugs [21, 22]. During the twentieth century, the enthusiasm of the pharmaceutical industry moved from the utilization of these natural-based items (for the production of new drugs without side effects) to the synthetic method. This trend has commanded research and improvements in the industry during the period. In this way, natural extracts have replaced synthetic molecules which are not associated with natural products. Although the use of synthetic drugs has helped to treat, forestall and spare numerous lives throughout the years, such medications come with side effects. This shortcoming in the use of synthesized drugs has stirred enthusiasm for the utilization of plant based natural products particularly medicinal plants as a source of pharmaceutical operators. The joined activity of these substances will increase the activity of the main medicinal constituent by accelerating or inhibiting its coordination in the body. Most biologically active natural products are secondary metabolites with complex structures. These optional metabolites, for example, alkaloids, glycosides, terpenoids, phenols and saponins are used by men as prescriptions [23]. For instance, a solitary plant may contain different secondary metabolites with diverse medicinal properties such as antimicrobial, anti-inflammatory, and diuretics [24].

2. MEDICINAL PLANTS AS THERAPEUTIC AGENTS

Traditional health care in early history was hinged on making primitive drug against natural catastrophes, diseases, sicknesses and the quest for food from certain medicinal plants. The ancient humans realized that some foods have explicit properties of relieving them of certain ailments and maintenance of vital health [25]. Ongoing methodology in the advancement of new drugs from being utilised for the treatment of diseases is gotten generally from different types of plants. Particularly in developing nations which are subject to customary therapeutic sources for their essential health services. Plants are the source of traditional medicine that have been in use for quite a long time and is still used today [26]. Several plants have been identified as good therapeutic agents; an example is *Olive* plant known for its antidiabetic, anticancer, diuretic, circulatory strain, fever, antibacterial, and hypoglycemic corrective abilities with signs against conditions such as schistosomiasis, malaria and lymphatic disarranges [27]. Lapachol, is a natural phenolic compound that was first obtained from the bark of *Lapacho* tree (*Handroamthus impetiginous*) and has been found to have antiviral, antibacterial, antimalarial, anti-inflammatory, antifungal, antiparasitic, and insusceptible modulatory action by results from animals and other laboratory experiments [26, 28]. Gilbert et al., (1970) adeptly demonstrated that Lapachol has antiviral features against different viruses including Herpes I and II, vesicular stomatitis virus, flu, and polio virus [29]. This was additionally approved by Cheever (1997); the use of drug for hostile actions against parasitic activities including malaria, schistosoma and trypanosoma which have been medically validated [30]. *Myrrh* an oleo-gum resin from the stem of the plant called *Commiphora mol* is another example of naturally occurring therapeutic agent. It is used for the treatment of liver disorders [31]. *Commiphora* extract (Mirazid) has been reported to be a good anti-fasciolicidal drug [32]. It has also been viable in the treatment of Schistosoma haematobium [33]. Likewise, Massoud et al. (2004) detailed that Mirazid caused disruption of *S. mansni* worms' covering and the destruction of tubercles causing a breakdown in worm trouble [34]. Naturally Purified *Commiphora* plant concentrate caused an important increment in adenosine, glucose, protein, and glycogen after decrease brought about by contamination. The upgrading capacity of this *Commiphora* plant might be identified with antioxidative properties [35]. *Citrus reticulata* has been reported to be hostile to leukaemia [36], microbial attack [37], cell reinforcement [38] and cancer activities [39]. The chloroform concentrate of *Ailanthus altissima* stem bark with a wide scope of natural activities has been utilized to demonstrate an improved impact against damage of organs (liver-kidney-spleen) brought about by parasitic contamination [40]. In addition, *A. altissimo* exhibit anti-tuberculosis, anti-plasmodial, and antitumor activities [41, 42]. *Curcuma longa* is another plant that has shown numerous theurapeutic properties which include antibilharzial [43], antidiabetics and antioxidant activities [44, 45]. Curcumin gotten from powdered rhizomes of plant *Curcuma longa* Linn is ubiquitously used as a colouring agent in foods, cosmetics and drugs [46], as an antitumor agent [47]. It has also been shown to forestall gullblader sickness [48, 49].

3. ETHNOPHARMACOLOGICAL APPROACH IN PLANT-BASED DRUG DISCOVERY

Drug discovery is pivotal due to the prevalence of several ailments without effective, reliable and less toxic medications. Medicinal researches constitute the backbone of drug discovery studies for pharmaceutical industries. A compound must be investigated thoroughly before the

registration of a new drug. The screening methods used to investigate the effective plant based compound can also be made either by selecting the candidate plant material randomly or by determining the potential candidate via databases developed for this purpose. However, these methods are expensive, time consuming, and low productive processes that often prove abortive. High throughput screening methods, genomics, and combinatorial chemistry technologies are now used to save the therapeutic innovation [50]. The most comprehensive of random screening programs were initiated by the National Cancer Institute in the United States and the Central Drug Research Institute in India. This evaluation is based on traditional use of folk remedies which relies on ethnomedical information and this method experimentally considers plants as a source of active agents [51]. The main aim of this method is to develop herbal medicines in the form of standardized crude extracts as well as discovering active components of these plants.

Every step of this methodology, from the collection of the plant material to the isolation of the active component, is followed by an ethnopharmacological aspect. Ethnopharmacology is an interdisciplinary and multidisciplinary approach in drug discovery involving observation, description, and biological activity investigation of folk remedies [52, 53]. When the ethnopharmacological studies are taken into consideration, the relevance of medicinal plants is clearly seen. Herein, plant-based biologically active agents cover whole plants or particular plant parts or herbal drug preparations (including essential oils, extracts, fractions, etc.) or plant derived active pharmaceutical ingredients. This depends on the active part of the plant that sometimes all of the ingredients act in a synergistic manner to display a particular biological activity but sometimes only one compound can be responsible from the bioactivity. Indeed, herbal materials and crude extracts contain a wide range of compounds that work synergistically or individually to provide poly-pharmaceutical effect. Synergy is an advantage; when the same effect is expected from a single synthetic compound. This may cause possible side effects due to a relatively higher dose. With the scientific ability to investigate the activities of the extracts or natural compounds on experimental models, ethnopharmacology has gained a modern sense rather than empirical aspects of indigenous.

Awareness on conceptual and methodological standards in this field has increased in recent years [54]. Indeed, a rational phytotherapy research focuses on plant-based products in the treatment of various diseases within a science-based medical practice and is different from medical herbalism which has an empirical approach [55]. Accordingly, standardized methods have been developed to obtain reproducible results in ethnopharmacological researches. Several disciplines including botany, pharmacognosy, pharmaceutical biology, natural product chemistry, plant physiology, biochemistry, pharmacology, toxicology, clinical research, anthropology, archaeology, etc. contribute to the discovery of novel drugs by using natural products [56]. Herein, candidate plants are determined according to ethnobotanical studies. In fact, ethnobotany focuses not only on the medicinal plants but also on the other natural products including colouring agents, foods, ornamentals, oil plants, etc. Nevertheless, medicinal plants are one of the main interests of ethnobotany studies which record treatment purposes of medicinal plants in a detailed way [57]. From the ancient civilizations, people have experienced various plants in order to figure out their biological effects. Through these trials, the knowledge regarding the specific plants and their application methods for particular disorders have been passed down through the various generations via verbal transfer. Eventually, the information on medicinal plants was scientifically recorded in ethno-botanical field studies [57, 58]. According to this recorded information, the plant material is collected and identified by a taxonomist. The species should be identified with its current taxonomically valid Latin binomial and voucher specimens should be deposited in an international accessible herbarium in order to provide a full botanical documentation [59, 60]. Ethnopharmacological studies should be conducted on the plant which is recorded to be used for medication. Afterwards, pre-clinical studies are carried out on these plant parts. The availability of adequate information regarding the use of the plant remedy in the fieldwork records provides significant advantages in the planning and implementation of experimental research [61].

Extracts from plant material are applied to animals after a suitable experimental model is established in experimental animals. The sub-extracts/fractions obtained by the phytochemical separation studies are subjected to the activity evaluation process in each step to find out the effective extracts/fractions and to determine the active compounds in the direction of bioactivity-guided fractionation and isolation studies. In other words, all the natural products begin as mixtures of closely related compounds from which the active component is isolated and purified by carrying out further extraction, chromatography, and crystallization methods. After purification, chemical structure elucidation studies and following various chemical syntheses are carried out to determine structure–activity [61, 62]. On the other hand, various compounds may also exhibit synergism in biological activity, which is also of interest for development of herbal medicines [63].

Ethnopharmacology research approach is commonly employed in developing countries of Asia, South American and African countries where there is basic knowledge of traditional medicinal system. In addition, during the last decade, ethnopharmacological studies have multiplied dramatically in Europe, focusing on Mediterranean region including Turkey, Spain and Italy. Scientific studies on traditionally used medicinal plants in these countries do not only provide essential information for community-based health management but also introduce poorly known local natural products [64]. In a study by Farnsworth et al.

(1985), it was reported that nearly 75% of the natural compounds used in the treatment have been discovered and developed according to their traditional use [65, 66]. On the other hand, there are also medicinal plants which have multipurpose medicinal applications. Drug discovery from these medicinal plants is complex due to the selection and implementation of appropriate bioactivity methods. More recently, researchers have suggested that medicinal plants that have different uses should also be considered for drug discovery. They proposed the concept of ''reverse ethnopharmacology'' as a drug discovery tool to reveal hidden associations between ethnomedicinal uses and biomedical indications of plant derived drugs with a set of statistical tools. Reverse ethnopharmacology confirmed the validity of the classical ethnopharmacology as well as exhibited the existence of relationships focusing on cancer therapy, where traditional knowledge has a limited predictive power [67]. Despite these classical and non-classical strategies, drug discovery from traditional knowledge has been reduced due to the advancement in innovative synthetic chemistry that plays a critical role in the discovery and development of new medicines. Indeed, within pharmaceutical industries, natural products approach in drug discovery process has little pursuance due to numerous challenges including inadequate number of well experienced researchers knowing the indigenous cultures, high cost of natural product sample collection, presence of artifacts in some extracts, long resupply time and large scale supply problems for active extracts and fractions, difficulty in isolating the active components, difficulties of complying with the regulations on the conservation of biodiversity [68].

4. IMPORTANCE OF MEDICINAL PLANTS IN DRUG DISCOVERY

Numerous methods have been utilized to acquire compounds for drug discovery including isolation from plants and other natural sources [69]. Despite the recent interest in molecular modeling, combinatorial chemistry, and other synthetic chemistry techniques by pharmaceutical companies and funding organizations, medicinal plants, remains an important source of new drugs, new drug leads, and new chemical entities (NCEs) [70]. In both 2001 and 2002, approximately one quarter of the bestselling drugs worldwide were derived from plants [71]. Plants have played an important role as new chemical entities (NCEs) approximately 28% of NCEs between 1981 and 2002 were plant-derived. Another 20% of NCEs during this time period were considered natural product mimics, meaning that the synthetic compound was derived from the study of natural products [72]. Combining these categories, research on natural products accounts for approximately 48% of the NCEs reported from 1981–2002. Natural products provide a starting point for new synthetic compounds, with diverse structures and often with multiple stereocenters that can be challenging synthetically [73-76]. Many structural features common to natural products (e.g., chiral centers, aromatic rings, and complex ring systems, degree of molecule saturation, and number and ratio of heteroatoms) have been shown to be highly relevant to drug discovery efforts [77-79]. Furthermore, since the escalation of interest in combinatorial chemistry and the subsequent realization that these compound libraries may not always be very diverse, many synthetic and medicinal chemists are exploring the creation of natural product and natural-product like libraries that combine the structural features of natural products with the compound-generating potential of combinatorial chemistry [80-84]. Drugs derived from medicinal plants can serve not only as new drugs themselves but also as drug leads suitable for optimization by medicinal and synthetic chemists. Even when new chemical structures are not found during drug discovery from medicinal plants, known compounds with new biological activity can provide important drug leads. Since the sequencing of the human genome, thousands of new molecular targets have been identified as important in various diseases [85]. With the advent of high throughput screening assays directed towards these targets, known compounds from medicinal plants may show promising and possibly selective activity. Several known compounds isolated from traditionally used medicinal plants have already been shown to act on newly validated molecular targets, as exemplified by indirubin, which selectively inhibits cyclin dependent kinases and kamebakaurin. Other known compounds have also been shown to act on novel molecular targets, thus reviving interest in members of these frequently isolated plant compound classes [86-89].

5. RECOMMENDATIONS

1. Efficient and effective exploration of medicinal plants should be carried out as this would improve the drug discovery process against the dreaded corona virus.
2. Medicinal plants with therapeutic effect against diseases similar with that of coronavirus should be investigated.
3. Standardization of herbal formulations obtained from combination of medicinal plants should be maximally explored.

6. CONCLUSIONS

Despite a period in which pharmaceutical companies cut back on their application of medicinal plants in drug discovery, there are many promising drug candidates in the current development pipeline that are of plant fashion. With the increasing acceptance that the chemical diversity constituents of medicinal plants is well suited to provide the core scaffolds for future drugs, there will be further developments in the use of novel chemical constituents of

plant fashion for the development of a sustainable vaccine against the dreaded coronavirus.

7. REFERENCES

1. Balick MJ, Cox PA. Plants, People, and Culture: the Science of Ethnobotany. New York: Scientific American Library; 1997.

2. Samuelsson G. Drugs of Natural Origin: a Textbook of Pharmacognosy. 5th ed. Stockholm: Swedish Pharmaceutical Press; 2004.

3. Kinghorn AD. Pharmacognosy in the 21st century. J Pharm Pharmacol. 2001;53(2):135-48. doi: 10.1211/0022357011775334.

4. Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery. Nat Prod Rep. 2000;17(3):215-34. doi: 10.1039/a902202c.

5. Butler MS. The role of natural product chemistry in drug discovery. J Nat Prod. 2004;67(12):2141-53. doi: 10.1021/np040106y.

6. Baker JT, Borris RP, Carte B, Cordell GA, Soejarto DD, Cragg GM, et al. Natural products drug discovery and development: new perspectives on international collaboration. J Nat Prod. 1995;58(9):1325-57. doi: 10.1021/np50123a003.

7. Pavunraj M, Ramasubbu G, Baskar K. Leucas aspera (Willd.) L.: Antibacterial, antifungal and mosquitocidal activities. Trends Phytochem Res. 2017;1(3):135-42.

8. Mohammadhosseini M. The ethnobotanical, phytochemical and pharmacological properties and medicinal applications of essential oils and extracts of different Ziziphora species. Ind Crops Prod. 2017;105:164-92.

9. Mohammadhosseini M, Sarker SD, Akbarzadeh A. Chemical composition of the essential oils and extracts of Achillea species and their biological activities: A review. J Ethnopharmacol. 2017;199: 257-315. doi: 10.1016/j.jep.2017.02.010.

10. Mohammadhosseini M, Venditti A, Sarker SD, Nahar L, Akbarzadeh A. The genus Ferula: Ethnobotany, phytochemistry and bioactivities - A review. Ind. Crops Prod. 2019;129:350-94.

11. Wansi JD, Sewald N, Nahar L, Martin C, Sarker SD. Bioactive essential oils from the Cameroonian rain forest: A review - Part II. Trends Phytochem Res. 2019;3(1):3-52.

12. Rai R, Nath V. Use of medicinal plants by traditional herbal healers in central India. Indian For. 2005;131(3):463-8.

13. Savithramma N, Yugandhar P, Prasad KS, Ankanna S, Chetty KM. Ethnomedicinal studies on plants used by Yanadi tribe of Chandragiri reserve forest area, Chittoor District, Andhra Pradesh, India. J Intercult.Ethnopharmacol. 2016;5(1):49-56. doi: 10.5455/jice.20160122065531.

14. Saha MR, Rai R, Kar P, Sen A, Sarker DD. Ethnobotany, traditional knowledge and socioeconomic importance of native drink among the Oraon tribe of Malda district in India. J Intercult Ethnopharmacol. 2015;4(1):34-9. doi: 10.5455/jice.20141202060743.

15. Ganesan K, Xu B. Ethnobotanical studies on folkloric medicinal plants in Nainamalai, Namakkal District, Tamil Nadu, India. Trends Phytochem Res. 2017;1(3):153-68.

16. Aidi-Wannes W, Mhamdi B, Saidani-Tounsi M, Marzouk B. Lipid and volatile composition of borage (Borago officinalis L.) leaf. Trends Phytochem Res. 2017;1(3):143-8.

17. Nunes HS, Miguel MG. Rosa damascena essential oils: a brief review about chemical composition and biological properties. Trends Phytochem Res. 2017;1(3):111-28.

18. Ganesan K, Xu B. Ethnobotanical studies on folkloric medicinal plants in Nainamalai, Namakkal District, Tamil Nadu, India. Trends Phytochem Res. 2017;1(3):153-68.

19. Camilo CJ, Alves-Nonato CdF, Galvão-Rodrigues FF, Costa WD, Clemente GG, Sobreira Macedo MAC, et al. Acaricidal activity of essential oils: a review. Trends Phytochem Res. 2017;1(4):183-98.

20. Kingston DG. Modern natural products drug discovery and its relevance to biodiversity conservation. J Nat Prod. 2010;74(3):496-511. doi: 10.1021/np100550t.

21. Ngo LT, Okogun JI, Folk WR. 21st Century natural product research and drug development and traditional medicines. Nat Prod Rep. 2013;30(4):584-92. doi: 10.1039/c3np20120a.

22. Iwu MM. Handbook of African Medicinal Plants. 2nd ed. CRC Press; 2014.

23. Baliah NT, Astalakshmi A. Phytochemical analysis and antibacterial activity of extracts from Terminalia chebulaRetz. Int J Curr Microbiol App Sci. 2014;3(3):992-9.

24. Suroowan S, Mahomoodally F. Complementary and alternative medicine use among Mauritian women. Complement Ther Clin Pract. 2013;19(1):36-43. doi: 10.1016/j.ctcp.2012.07.002.

25. Baliga MS, Jagetia GC, Ulloor JN, Baliga MP, Venkatesh P, Reddy R, et al. The evaluation of the acute toxicity and longterm safety of hydroalcoholic extract of Sapthaparna (Alstoniascholaris) in mice and rats. Toxicol Lett. 2004;151(2):317-26. doi: 10.1016/j.toxlet.2004.01.015.

26. Jellin JM, Batz F, Hitchens K. Natural Medicines Comprehensive Database. 5th ed. California: Therapeutic Research Center; 2003.

27. Privitera JD. Olive Leaf Extract: A New/Old Healing Bonanza for Mankind. California: NutriScreen Inc; 1996.

28. Austin FG. Schistosoma mansoni chemoprophylaxis with dietary lapachol. Am J Trop Med Hyg. 1979;23(3):412-9. doi: 10.4269/ajtmh.1974.23.412.

29. Gilbert B, De-Souza J, Fascio M, Kitagaw MSN. Schistosomiasis. Protection against infection by terpenoids. Acad Brasil Cienc. 1970;42:397-400.

30. Cheever AW. Differential regulation of granuloma size and hepatic fibrosis in schistosome infections. Mem. Inst Oswaldo Cruz. 1997;92(5):689-92. doi: 10.1590/s0074-02761997000500024.

31. Sheir Z, Nasr AA, Massoud A, Salama O, Badra GA. A safe, effective, herbal anti-schistosomal therapy derived from myrrh. Am. J Trop Med Hyg. 2001;65(6):700-4. doi: 10.4269/ajtmh.2001.65.700.

32. Hassan M, El-Motaiem M, Afify H, Abaza B, El-Shafei M, Massoud AM. In vitro effect of Mirazid on Schistosoma mansoniin worms. J Egypt Soc Parasitol. 2003;33(3):999-1008.

33. El-Baz MA, Morsy TA, El-Bandary mm Motawea SM. Clinical and parasitologicals studies on the efficacy of Mirazid treatment of Schistosomiasis haematobium in Tatoon, Etsa Center, El Fayoum Governorate. J Egypt Soc Parasitol. 2003;33(3):761-76.

34. Massoud AM, El-Kholy NM, El-Shennawy FA, Farag RE. Study of some immune aspects in patients with fascioliasis before and after Chommiphoramolmol (Mirazid) treatment. J. Egypt. Soc. Parasitol. 2004;34(1):315-32.

35. Aly HF, Aly SA. Essential role of Citrus reticulata and Mirazid in treatment of Schistosoma mansoniinfected mice: Biochemical and parasitological studies. Pol J Food Nutr Sci. 2006;56(4):461-7.

36. Mak NK, Wong-Leung YL, Chan SC, Wen J, Leung KN, Fung MC. Isolation of anti-leukemia compounds from citrus reticulate. Life Sci. 1999;58(15):1269-76. doi: 10.1016/0024-3205(96)00088-4.

37. Tkachenko JG, Kazarinova NV, Muzyehenko LM, Shurgaya AM, Pavlova OV, Safonova, NG. Antibiotic properties of essential oils of some plant species. Rastit Resur. 1999;35:11-24.

38. Tanizawa H, Ohkawa Y, Takino Y, Ueno A, Kageyama T, Hara S. Studies on natural antioxidants in Citrus species. Determination of antioxidant activity of citrus fruits,. Chem Pharm Bull (Tokyo). 1992;40(7):1940-2. doi: 10.1248/cpb.40.1940.

39. Tian Q, Miller EG, Hassan A, Tang L, Patil BS. Differential inhibition of human cancer cell proliferation by citrus limonoids. Nutr Cancer. 2001;40(2):180-4. doi: 10.1207/S15327914NC402_15.

40. Aly SA, Hamed MH. Effect of Ailanthus altissima and Zizyphus spina christion bilharzial infestation in mice: Histological and histopathological studies. J Applied Sci. 2006;6(7):1437-46.

41. Okunade AL, Bikoff RE. Casper SJ, Oksman A, Goldberg DE, Lewis WH. Antiplasmodial activity of extracts and quassinoids isolated from seedlings of ailanthus altissima (simaroubaceae). Phytother Res. 2003;17(6):675-7. doi: 10.1002/ptr.1336.

42. Tamura S, Fukamiya N, Okano M, Koyama J, Koike K, Tokuda H, et al. Three new quassinoids, ailantinol, E, F and G from Ailanthus altissima. Chem Pharm Bull (Tokyo). 2003;51(4):385-9. doi: 10.1248/cpb.51.385.

43. Olajide OA. Investigation of the effects of selected medicinal plants on experimental thrombosis. Phytother Res. 1999;13(3):231-2. doi: 10.1002/(SICI)1099-1573(199905)13:3<231::AID-PTR414>3.0.CO;2-2.

44. El-Banhawey MA, Ashry MA, El-Ansary AK, Aly SA. Effect of Curcuma longa or parziquantel on Schistosoma mansoni infected mice liver-histological and histochemical studies. Indian J Exp Biol. 2007;45(10):877-89.

45. El-Ansary A, Farouk H. Effect of schistosomal infection and its treatment with Curcuma longa extract on some bioenergetics parameters in mice livers. Bull N R C Egypt. 2001;26:61-69.

46. Chuang SE, Cheng AL, Lin JK, Kuo ML. Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. Food Chem Toxicol. 2000;38(11):991-5. doi: 10.1016/s0278-6915(00)00101-0.

47. Mohanty I, Arya DS, Dinda A, Joshi S, Talwar KK, Gupta SK. Protective effects of Curcuma longa on ischemia-reperfusion induced myocardial injuries and their mechanisms. Life Sci. 2004;75(14):1701-11. doi: 10.1016/j.lfs.2004.02.032.

48. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect. 2001;109 Suppl 1(Suppl 1):69-75. doi: 10.1289/ehp.01109s169.

49. Siddiqui AA, Iram F, Siddiqui S, Sahu K. Role of natural products in drug discovery process. Int J Drug Dev Res. 2014;6(2):172-204.

50. Cordell GA, Colvard MD. Some thoughts on the future of ethnopharmacology. J Ethnopharmacol. 2005;100(1-2):5-14. doi: 10.1016/j.jep.2005.05.027.

51. Patwardhan B. Ethnopharmacology and drug discovery. J Ethnopharmacol. 2005;100(1-2):50-2. doi: 10.1016/j.jep.2005.06.006.

52. Heinrich M, Gibbons S. Ethnopharmacology in drug discovery: an analysis of its role and potential contribution. J Pharm Pharmacol. 2001;53(4):425-32. doi: 10.1211/0022357011775712.

53. Heinrich M. Ethnopharmacology: a short history of a multidisciplinary field of research. In: Heinrich M, Jager AK, editors. Ethnopharmacology. West Sussex: Wiley; 2001.

54. Sam TW. Toxicity testing using the brine shrimp: Artemia salina. In: Colegate SM, Moluneux RJ, editors. Bioactive natural products. Detection, isolation and structural determination. Boca Raton: CRC Press; 1993:441-56.

55. Berlin B. Ethnobiological Classification: Principles of categorization of plants and animals in traditional societies. Princeton: Princeton University Press; 1992.

56. Hamburger M, Hostettmann K. Bioactivity in plants: the link between phytochemistry and medicine. Phytochemistry. 1991;30(12):3864-74. doi: https://doi.org/10.1016/0031-9422(91)83425-K.

57. Yesilada E, Honda G, Sezik E, Tabata M, Goto K, Ikeshiro Y. Traditional medicine in turkey IV. Folk medicine in the Mediterranean subdivision. J Ethnopharmacol. 1993;39(1):31-8. doi: 10.1016/0378-8741(93)90048-a.

58. Heinrich M, Edwards S, Moerman DE, Leonti M. Ethnopharmacological field studies: a critical assessment of their conceptual basis and methods. J Ethnopharmacol. 2009;124(1):1-17. doi: 10.1016/j.jep.2009.03.043.

59. Bennett BC, Balick MJ. Does the name really matter? The importance of botanical nomenclature and plant taxonomy in biomedical research. J Ethnopharmacol. 2014;152(3):387-92. doi: 10.1016/j.jep.2013.11.042.

60. Bambhole VD, Jiddewar GG. Antiobesity effect of Iris versicolor and Holoptelea integrifolia in rats. Sachitra Ayurveda. 1985;37:557-61.

61. Khalid S, Rizwan GH, Yasin H, Perveen R, Abrar H, Shareef H, et al. Medicinal importance of Holoptelea integrifolia (Roxb). Planch-its biological and pharmacological activities. Nat Prod Chem Res. 2013;2(1):1-4. doi: 10.4172/2329-6836.1000124.

62. Wahab NZ, Rahman RA, Ismail A, Mustafa S, Hashim P. Assessment of antioxidant capacity, anti-collagenase and anti-elastase assays of Malaysian unfermented cocoa bean for cosmetic application. Nat Prod Chem Res. 2014;2(3):1-6. doi: 10.4172/2329-6836.1000132.

63. Verpoorte R. Exploration of nature's chemodiversity: the role of secondary metabolites as leads in drug development. Drug Discov Today. 1998;3(5):232-8. doi: https://doi.org/10.1016/S1359-6446(97)01167-7.

64. Pieroni A, Privitera S. Ethnobotany and its links to medical sciences and public health: quo vadis? Z Phytother. 2014;35(02):58-62. doi: 10.1055/s-0034-1371719.

65. Farnsworth NR, Akerele O, Bingel AS, Soejarto DD, Guo Z. Medicinal plants in therapy. Bull World Health Organ. 1985;63(6):965-81.

66. Gullo VP. Discovery of novel natural products with therapeutic potential. Approaches to the discovery of drugs from plant sources. New Jersey: Schering-Plough Research Institute; 1994.

67. Leonti M, Stafford GI, Cero MD, Cabras S, Castellanos ME, Casu L, et al. Reverse ethnopharmacology and drug discovery. J Ethnopharmacol. 2017;198:417-31. doi: 10.1016/j.jep.2016.12.044.

68. Flick AC, Ding HX, Leverett CA, Kyne RE, Liu KKC, Fink SJ, et al. Synthetic approaches to the new drugs approved during 2015. J Med Chem. 2017;60(15):6480-515. doi: 10.1021/acs.jmedchem.7b00010.

69. Lombardino JG, Lowe 3rd JA. The role of the medicinal chemist in drug discovery--then and now. Nat Rev Drug Discov. 2004;3(10):853-62. doi: 10.1038/nrd1523.

70. Li G, Lou HX. Strategies to diversify natural products for drug discovery. Med Res Rev. 2018;38(4):1255-94. doi: 10.1002/med.21474.

71. Baker DD, Chu M, Oza U, Rajgarhia V. The value of natural products to future pharmaceutical discovery. Nat Prod Rep. 2007;24(6):1225-44. doi: 10.1039/b602241n.

72. Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. J Nat Prod. 2003;66(7):1022-37. doi: 10.1021/np030096l.

73. Clardy J, Walsh C. Lessons from natural molecules. Nature. 2004;432(7019):829-837. doi: 10.1038/nature03194.

74. Nicolaou KC, Snyder SA. The essence of total synthesis. Proc Natl Acad Sci U S A. 2004;101(33):11929-36. doi: 10.1073/pnas.0403799101.

75. Peterson EA, Overman LE. Contiguous stereogenic quaternary carbons: a daunting challenge in natural products synthesis. Proc Natl Acad Sci U S A. 2004;101(33):11943-8. doi: 10.1073/pnas.0402416101.

76. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov. 2005;4(3):206-20. doi: 10.1038/nrd1657.

77. Lee D, Bhat KPL, Fong HHS, Farnsworth NR, Pezzuto JM, Kinghorn AD. Aromatase inhibitors from Broussonetia papyrifera. J Nat Prod. 2001;64(10):1286-93. doi: 10.1021/np010288l.

78. Feher M, Schmidt JM. Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. J Chem Inf Comput Sci. 2003;43(1):218-27. doi: 10.1021/ci0200467.

79. Piggott AM, Karuso P. Quality, not quantity: the role of natural products and chemical proteomics in modern drug discovery. Comb Chem High Throughput Screen. 2004;7(7):607-30. doi: 10.2174/1386207043328409.

80. Hall MG, Wilks MF, Provan WM, Eksborg S, Lumholtz B. Pharmacokinetics and pharmacodynamics of NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione) and mesotrione, inhibitors of 4-hydroxyphenyl pyruvate dioxygenase (HPPD) following a single dose to healthy male volunteers. Br J Clin Pharmacol. 2001;52(2):169-77. doi: 10.1046/j.0306-5251.2001.01421.x.

81. Eldridge GR, Vervoort HC, Lee CM, Cremin PA, Williams CT, Hart SM, et al. High-throughput method for the production and analysis of large natural product libraries for drug discovery. Anal Chem. 2002;74(16):3963-71. doi: 10.1021/ac025534s.

82. Burke MD, Berger EM, Schreiber SL. A synthesis strategy yielding skeletally diverse small molecules combinatorially. J Am Chem Soc. 2004;126(43):14095-104. doi: 10.1021/ja0457415.

83. Ganesan A. Natural products as a hunting ground for combinatorial chemistry. Curr Opin Biotechnol. 2004;15(6):584-90. doi: 10.1016/j.copbio.2004.09.002.

84. Tan DS. Current progress in natural product-like libraries for discovery screening. Comb Chem High Throughput Screen. 2004;7(7):631-43. doi: 10.2174/1386207043328418.

85. Kramer R, Cohen D. Functional genomics to new drug targets. Nat Rev Drug Discov. 2004;3(11):965-72. doi: 10.1038/nrd1552.

86. Hoessel R, Leclerc S, Endicott JA, Nobel ME, Lawrie A, Tunnah P, et al. 1999. Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases. Nat Cell Biol. 1999;1(1):60-7. doi: 10.1038/9035.

87. Eisenbrand G, Hippe F, Jakobs S, Muehlbeyer S. Molecular mechanisms of indirubin and its derivatives: novel anticancer molecules with their origin in traditional Chinese phytomedicine. J Cancer Res Clin Oncol. 2004;130(11):627-35. doi: 10.1007/s00432-004-0579-2.

88. Hwang BY, Lee JH, Koo TH, Kim HS, Hong YS, Ro JS, et al. Kaurane diterpenes from Isodon japonicus inhibit nitric oxide and prostaglandin E2 production and NF-kappaB activation in LPS-stimulated macrophage RAW264.7 cells. Planta Med. 2001;67(5):406-10. doi: 10.1055/s-2001-15808.

89. Lee JH, Koo TH, Hwang BY, Lee JJ. Kaurane diterpene, kamebakaurin, inhibits NF-kappa B by directly targeting the DNA-binding activity of p50 and blocks the expression of antiapoptotic NF-kappa B target genes. J Biol Chem. 2002;277(21):18411-20. doi: 10.1074/jbc.M201368200.