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Review

Medicinal plants: Prospective drug candidates against the dreaded Coronavirus

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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.

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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.,

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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].

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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. mansoni* 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 therapeutic 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 gullbladder 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.

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