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Natural products as veritable source of novel drugs and medicines: A review

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Abstract
Natural medicine has become a popular form of healthcare worldwide. Its impact on global healthcare delivery has progressed significantly over the years. The contribution of natural products to global healthcare is enormous, having provided key lead compounds from the metabolites for the development of synthetic molecules. Natural products are expected to play an invaluable role as one of the major sources of novel drugs in the years ahead. This is due to the incomparable structural diversity, relatively small dimensions of them and the seemingly drug-like properties. The renewed interest in natural products research in the last three decades is fueled by the landmark developments in separation methods, spectroscopic techniques and sensitive biological assays, as well the failure of currently available medicines to combat resurgent and emerging diseases. The review will describe the critical role of natural products in drug discovery and development, and the clinical applications of drugs of ethnic origin in the treatment and management of human diseases.

Keywords: Natural products, medicinal plants, metabolites, drugs, medicines, drug discovery and development

1. Introduction
A drug or medicine is any substance out side food or water, which when ingested, inhaled, injected, sniffed, smoked, absorbed through a skin patch, or dissolved under the tongue brings about an alteration or modification of physiological (body) function [1, 2]. Drugs are primarily used in the prevention (prophylaxis), mitigation, diagnosis and/or treatment (management) of human or animal diseases. Aside therapeutics (a branch of medicine concerned with the treatment of pathological conditions in humans), drugs are also used for pleasure or recreation, as well as for religious or spiritual activities (non-medical purposes). The drugs (e.g. entheogens) used for religious and spiritual functions could be neurostimulants, sedative-hypnotics, euphoriants or anaesthetics. The terms drugs and medicines can be used interchangeably, although there is a subtle difference between them. All medicines are drugs, but not all drugs are medicines. Thus, prescription or pharmaceutical drugs are best referred to as medicines, since these agents are exclusively employed for patient healthcare and wellbeing. Although, certain drugs which were hitherto labeled as illicit and associated with a lot of stigma, are gradually creeping into clinical medicine. Some of these agents have been found to possess potential clinical utility, but they are not approved for clinical use by the regulatory authorities in many countries of the world. These illegal drugs with legal clinical applications include cannabis, cocaine, heroin, etc [3]. For instance, cocaine in low dose is used in tooth extraction as a topical dental anaesthetic agent. Heroin has also been used as an analgesic in palliative care. It, therefore, implies that once a drug, which hitherto was regarded as illicit (whose use is socially unacceptable) creeps into medical practice, it ceases to be an illicit drug, but a medicine, and becomes a licit therapeutic agent. Natural medicine has become a popular form of healthcare worldwide. The use of natural medicine in the treatment of human ailments has progressed significantly in the last three decades. Since the 1990s, interest in natural product research has increased considerably. As a result of outstanding developments in the areas of separation methods, spectroscopic techniques, and sensitive bioassays, natural product research has gained new attention for providing novel chemical entities [4]. Natural products, including plants, microbes and animals, marine organisms and minerals (both organic and inorganic in nature) have been the basis of treatment of human diseases [5].

Many centuries ago, an extensive use of plants as medicines have been reported and were initially taken in the form of crude drugs such as tinctures, elixirs, poultices, powders, and other herbal formulations [6].

However, the use of herbal products should be based on scientific origin; otherwise they would be useless and unsafe [7]. Furthermore, the irrational use of these herbal products may cause serious toxicity for humans. Unfortunately, many people underestimate the toxicity of natural products and do not realize that these agents could be as toxic or even more than the synthetic drugs [7]. A typical example of a toxic herbal product are the leaves of *Atropa belladonna* [8] and *Digitalis purpurea* [9, 8], which show severe systemic toxicity if taken orally. The medical use of plants in their natural and unprocessed form undoubtedly began when the first intelligent animals observed that certain foods of ethnic origin altered specific body functions.[10]A vast majority of the natural products used as drugs are of plant origin. The poisonous or therapeutic potential of plants were discovered by man in his search for food. Some plants were found to have very dramatic effects on the body and some were found to cure certain ailments [11]. The knowledge of the plants was passed on through the generations, and man accumulated considerable experience of drugs which could be obtained from plants in his surrounding environment.

2. Natural Products in Drug Development

The recent advances in analytical chemistry (e.g. nuclear magnetic resonance spectroscopy, mass spectrometry, electrochemical and thermal analyses, hybrid techniques, etc.) and computer-aided molecular designs have created new frontiers in natural products research. These sophisticated techniques have made it possible to elucidate the molecular structures of complex natural products, and thus furnish valuable lead compounds and new drugs. Some of these drugs have been used clinically to treat certain diseases afflicting mankind [12]. Up to the end of the 18th century, crude drugs were still being used in the form of powders, simple extracts, or tinctures. In 1803, Serturner isolated morphine from opium, and this landmark discovery ushered in a new era in the annals of medicine, characterized by the isolation and chemical identification of pharmacologically active compounds from crude drugs. The discovery of morphine was soon followed by the isolation of many other important compounds, such as strychnine (1817), quinine and caffeine (1820), nicotine (1828), cocaine (1855), atropine (1933), and the mixture of cardiac glycosides digitalline, from fox glove leaves in 1968. With the development of organic chemistry, the chemical structures of many of the isolated compounds were elucidated. This development progressed with ever-increasing speed in the 20th century, and today, the main constituents of all important crude drugs have been isolated and their structures determined [11]. Researchers have identified 122 compounds used in modern medicine which were derived from plant sources; 80 % of these have had an ethno medical use identical or related to the current use of the active constituents of the plant [13]. The steroid hormones (sex steroids, corticosteroids, contraceptive drugs etc.) for instance, are prepared from plant-derived compounds, *sapogenins* (e.g. diosgenin, hecogenin), the plant *sterols*-stigmasterol and sitosterol, *alkaloids*- solasodine); the chemical structures permit their conversion to the desired drugs, while others have to be manufactured through the technique of biotechnology [11]. Natural products produced by micro-organisms have become a veritable source of drugs yielding antibiotics, immunosuppressive agents and anti-dyslipidaemic drugs. Most antibiotics are natural products, produced by microorganism such as bacteria or fungi. Natural products are expected to play an important role as one of the major sources of new drugs in the years ahead, because of: (i) their incomparable structural diversity, (ii) the relatively small dimensions of many of them (< 2000 Da), and (iii) their 'drug-like' properties, i.e., their ability to be absorbed and biologically transformed [14].

3. Modern Drugs from Natural Products

The *kingdom plantae* is indeed a veritable source of medicinal plants and an extraordinary reservoir of molecules [15]. Plants have been used by humans since time immemorial to cure diseases and to promote relief from ailments [16]. Plants have been the core of many traditional medicine systems the world over for thousands of years and continue to provide mankind with new remedies [11]. Plant-based medicines initially dispensed in the form of crude drugs, such as tinctures, teas, powders, and other herbal formulations, now serve as the basis of novel drug discovery [17, 18, 6]. Plants are also, sources of substances such as oils, starch, flavouring and sweetening agents, gums, wax etc., which can be used in the manufacture of pharmaceuticals and cosmeceuticals, foods (or nutraceuticals) and beverages [9]. Natural products used in the preparation of cosmetics and other personal and skin care have very low systemic toxicity. An example is castor bean (*Ricinus communis*) from where castor oil is derived. It protects against harsh weather conditions and soothes the skin [20].

Natural products are small biomolecules or biological materials produced in nature by any living organisms, including its primary and secondary metabolites [21, 22, 23]. A natural product can be an entire organism such as plant, an animal or a micro-organism, which has not been subjected to any treatment except, perhaps, to a simple process of preservation such as drying; a natural product can also be part of an organism, e.g., a leaf or flower of a plant, or an isolated gland or organ of an animal; an extract of an organism or an exudate, as well as pure compound(s) isolated from a plant, an animal or a micro-organism [11].

Natural products were for centuries the only drugs available, and among the modern drugs in use today that are produced by the industrialized nations of the world, 60 % are of natural product origin [24, 25]. Cardiac glycosides, morphines and antibiotics are but a few examples. These are isolated from the producing organism, purified and compounded into tablets, injectables, etc. for direct use as drugs. Other drugs are derivatives of natural products, where the chemical structure has been modified to yield a product with the desired pharmacological properties. An example is the large group of steroids − sex hormones, corticosteroids, contraceptives, among others, which are made from plant steroids. Drugs produced by total chemical synthesis can also be considered to be of natural origin [11]. In some cases, the structure(s) of pharmacologically active, naturally occurring substances have served as models/leads for the synthetic compound and it has been possible to modify the structure and still retain or even improve the pharmacological properties. For instance, the alkaloid tubocurarine derived from *Chondrodendron tomentosum* employed in surgery (and up-to-date) as a muscle relaxant (neuromuscular blocker) causes the relaxation of the skeletal muscles through the blockade of ACh receptors on the motor end plates. Intensive studies on the relation between structure and pharmacological effects have led to the synthesis of several other substances having the same effect. One of the most recent of these is atracurium. The drug tubocurarine is a classic example of the structure of a natural product of ethnic origin being used as a model for the

synthesis of drugs with improved properties [11].

Natural products play a major and significant role as drugs, and as lead structures for the development of synthetic molecules. These new molecules of interest in drug design specialties focus on the re-arrangement of chemical entities or structural isomers of naturally occurring products in order to generate novel molecules, which may be formulated into clinically useful therapies [26]. About60-70 % of the drugs introduced to the market during the last three decades are derived from small biogenic molecules either directly or indirectly (i.e. either sourced directly from natural products or their metabolites). It is estimated that approximately 420,000 plant species exist in nature, and over 250,000 of these are higher plants that can be chosen for pharmacological screening. Screening for neo-drugs in plants implies screening of extracts for the presence of novel compounds and an investigation of their biological properties [27].

Many developing world governments and peoples, including International Funding Agencies, e.g., WHO are convinced that research into natural products medicine is worthwhile, and thus has encouraged countries to study it and integrate it into their health care system [28]. The need to support research into natural product medicine has also been stressed [29]. There has been a global upsurge of interest in Traditional Medicine or Complementary and Alternative Medicine [30]. Up to 25 % of all prescriptions in Europe and America, is said, to contain plant products or were originally derived from them [31, 32]. Plants are potential sources of chemicals with well-defined pharmacological activities for use in the treatment of specific disease conditions [16, 33]. But, even more importantly, plants are also sources of substances, such as oils, starch, gums, wax, flavouring and sweetening agents which can be employed in the manufacture of pharmaceuticals and other products [19]. Over 50 % of the best-selling pharmaceuticals in use today are derived from natural products [34, 35].

Higher plants have been described as the 'sleeping giant' of drug development [36], who demonstrated that, over the period 1969 – 1973, the total number of prescriptions dispensed by public pharmacies in the USA had consistently contained about 25 % of plant–derived drugs, either in the form of crude plant material or a crude extract obtained from plant(s), or purified active principle obtained from plants. WHO has been promoting traditional medicines as a source of less expensive, comprehensive medical care, especially in developing countries [5]. This is even more important, since 80 % of the population in the developing world relies on medicinal plant preparations for their primary health care needs. Such herbal remedies are easily available, cheaper, time tested and considered safer than some modern orthodox drugs.

Natural products from plants in human history have been used as medicines, fragrances, food additives and pesticides [27]. Through the use of plants, man has taken advantages of the defensive, attractive and medicinal compounds present in leaves, flowers, roots, sap and bark species around the world [37]. Even though, very large numbers of plants are constantly being screened for their possible pharmacological value, it is estimated that only about 1 % of medicinal plants has been subjected to scientific evaluation for potential chemotherapeutic value [38].

Presently, plants are the most exclusive source of drugs and medicines for the majority of the world's population. Most potent medicines used in western medicine today were extracted from plants, and several synthetic drugs are made from starting molecules extracted from plant sources [28, 27, 5]. Recently, there has been a rekindled interest in natural products research due to failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas, such as immunosuppression, anti-microbials and metabolic diseases [27].

Natural products have long been an important source of medicines for humans. Each plant is a chemical factory capable of synthesizing unlimited number of highly complex and unusual compounds [27]. There are no less than 120 distinct chemical substances derived from plants that are considered important drugs currently in clinical use in the world, while several other drugs are simple synthetic modifications of these natural products [39].

Therapeutic agents from medicinal plants have been incorporated into conventional (orthodox) medicine for no less than a century, and an example is the sesquiterpene endoperoxide, artemisinin from the Chinese herbal plant, *Artemisia annua* Linn. Used as an anti-malaria drug [40]; and taxol from *Taxus brevifolia*, used in metastatic breast cancer [41].

Other classical instances of drugs of phyto-origin include atropine, an anti-muscarinic anti-cholinergic alkaloid from *Atropa belladonna* (Deadly night shade) used as mydriatic, spasmolytic and anti-ulcer agent; morphine and papaverine isolated from *Papaver somniferum* for the synthesis of analgesic and spasmolytics; quinine and quinidine derived from *Cinchona succirubra* bark used as anti-malarial and anti-dysrthymic agents; digoxin, the cardiac glycoside anti-failure agent used in the management of congestive cardiac failure from *Digitalis purpurea* (Fox glove plant); cocaine, a stimulant with high potential for abuse, from *Erythroxylon coca* (coca plant) for the synthesis of local anaesthetic agents; Ephedrine from *Ephedra sinica* for synthesis of sympathomimetic drugs; Reserpine from *Rawolfia serpentina* for the synthesis of anti-hypertensives; Emetine, an alkaloid isolated from *Ipecacuanha* is used in the induction of emesis in emergency poisoning; podophyllotoxin, an isolate from *Podophyllum pelatum* used as cathartics in herbal medicine was developed etoposide and teniposide, both are potent anti-neoplatic drugs indicated in the management of small-cell carcinoma of the lungs, testicular carcinoma, the lymphomas and leukaemias [42]. Anthraquinone glycosides, an irritant laxative derived from the cassia leaf is used for the treatment of constipation [27].

The late 1950s and the early 1960s witnessed a strong and vigorous search for novel anti-tumour drugs, and this effort culminated in the development of the first ever clinically useful anti-neoplatic agents, the vinca alkaloids (vincristine and vinblastine) isolated from the Madagascan periwinkle (*Catharantus roseus, Vinca rosea)* [27]. These vinca alkaloids have been commercially developed and have been employed in the maanagement of Hodgkin's disease, non-Hodgkin's lymphoma, chorion carcinoma, cancers of the head and neck, renal and testicular cancers, as well as lymphoblastic leukaemia.

Angiotensin converting enzyme was discovered from the venom of the Pit viper *Bothrops jararaca* (Viperidae) [27]. This effort led to the development of the potent anti-hypertensive agents, captopril and enalapril [43]. The fagara (*Zanthoxylum zanthoxyloides*) isolate has a number of anti-sickling compounds [44, 45]. Ciklavit, a natural product derivative for the management of Sickle cell disease has been developed from *Cajanus cajan* extract [46]. Forskolin, a novel cardiovascular agent of phyto-origin was isolated from *Coeleus forskolii*, and current clinical trials have centred on the cardiovascular, Broncho spasmolytic effects and on the treatment of glaucoma because of its biochemical and

physiologic properties (vasodilatation, positive inotropy, reduction of intra-ocular pressure, inhibition of platelet aggregation) [27].

Anti-viral agents with potential clinical and therapeutic utility have been developed from plant sources. These two plant-derived compounds, castanospermine and hypericin from *Casternospermum australe* and *Hypericum perforatum* respectively have been shown to inhibit the replicaiton of human immunodeficiency virus (HIV). A number of compounds exhibiting anti-retroviral activity and isolated from natural products is on steady increase [27]. Calanolide A, a coumarine isolated from *Callophyllum lanigerum*, and two other natural Product–derived molecules are in phase II clinical trials [47].

The marine kingdom has also provided mankind with valuable chemical compounds/leads that have led to the development of novel drugs. The discovery of these two compounds, arabino- and ribo-pentosyl nucleosides obtained from marine sponges collected in Florida, USA, and the subsequent development of the chemical derivatives ara-A and ara-C led to the development of two potentdrugs, Vidarabine and Cytarabine respectively [48]. These two nucleosides possess significant anticancer activity, and have been in clinical medicine for several decades now. Ziconotide, a peptide derived from marine cone snail was the earliest drug from the sea. It was approved in 2004 by the US Food and Drug Administration (FDA) for the treatment of chronic pain of spinal origin. The antineoplastic agent, Trabectedin, from tropical sea-squirt was the second drug from the marine environment, and was approved by the European Union in 2007 for the treatment of soft-tissue sarcoma [48]. A host of other candidates are currently at various phases of clinical trials for possible anti-tumour activity.

Natural products are known for their broad diversity, both in chemical structure and biological functionality. These properties have endeared researchers, and as a major source of lead compounds for novel drug development [49]. Natural products have long been utilised in clinical medicine and hold potential prospects to target resurgent and emerging diseases [50]. They canbe used in biological therapies (immunotherapies) either to enhance or suppress immune response (immunomodulation). This is due to the immuno-active activity that has been demonstrated in natural products research.

4. Conclusions

Natural products have for several decades played a fantastic role as source of novel drugs and medicines, being ideal raw materials in the drug discovery and development process. The application of plant-based drugs in clinical oncology has revolutionized the therapeutic management of malignancies, as well as other communicable and non-communicable diseases. There is great hope for the future of natural products in combating the scourge of multitude of health challenges plaguing mankind, in which the currently available medicines have failed to provide the needed therapeutic benefits. Chemical compounds isolated from nature will continue to provide humankind with veritable therapeutic leads for the development of clinically efficacious and effective pharmaceutical products. There is, therefore, a compelling necessity to tilt towards translational researches, that is, the commercialization and patenting of bench (laboratory) studies using well validated, up-to-date, and appropriate scientific tools and protocols. This can only be achieved by direct engagement with the pharmaceutical industries.

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