

A review of nature's pharmacy: Unveiling the sources, classes and therapeutic potentials of natural products in drug discovery

Juliet Chiamaka Muoegbunam ^{1, *}, Valerie Ezinne Nwankwo ¹, Amarachukwu Ukamaka Onwuzuligbo ², Blessing Ogechukwu Umeokoli ¹, Chika Christiana Abba ¹, Festus Basden C. Okoye ¹, and Kenneth Gerald Ngwoke ¹

¹ Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

² Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

GSC Biological and Pharmaceutical Sciences, 2025, 30(03), 053-063

Publication history: Received on 14 January 2025; revised on 24 February 2025; accepted on 27 February 2025

Article DOI: <https://doi.org/10.30574/gscbps.2025.30.3.0075>

Abstract

Natural products have been an important source of inspiration for the discovery of new drugs, with many successful drugs derived from natural sources. This review aims at providing an overview of the current state of natural products in drug discovery, highlighting their sources, classes, importance and therapeutic potentials. The findings of this review underscore the significant contribution of natural products in drug discovery with an ongoing stream of new compounds being discovered and developed into effective medicines. Furthermore, this review emphasizes the importance of natural products derived from a wide range of sources, including plants, animals, microorganisms and marine organisms. The review concludes with a focus on plants in drug discovery, tracing the historical significance of medicinal plants and highlighting the various bioactive metabolites obtained from plants with potential therapeutic applications.

Keywords: Natural Products; Drug Discovery; Medicinal Plants; Bioactive Metabolites

1. Introduction

1.1. General Overview of Natural Products

A natural product is broadly defined as any substance derived from living organisms. This includes biotic materials such as wood, crude oil, and silk; bio-based materials like starch, bio-plastics, and casein; bodily fluids such as milk and plant exudates; and other naturally occurring substances that were once found in living organisms like soil and coal [1]. A more restrictive definition describes natural products as organic compounds synthesized by living organisms. Alternatively, one can also say that natural products are chemical organic substances produced by living organisms through primary and secondary metabolic pathways [2].

From ancient times, natural products have been the foundation of traditional system of healing globally and have remained an essential part of history and culture [3]. Humans have used natural products like plants, animals, microorganisms and marine organisms in the alleviation and treatment of diseases. According to available fossil records, man's use of plants as medicines can be traced back to at least 60,000 years [4]. In spite of the fact that the use of bioactive natural products as herbal drug preparations dates back to thousands of years ago, their application in the form of isolated and characterized compounds to modern drug discovery and development only started in the 19th

* Corresponding author: Juliet Chiamaka Muoegbunam.

century [5]. So far, it has been documented that natural products (considering their unparalleled chemical diversity) play pivotal roles in modern drug development, especially in the cases of substances with antibacterial and antitumor activities [4]. Among the anti-cancer drugs approved within the time frame of about 1940 - 2002, about 54 % were gotten from natural products. Vinca alkaloids obtained from *Catharanthus roseus*, and the terpene paclitaxel from *Taxus baccata*, are among the successful anticancer agents derived from plants [6, 7]. Between 1981 and 2002, the use of natural products in developing new therapeutic agents especially in the search for new chemical structures showed great success [8]. Within that 22-year timespan, drugs derived from natural products have been notable. This is especially true in the case of anti-hypertensive agents, where about 64 % of newly synthesized drugs had their source from natural products [9].

In as much as the popularity of synthetic medicinal products increased due to factors like favorable production cost, shorter production timeline, easy quality control, strict regulation and quick effects, their safety and efficacy have been and would remain a viable cause for concern [5]. This has resulted in about 80 % of the total population of the developing world depending on natural products for their healthcare needs due to their tested and tried safety and efficacy [5].

Natural products will undoubtedly remain vital sources of medicinal agents. In addition to the natural products that have been found to have direct medicinal application as drug moieties, several others serve as chemical models or templates for design, synthesis and semi-synthesis of new substances for treating man's diseases [10]. There are currently new approaches to drug discovery like combinatorial chemistry and computer based molecular modeling design. Many drugs are made by synthetic chemistry but none of these approaches can replace the important role of natural products in drug discovery and development as many of the core structures for synthetic chemicals are based on natural products. With time these natural products have undergone many developments in their ability to interact with several different biological targets and some have also become very important drugs in the healthcare system [11]. Therefore, it is notable that there is increasing convergence of traditional medicine and modern medicine. A good example of a successful drug development from natural products is artemisinin and its analogues which are used currently worldwide for antimalarial treatment. This shows how research using natural products has made notable contribution in drug development [12, 13].

1.2. Sources of Natural Products

Active drug substances have been derived from various sources such as: plants, animals, microbial and marine sources.

1.2.1. Plant Sources

Plants have been a part of traditional medicine systems and have been used for thousands of years to treat many ailments throughout human history. Currently, most prescription drugs are derived from plant products, a proportion that is expected to increase further with the discovery of more plant with medicinal values [14]. Some examples of drugs derived from plant sources include: anti-inflammatory agents, cardio-vascular agents, anti-diabetic agents, anti-obesity agents, anti-malarial agents, immunomodulators, anti-leishmanial agents, anti-viral agents and anti-neoplastic agents [15]. Researchers have also isolated and characterized bioactive compounds from plants like *Newbouldia laevis* [16] and *Talinum triangulare* [17], demonstrating the potential of plant-based natural products in drug discovery.

1.2.2. Animal Sources

Animals have also served as sources for some drugs. Epibatidine, an analgesic that is ten times more potent than morphine is gotten from the skin of an Ecuadorian poison frog [18, 19]. Many diseases have been cured with venoms and toxins of several animals. Cilazapril [20] and captopril [21], both effective anti-hypertensive agents, were developed from teprotide, an extract of Brazilian viper.

1.2.3. Microbial Sources

Since the serendipitous discovery of penicillin from the filamentous fungus *Penicillium notatum* by Fleming in 1929 [22], microbes have been a major source and further focus into newer antibiotic therapies especially with the worsening resistance to current antimicrobial agents. Tetracycline is another antibiotic gotten from microbes (*Streptomyces aureofaciens*) used in the treatment of urinary tract infections, acne and in several dental infections [23]. Chloramphenicol from *Streptomyces venezuelae* is another prominent example and it is used in the treatment of typhoid, cholera and in brain abscesses [24]. Other drugs that have been derived from microbes so far include: imipenem, norcardicin, aztreonam, erythromycin amongst many others [25]. In the recent years, intensive research efforts have been directed to endophytic fungi for the purpose of discovering novel therapeutic agents. Endophytes are special types of microorganisms inhabiting the plants biotope. They represent an underexplored source of unique bioactive

molecules, which can be developed into drugs for diverse therapeutic applications. Our research group has devoted a lot of research effort in this regards and the results so far are quite fascinating [26-32]. This class of microorganisms is unique in that they are amenable to manipulation at a laboratory scale and their production of novel secondary metabolites can be enhanced by various modulating techniques [33, 34]. Studies have also shown that they may be responsible for generating some novel bioactive metabolites of their host plants [35, 36].

1.2.4. Marine Sources

About 70 % of the earth's surface is covered with water. Pharmaceutical companies realized that the ocean may be a viable source for unique biodiversity and may be a possible source for potential drug candidates [37]. The exploration of the marine environment has resulted in the isolation of thousands of structurally unique bioactive marine natural products [38]. Some examples include: ziconotide, a peptide first discovered in a tropical cone snail used in the treatment of pain, plitidepsin, a depsipeptide isolated from Mediterranean Tunicate, *Aplidium albicans* [39], used in the treatment of various cancers, spissulosine, isolated from marine clam *Spisula polynyma*, exhibited substantial selective activity against tumor cells compared to normal cells [40]. Furthermore, recent studies have also explored the potential of marine-derived fungi as sources of novel bioactive compounds [41].

1.3. Classification of Natural Products

Natural products can be classified according to their biological function, biosynthetic pathway or their source [42]. Based on their biological function, natural products can be divided into two major classes which include: primary metabolites and secondary metabolites. Based on their biosynthetic pathway, they can be classified into four major groups, including: alkaloids, phenylpropanoids, polyketides and terpenoids [43]. Based on their source, there are examples of biological sources used to find new natural products including, prokaryotic organisms (divided into two domains; Archea and Bacteria) and eukaryotic organisms (which include four major kingdoms; Protista, Fungi, Plantae and Animalia) [44].

1.3.1. Classification Based on Biological Function

Primary Metabolites

Primary metabolites are organic molecules that have an intrinsic function that is essential to the survival of the organism that produces them (that is, the organism is likely to die without them). The primary metabolite is typically a key component in maintaining normal physiological function; thus, it is often referred to as the central metabolite [45]. Examples of primary metabolites are the core building block molecules (nucleic acids, amino acids, sugars, and fatty acids) that are required to produce the major macro molecules (DNA, RNA, proteins, carbohydrates, and lipids) that are responsible for sustaining life. Other examples are alcohols (such as ethanol), lactic acid and certain amino acids. Primary metabolites can be simply described as components of basic metabolic pathways that are required for life. They are associated with important cellular functions like nutrient assimilation, energy production, and growth and development.

Secondary Metabolites

Unlike primary metabolites, secondary metabolites are unessential and not totally required for survival but usually have important ecological functions. They are organic molecules that have extrinsic (relational) function that mainly affects other organisms outside of the producer so as to increase its competitiveness within its habitat. Secondary metabolites do not play a role in growth, development, and reproduction like primary metabolites do and are mainly formed during the end or near the stationary phase of growth [46]. Some common examples include: antibiotics, terpenoids, ergot alkaloids, peptides, steroids, essential oils etc.

Both primary and secondary metabolites can be used industrially to obtain amino acids, develop vaccines and antibiotics, and isolate chemicals needed for organic synthesis.

1.3.2. Classification Based on Biosynthetic Pathway

Alkaloids

Alkaloids are secondary metabolites containing nitrogen as a component of their organic structure. They are divided into many subclasses of compounds including; pyrrolidines, pyridines, tropanes, pyrrolizidines, isoquinolines, indoles and quinolones. An example of alkaloid is morphine; a strong narcotic used to relief pain.

Phenylpropanoids

These are a broad family of organic compounds synthesized from the amino acids phenylalanine and tyrosine. An example of a phenylpropanoid is cinnamic acid, one of the volatile flavor molecules found in cinnamon.

Polyketides

Polyketides are assembled from acetate and malonate building blocks to form large, complex molecules. Aflatoxin B₁ is a polyketide structure produced by fungi from the *Aspergillus* genus. They commonly grow on stored food crops like corn and groundnut contaminating them with aflatoxins. Aflatoxins induce DNA damage and exhibit carcinogenic properties. Food crops contaminated with aflatoxins have been associated with liver cancer. Recent studies have explored the potential of marine-derived fungi as sources of novel polyketide derivatives, highlighting the diversity of polyketide structures and their potential applications [47].

Terpenoids

These are a large class of natural products constructed from isoprene (a 5-carbon monomer unit). A good example of a terpenoid based structure is natural rubber (assembled from multiple repeating of isoprene units).

1.3.3. Classification Based on Source

Prokaryotic Organisms

Prokaryotic organisms are unicellular organisms lacking a membrane-bound nucleus, mitochondria, or any other membrane bound organelle. They are divided into two domains, Archaea and Bacteria. All intracellular, water soluble component (DNA, proteins and metabolites are located together in the cytoplasm enclosed by the cell membrane and not separate cellular compartments. Bacteria are a prominent source of natural products. A few examples of natural products that have been derived from bacteria include: streptomycin, tetracycline, neomycin B, erythromycin, chloramphenicol and many others. Archaea species are also known as extremophiles because they have adapted to life in extreme environments. They therefore have enzymes that can function in extreme conditions offering applications in food, chemical, and pharmaceutical industries. Lactase from *Pyrococcus furiosus* is an example of natural product from the Archaea species [48]

Eukaryotic Organisms

Eukaryotic organisms are organisms with clearly defined, membrane-bound nucleus. All animals, plants, fungi and many unicellular organisms are eukaryotes. These make up the four kingdoms represented in this group namely; Animalia, plantae, fungi and Protista. Many natural products have been produced from eukaryotes including: penicillins, cephalosporins, griseofulvin etc. from fungi; artemisinin, morphine, vinblastine etc. from plants, chlorotoxin, teprotide, conotoxin etc. from animals and carrageenan, agar etc. from protists [44].

1.4. Importance of Natural Products in Drug Discovery

Natural products play a major role in human therapy and represent a huge reservoir of bioactive chemical diversity and help to understand the cellular pathways that are essential component of the drug discovery process [49]. The following are some reasons why natural products are of great importance in drug discovery:

- Cost effectiveness: natural products are cost effective sources of lead compounds, thereby reducing the cost of extensive synthetic chemistry research.
- Low toxicity profiles: many known natural products have been proven to have low toxicity and this makes them good candidates for new drug development.
- Cultural/traditional significance: folkloric uses of natural products show that they have cultural significance and their use in drug discovery can preserve traditional knowledge and practices.
- Sustainable source: natural products are sustainable sources of lead compounds because they are readily produced by their environment thereby also reducing the environmental impact of drug discovery.
- Inspiration for synthetic compounds: many synthetic compounds were inspired by natural products. Therefore, they will continue to serve as inspiration for the development of novel drugs.
- Diverse chemical structures: natural products offer a wide range of unique chemical structures which may be beneficial in the discovery of new drugs
- By harnessing natural products, researchers can fast-track drug discovery, develop new therapeutics and tackle pressing medical needs [50].

1.5. Plants in Drug Discovery

The extent of plant diversity worldwide is estimated at more than 500,000 species [51]. Plants with medicinal values will continue to serve as important sources of natural products for treating various health conditions. An estimate of more than 150,000 plant species have been studied, many of which contain valuable therapeutic agents and the application of new compounds from plants for pharmaceutical purposes have been on the increase in recent years [52]. Since ancient times, plants have played a pertinent role in human health care. In a bid to adapt against attacking pathogens and environmental stress, plants produce several substances that perform biological activities. These substances are organic molecules that come from secondary metabolism and have varying biological activities. Among these various activities, anti-inflammation is highlighted [53]. Notably, researchers have investigated the anti-inflammatory and antimicrobial properties of plants such as *Newbouldia laevis* and *Buchholzia coriacea* seed (Wonderful kola), demonstrating the potential of plant-based natural products in drug discovery [16, 54].

1.6. History of Medicinal Plants

Man, for hundreds of centuries have been experimenting by trial and error to discover foods from plants and also plants that have abilities to solve their health problems. This method came with its own disadvantages too in that lives were lost especially when poisonous plants were consumed. This experimenting led to vast knowledge available today from medicinal plants [25]. A very good example is the plant genus *Salvia*, which grows abundantly in the southwestern region of the United States and also in northwestern Mexico. This plant genus are used by the Indian tribes of southern California as an aid in childbirth [55]. Newborn male babies were “cooked” in hot *Salvia* ashes and it was believed that these babies grew up to be the strongest and healthiest of their tribes. They are also believed to have a lifelong immunity against all forms of respiratory diseases. Another notable example is the plant *Alhagi maurorum* Medik commonly known as camels thorn which secretes as sweet gummy material from its stems and leaves during hot days. This gummy sap consists of melezitose, sucrose and invert sugar and is known as “manna” [56]. The Ayurvedic people claim that the plant can be used to treat anorexia, constipation, dermatosis, epistaxis, fever, leprosy and obesity [57]. The Israelis usually boil the roots to get the extract that is believed to have the ability to stop bloody diarrhea. The Konkani people used the smoked plant for treating asthma and the Romans used the plant for nasal polyps [58]. The plant *Ligusticum scoticum* Linnaeus found in northern Europe and also Eastern North America was eaten first thing in the morning raw and it was believed that the plant gives a daily protection from infections. The root was used in the treatment of flatulence and also used as an aphrodisiac and a sedative [56]. Also *Atropa belladonna* Linnaeus commonly known as deadly nightshade is found in central and Southern Europe, Western Asia, North Africa, North America and New Zealand. It is poisonous in nature (just three of its berries are enough to kill a child) and this excluded it from folk medicine compilation and has been marked as “dangerous” to handle or experiment with [25].

1.7. Metabolites from Plant

The vast and versatile pharmacological effects of plants with medicinal value are dependent on their phytochemical constituents. These phytochemical constituents can be grouped into two categories based on their role in basic metabolic processes which include: primary and secondary metabolites. Plant metabolites are a source of several medicinal compounds, while the diversity of their multidimensional chemical structures has made them superior to treat serious diseases. Primary plant metabolites are involved in carrying out basic life functions such as cell division and growth, respiration, storage and reproduction. They include the components of processes like glycolysis, the Krebs cycle, photosynthesis and associated pathways. Examples of primary plant metabolites include sugars, amino acids, tricarboxylic acids or Krebs cycle intermediates, proteins, nucleic acids and polysaccharides. Primary metabolites are similar in all living cells [59]. Secondary plant metabolites on the other hand are products of metabolic pathways of plant cells that are derived from primary metabolic pathways. Albrecht Kossel, a Nobel Prize winner for physiology in 1910 first described the concept of secondary metabolite [60]. Then about 30 years later, Czapek took it a step further by describing them as end-products in an entire volume of his plant biochemistry series [61]. According to him, these products are gotten from nitrogen metabolism by what he called ‘secondary modifications’ such as deamination. Advances of analytical techniques like chromatography have led to the recovery of more of these molecules, and this was the foundation for the establishment of the discipline of phytochemistry [62]. Secondary plant metabolites have shown to possess many biological effects that have provided the scientific base for the use of plants in the treatment of ailments by ancient communities [59]. They have been described as antibiotic, antifungal and antiviral, these shows that they have the ability to protect plants from pathogens and also insects and herbivores. They also possess important UV absorbing compounds therefore protecting plants against serious leaf damage from light [62]. About 12000 of these secondary metabolites have been isolated and this number is estimated to be less than 10 % of the total in natural reservoir [63]. Secondary plant metabolites can be classified into several classes according to their chemical structures namely: phenolics, alkaloids, saponins, terpenes, sterols, glycosides, cardiac glycosides, lipids and carbohydrates [64].

1.7.1. Phenolics

Phenolics are probably the largest group of plant secondary metabolites with about 8000 phenolic structures that are known [65]. They contain one or more hydroxyl (phenol) groups and range from simple structures with one aromatic ring like phenolic acids to highly complex polymeric compounds like tannins [66]. They are the most abundant secondary metabolites of plants and they are well distributed in the plant kingdom. Plant phenolics are generally involved in defense against ultraviolet radiation or attack by pathogens, parasites and predators. They are ubiquitous in all plant organs and are therefore an important part of man's diet. They have significant contribution to the color, taste and flavor of many herbs, foods and drinks. Phenolics play a role in the bitterness and astringency of fruits and fruit juices and this is as a result of the interaction between phenolics (mainly procyanidin) and the glycoprotein in saliva [67]. Anthocyanins, which belong to one of the six subgroups of flavonoids (a large group of plant polyphenol constituents), are responsible for the orange, blue, purple and red colours of many fruits and vegetables like apples, beets, berries and onions. Phenolics also are responsible for the flavor and color difference amongst white, pink and red wines [65]. Some phenolics have been found to have anti-inflammatory activity like quercetin or antihepatotoxic properties like silybin. Other examples include: genistein with phytoestrogenic activity and naringenin with insectidal activity [68]. Many of the phenolics are also effective antioxidants and free radical scavengers, especially flavonoids. Plant phenolics include phenolic acids, flavonoids, tannins and the less common stilbenes and lignans [69].

1.7.2. Phenolic Acids

The term "phenolic acids" simply describes the phenolic compounds that have one carboxylic acid group. Phenolic acids can be grouped into two classes which include: derivatives of benzoic acid such as gallic acid, and derivatives of cinnamic acid such as coumaric, caffeic and ferulic acid [67]. The most abundant of the phenolic acids is caffeic acid and it is found in many fruits and vegetables, most often esterified with quinic acid in the form of chlorogenic acid (the major phenolic compound in coffee). Ferulic acid is also another common one found in cereals and is esterified to hemicelluloses in the cell wall [70].

1.7.3. Flavonoids

Flavonoids are the most abundant polyphenols in man's diet. They are divided into six subgroups which include: flavones, flavonols, flavanols, flavanones, isoflavones and anthocyanins. Common examples of flavonoids include: quercetin, a flavonol found in onions, broccoli, and apple; catechin, a flavanol found in tea and many fruits; naringenin, the main flavanone in grapefruit; cyanidin-glycoside, an anthocyanin found in berry fruits (blackberry and raspberry) and daidzein, genistein and glycitein, the main isoflavone in soybean [69]. Flavonoids have shown to possess a good number of biological and pharmacological activities which includes: anti-inflammatory, anti-allergic, antioxidant, antibacterial, anti-fungal, anti-cancer, anti-viral and antidiarrheal activities [71, 72].

1.7.4. Tannins

Tannins, which are also commonly referred to as tannic acid are water-soluble polyphenols present in many plant foods [73]. They are astringent, bitter polyphenols that bind and precipitate or shrink proteins. The astringency from tannins results in the dry and pucker feeling that accompanies the consumption of red wine, strong teas or unripe fruits [74]. Tannins are divided into two groups which include: hydrolysable tannins and condensed tannins. Hydrolysable tannins contain a central core of glucose or another polyol esterified with gallic acid, also called gallotannins, or with hexahydroxydiphenic acid, also called ellagitannins. The vast variety in the structure of these compounds is as a result of the many possibilities in forming oxidative linkage [67].

1.7.5. Alkaloids

Alkaloids are substances containing nitrogen based heterocyclic ring within their molecules. Alkaloids are found primarily in plants and are especially common in some families of flowering plants. Many alkaloids have toxic effects and they give protective effects to the organism producing them [75]. There is really no straight forward definition for alkaloids because they do not represent a homogenous group of compounds from any viewpoint, whether chemical, biochemical or physiological. Apart from the fact that they are all nitrogen containing compounds, there is no one definition that fits all alkaloids. Alkaloids contain at least one nitrogen atom in an amine-type structure (one gotten from ammonia by replacing hydrogen atoms with hydrocarbons). The nitrogen in their structure acts like a base in acid-base reactions. The term "alkaloid" (alkali-like) was originally applied to substances because they react with acids to form salts just like the inorganic alkalis. The names of different alkaloids generally end with the suffix "-ine" because of their chemical classification as amines. Alkaloids are colorless, nonvolatile, crystalline solids in their pure form and they generally have a bitter taste. There are different types of alkaloids based on their basic chemical structure and they include: acridones, aromatics, carbolines, ephedras, ergots, imidazoles, indoles, bisindoles, indolizidines, manzamines,

oxindoles, quinolones, quinoxalines, phenylisoquinolines, phenylethylamines, piperidines, purines, pyrrolidines, pyrrolizidines, pyrroloindoles, pyridines and simple tetrahydroisoquinolines [76]. Alkaloids have a vast array of pharmacological actions which include: analgesia, local anesthesia, cardiac stimulation, respiratory stimulation and relaxation, vasoconstriction, muscle relaxation and toxicity as well as antineoplastic, hypertensive and hypotensive properties. Many alkaloids are sufficiently toxic to animals to cause death if eaten. Some are also used as insecticides [77].

Some examples of alkaloids include: nicotine, a tranquilizer found in tobacco plant (*Nicotiana tabacum*) and other *Nicotiana* species, caffeine, a CNS stimulant present in tea (*Camellia sinensis*) and coffee (*Coffea* spp.) and vinblastine isolated from *Catharanthus roseus* used in treating diabetes, high blood pressure and cancer [78].

1.7.6. Sterols

Plant sterols are similar to cholesterol but are produced in plants. They are plant-originated steroids usually found in plant cell membranes [79]. Over 250 plant sterols have been isolated and each plant species has a characteristic phytosterol composition. All plant species have its characteristic phytosterol composition [80]. But they are present in high amounts in vegetable, nuts and olive oils such as sesame, safflower, soybeans, peas, macadamia and almonds. Other great dietary sources of plant sterols are nuts, seeds, whole grains and legumes [79]. They may help in reducing the level of cholesterol by limiting the amount of cholesterol that enters the body and also reduces the quantity the body produces. Plant sterols are also used for heart disease, colon cancer, stomach cancer, obesity, heart attack and many other conditions. They also modulate inflammation; have antioxidant, antibacterial, antiulcer, immunomodulatory and antifungal effects; and also promote wound healing and inhibition of platelet aggregation [81, 82].

1.7.7. Saponins

The term “saponin” is derived from the Latin word *sapo*, which means soap-like or foam-generating ability. Saponins are found in plants and marine animals where they are involved in defending their host against pathogens and herbivores [83]. Saponins can be classified into two groups based on their sapogenin skeleton and they are: Triterpenoid saponins and steroid saponins [84]. Saponins are present in many medicinal plants and they exhibit a plethora of pharmacological and biological activities including: antifungal, antimicrobial, antiviral, anti-inflammatory, anticancer, antioxidant and immunomodulatory effects. Therefore, saponins can serve as a good starting point for the development of naturally-derived drugs [85].

2. Conclusion

In conclusion, natural products continue to play an important role in the discovery of new drugs. This review has highlighted the importance of natural products from various sources including plants, animals, microorganisms, and marine organisms. Plants, in particular, have played a huge role in the history of medicine and their metabolites, such as; flavonoids, tannins, alkaloids, sterols, saponins, etc. have shown significant potential in drug discovery. To drive progress in drug discovery, it is crucial to continue to explore and harness the rich biodiversity of natural products. This approach may lead to the identification of new leads and solutions to address the complex and evolving health concerns of modern times.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest disclosed.

References

- [1] Rehman MU, Abdullah, Khan F, Niaz K. Introduction to natural products analysis. 2020:3-15.
- [2] Sean K. Natural Products Research. Natural Products Chemistry & Research. 2014;1(1).
- [3] Petrovska B. Historical review of medicinal plants' usage. Pharmacognosy Reviews. 2012;6(11):1.
- [4] Yuan H, Ma Q, Ye L, Piao G. The Traditional Medicine and Modern Medicine from Natural Products. Molecules. 2016;21(5):559.

- [5] Veeresham C. Natural products derived from plants as a source of drugs. *Journal of Advanced Pharmaceutical Technology & Research*. 2012;3(4):200.
- [6] Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981-2002. *Journal of natural products*. 2003;66(7):1022-37. Epub 2003/07/26.
- [7] Li-Weber M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer treatment reviews*. 2009;35(1):57-68. Epub 2008/11/14.
- [8] Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of natural products*. 2020;83(3):770-803.
- [9] Saklayen MG, Deshpande NV. Timeline of History of Hypertension Treatment. *Frontiers in cardiovascular medicine*. 2016;3:3. Epub 2016/03/05.
- [10] Dzobo K. The Role of Natural Products as Sources of Therapeutic Agents for Innovative Drug Discovery. 2022:408-22.
- [11] Zhu F, Ma XH, Qin C, Tao L, Liu X, Shi Z, et al. Drug discovery prospect from untapped species: indications from approved natural product drugs. *PloS one*. 2012;7(7):e39782. Epub 2012/07/19.
- [12] Muschietti L, Vila R, Filho VC, Setzer W. Tropical protozoan diseases: natural product drug discovery and development. Evidence-based complementary and alternative medicine : eCAM. 2013;2013:404250. Epub 2013/12/19.
- [13] Cragg GM, Newman DJ. Natural products: a continuing source of novel drug leads. *Biochimica et biophysica acta*. 2013;1830(6):3670-95. Epub 2013/02/23.
- [14] Nasim N, Sandeep IS, Mohanty S. Plant-derived natural products for drug discovery: current approaches and prospects. *The Nucleus*. 2022;65(3):399-411.
- [15] Batista R, De Jesus Silva Júnior A, De Oliveira AB. Plant-Derived Antimalarial Agents: New Leads and Efficient Phytomedicines. Part II. Non-Alkaloidal Natural Products. *Molecules*. 2009;14(8):3037-72.
- [16] Umeokoli BO, Ekeh MN, Eze P, Umeyor C, Abba C. Improved gastric lesion of ulcerogenic mice treated with bark extracts and fractions of *Newbouldia laevis*. *African Journal of Pharmacy and Pharmacology*. 2015;9(21):553-60.
- [17] Umeokoli BO, Muharini R, Liu Z, Okoye FB, Ajiwe VI, Akpuaka MU, et al. New natural products from the root of *Talinum triangulare* (Portulacaceae) growing in Nigeria. *Planta medica*. 2015;81(16).
- [18] Krawinkel MB, Keding GB. Bitter gourd (*Momordica Charantia*): A dietary approach to hyperglycemia. *Nutrition reviews*. 2006;64(7 Pt 1):331-7. Epub 2006/08/17.
- [19] Narasimhan TR, Harindranath N, Premlata S, Murthy BS, Rao PV. Toxicity of the sesquiterpene lactone parthenin to cultured bovine kidney cells. *Planta medica*. 1985(3):194-7. Epub 1985/06/01.
- [20] Sugihara Y, Nojima H, Matsuda H, Murakami T, Yoshikawa M, Kimura I. Antihyperglycemic effects of gymnemic acid IV, a compound derived from *Gymnema sylvestre* leaves in streptozotocin-diabetic mice. *Journal of Asian natural products research*. 2000;2(4):321-7. Epub 2001/03/16.
- [21] Zhang Z, Jiang J, Yu P, Zeng X, Larrick JW, Wang Y. Hypoglycemic and beta cell protective effects of andrographolide analogue for diabetes treatment. *Journal of translational medicine*. 2009;7:62. Epub 2009/07/18.
- [22] Lindsay CA, Kinghorn AD, Rakotonandraibe HL. Bioactive and unusual steroids from *Penicillium* fungi. *Phytochemistry*. 2023;209:113638.
- [23] Abraham EP, Chain E, Fletcher CM, Florey HW, Gardner AD, Heatley NG, et al. Further observations on penicillin. 1941. *European journal of clinical pharmacology*. 1992;42(1):3-9. Epub 1992/01/01.
- [24] Oong GC, Tadi P. Chloramphenicol. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Prasanna Tadi declares no relevant financial relationships with ineligible companies.2025.
- [25] Dias DA, Urban S, Roessner U. A historical overview of natural products in drug discovery. *Metabolites*. 2012;2(2):303-36. Epub 2012/01/01.
- [26] Okoye FBC, Nworu CS, Akah PA, Esimone CO, Debbab A, Proksch P. Inhibition of inflammatory mediators and reactive oxygen and nitrogen species by some depsidones and diaryl ether derivatives isolated from *Corynespora*

cassiicola, an endophytic fungus of *Gongronema latifolium* leaves. *Immunopharmacology and Immunotoxicology*. 2013;35(6):662-8.

- [27] Okoye FBC, Lu S, Nworu CS, Esimone CO, Proksch P, Chadli A, et al. Depsidone and diaryl ether derivatives from the fungus *Corynespora cassiicola*, an endophyte of *Gongronema latifolium*. *Tetrahedron Letters*. 2013;54(32):4210-4.
- [28] Okoye FBC, Nworu CS, Debbab A, Esimone CO, Proksch P. Two new cytochalasins from an endophytic fungus, KL-1.1 isolated from *Psidium guajava* leaves. *Phytochemistry Letters*. 2015;14:51-5.
- [29] Chen H, Daletos G, Okoye F, Lai D, Dai H, Proksch P. A New Cytotoxic Cytochalasin from the Endophytic Fungus *Trichoderma harzianum*. *Natural Product Communications*. 2015;10(4).
- [30] Ngwoke K, Tochukwu N, Ekwealor C, Nwankwo V, Obi-Okafor U, Izundu C, et al. Antibacterial, anti-inflammatory and peroxidase-mediated cyclooxygenase-1 inhibitory properties of *Fusarium solani* extract. *Pharmaceutical Biology*. 2019;57(1):310-7.
- [31] Eze PM, Liu Y, Simons VE, Ebada SS, Kurtán T, Király SB, et al. Two new metabolites from a marine-derived fungus *Penicillium ochrochloron*. *Phytochemistry Letters*. 2023;55:101-4.
- [32] Abba CC, Eze PM, Ebada SS, Eze NK, Proksch P, Teusch N, et al. Rare Chlorinated Fungal Metabolite and Alpha-Pyrones from an Endophytic Fungus *Nigrospora* sp. *ACS Omega*. 2025;10(6):5722-9.
- [33] Wang H, Eze PM, Höfert S-P, Janiak C, Hartmann R, Okoye FBC, et al. Substituted l-tryptophan-l-phenyllactic acid conjugates produced by an endophytic fungus *Aspergillus aculeatus* using an OSMAC approach. *RSC Advances*. 2018;8(14):7863-72.
- [34] Nwobodo DC, Okoye NN, Sifir Mudkhur M, Ikem JC, Eze PM, Okoye FBC, et al. In vitro antiplasmodial and anticancer analyses of endophytic fungal extracts isolated from selected Nigerian medicinal plants. *Scientific Reports*. 2024;14(1).
- [35] Uzor PF, Ebrahim W, Osadebe PO, Nwodo JN, Okoye FB, Müller WEG, et al. Metabolites from *Combretum dolichopetalum* and its associated endophytic fungus *Nigrospora oryzae* — Evidence for a metabolic partnership. *Fitoterapia*. 2015;105:147-50.
- [36] Ebada SS, Eze P, Okoye FBC, Esimone CO, Proksch P. The Fungal Endophyte *Nigrospora oryzae* Produces Quercetin Monoglycosides Previously Known Only from Plants. *ChemistrySelect*. 2016;1(11):2767-71.
- [37] Feling RH, Buchanan GO, Mincer TJ, Kauffman CA, Jensen PR, Fenical W. Salinosporamide A: a highly cytotoxic proteasome inhibitor from a novel microbial source, a marine bacterium of the new genus *salinospora*. *Angew Chem Int Ed Engl*. 2003;42(3):355-7. Epub 2003/01/28.
- [38] Ebube Samuel I, Blessing Ogechukwu U, Onyeka Chinwuba O, Ugochukwu MO, Chukwubuike Chinaeze O, Damilola Caleb A, et al. Screening of secondary metabolites produced by a mangrove-derived *Nigrospora* species an endophytic fungus isolated from *Rhizophora racemosa* for antioxidant and antimicrobial properties. *GSC Advanced Research and Reviews*. 2023;15(2):047-60.
- [39] Haefner B. Drugs from the deep: marine natural products as drug candidates. *Drug discovery today*. 2003;8(12):536-44. Epub 2003/06/25.
- [40] Mayer AM, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, et al. The odyssey of marine pharmaceuticals: a current pipeline perspective. *Trends in pharmacological sciences*. 2010;31(6):255-65. Epub 2010/04/07.
- [41] Umeokoli BO, Ebrahim W, El-Neketi M, Müller WEG, Kalscheuer R, Lin W, et al. A new depsidone derivative from mangrove sediment derived fungus *Lasiodiplodia theobromae*. *Natural product research*. 2018;33(15):2215-22.
- [42] Winter JM, Tang Y. Synthetic biological approaches to natural product biosynthesis. *Current Opinion in Biotechnology*. 2012;23(5):736-43.
- [43] Springob K, Kutchan TM. Introduction to the Different Classes of Natural Products. 2009:3-50.
- [44] Cragg GM, Newman DJ. Natural products: A continuing source of novel drug leads. *Biochimica et Biophysica Acta (BBA) - General Subjects*. 2013;1830(6):3670-95.
- [45] Dwivedi GR, Sisodia BS, Shikha. Secondary Metabolites: Metabolomics for Secondary Metabolites. 2019:333-44.
- [46] Salam U, Ullah S, Tang Z-H, Elateeq AA, Khan Y, Khan J, et al. Plant Metabolomics: An Overview of the Role of Primary and Secondary Metabolites against Different Environmental Stress Factors. *Life*. 2023;13(3):706.

- [47] Yu X, Müller WEG, Meier D, Kalscheuer R, Guo Z, Zou K, et al. Polyketide Derivatives from Mangrove Derived Endophytic Fungus *Pseudoestalotiopsis theae*. *Marine Drugs*. 2020;18(2):129.
- [48] Li B, Wang Z, Li S, Donelan W, Wang X, Cui T, et al. Preparation of lactose-free pasteurized milk with a recombinant thermostable β -glucosidase from *Pyrococcus furiosus*. *BMC Biotechnology*. 2013;13(1).
- [49] Atanasov AG, Zotchev SB, Dirsch VM, Orhan IE, Banach M, Rollinger JM, et al. Natural products in drug discovery: advances and opportunities. *Nature Reviews Drug Discovery*. 2021;20(3):200-16.
- [50] Chaachouay N, Zidane L. Plant-Derived Natural Products: A Source for Drug Discovery and Development. *Drugs and Drug Candidates*. 2024;3(1):184-207.
- [51] Corlett RT. Plant diversity in a changing world: Status, trends, and conservation needs. *Plant diversity*. 2016;38(1):10-6. Epub 2016/05/24.
- [52] Abima Shazhni JR, Renu A, Vijayaraghavan P. Insights of antidiabetic, anti-inflammatory and hepatoprotective properties of antimicrobial secondary metabolites of corm extract from *Caladium x hortulanum*. *Saudi journal of biological sciences*. 2018;25(8):1755-61. Epub 2018/12/29.
- [53] Locatelli C, Nardi G, anuário AdF, Freire C, Megiolaro F, Schneider K, et al. Anti-inflammatory activity of berry fruits in mice model of inflammation is based on oxidative stress modulation. *Pharmacognosy Research*. 2016;8(5):42.
- [54] Blessing Ogechukwu U. Antimicrobial, Anti-inflammatory, and Chemical Evaluation of <i>Buchholzia coriacea</i> Seed (Wonderful Kola). *American Journal of Life Sciences*. 2016;4(5):106.
- [55] Kong J, Li S, Li Y, Chen M. Effects of *Salvia miltiorrhiza* active compounds on placenta-mediated pregnancy complications. *Frontiers in Cell and Developmental Biology*. 2023;11.
- [56] Upmanyur P. Medicinal and Organic Natural Products Drug Discovery. *Journal of Medicinal and Organic Chemistry*. 2023;6(1).
- [57] Moloudizargari M, Asghari M, Fallah M, Mehdikhani F, Sepehrnia P, Moradi B. A systematic and mechanistic review on the phytopharmacological properties of *Alhagi* species. *Ancient Science of Life*. 2016;36(2):65.
- [58] Duke JA. 2008.
- [59] James KD. *Animal Metabolites*. 2017:401-11.
- [60] Jones ME. Albrecht Kossel, a biographical sketch. *The Yale journal of biology and medicine*. 1953;26(1):80-97. Epub 1953/09/01.
- [61] Bourgaud F, Gravot A, Milesi S, Gontier E. Production of plant secondary metabolites: a historical perspective. *Plant Science*. 2001;161(5):839-51.
- [62] A. Hussein R, A. El-Anssary A. *Plants Secondary Metabolites: The Key Drivers of the Pharmacological Actions of Medicinal Plants*. 2019.
- [63] Torres-Contreras AM, Garcia-Baeza A, Vidal-Limon HR, Balderas-Renteria I, Ramírez-Cabrera MA, Ramirez-Estrada K. Plant Secondary Metabolites against Skin Photodamage: Mexican Plants, a Potential Source of UV-Radiation Protectant Molecules. *Plants*. 2022;11(2):220.
- [64] Al-Khayri JM, Rashmi R, Toppo V, Chole PB, Banadka A, Sudheer WN, et al. Plant Secondary Metabolites: The Weapons for Biotic Stress Management. *Metabolites*. 2023;13(6):716.
- [65] Alara OR, Abdurahman NH, Ukaegbu CI. Extraction of phenolic compounds: A review. *Current Research in Food Science*. 2021;4:200-14.
- [66] Lin D, Xiao M, Zhao J, Li Z, Xing B, Li X, et al. An Overview of Plant Phenolic Compounds and Their Importance in Human Nutrition and Management of Type 2 Diabetes. *Molecules*. 2016;21(10):1374.
- [67] Dai J, Mumper RJ. Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties. *Molecules*. 2010;15(10):7313-52.
- [68] Golawska S, Sprawka I, Lukasik I, Golawski A. Are naringenin and quercetin useful chemicals in pest-management strategies? *Journal of pest science*. 2014;87:173-80. Epub 2014/02/25.
- [69] Oluwole O, Fernando WB, Lumanlan J, Ademuyiwa O, Jayasena V. Role of phenolic acid, tannins, stilbenes, lignans and flavonoids in human health – a review. *International Journal of Food Science & Technology*. 2022;57(10):6326-35.

- [70] D'Archivio M, Filesi C, Di Benedetto R, Gargiulo R, Giovannini C, Masella R. Polyphenols, dietary sources and bioavailability. *Annali dell'Istituto superiore di sanita*. 2007;43(4):348-61. Epub 2008/01/23.
- [71] Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. *TheScientificWorldJournal*. 2013;2013:162750. Epub 2014/01/29.
- [72] Okoye FB, Sawadogo WR, Sendker J, Aly AH, Quandt B, Wray V, et al. Flavonoid glycosides from *Oxalys mannii*: Structure elucidation and effect on the nuclear factor kappa B pathway. *Journal of ethnopharmacology*. 2015;176:27-34. Epub 2015/10/18.
- [73] Chung KT, Wong TY, Wei CI, Huang YW, Lin Y. Tannins and human health: a review. *Critical reviews in food science and nutrition*. 1998;38(6):421-64. Epub 1998/10/06.
- [74] Soares S, Brandão E, Guerreiro C, Soares S, Mateus N, de Freitas V. Tannins in Food: Insights into the Molecular Perception of Astringency and Bitter Taste. *Molecules*. 2020;25(11):2590.
- [75] Ncube B, Van Staden J. Tilting Plant Metabolism for Improved Metabolite Biosynthesis and Enhanced Human Benefit. *Molecules*. 2015;20(7):12698-731.
- [76] Bhambhani S, Kondhare KR, Giri AP. Diversity in Chemical Structures and Biological Properties of Plant Alkaloids. *Molecules*. 2021;26(11):3374.
- [77] Divekar PA, Narayana S, Divekar BA, Kumar R, Gadratagi BG, Ray A, et al. Plant Secondary Metabolites as Defense Tools against Herbivores for Sustainable Crop Protection. *International journal of molecular sciences*. 2022;23(5):2690.
- [78] Pengelly A. Alkaloids. 2021:168-201.
- [79] Salehi B, Quispe C, Sharifi-Rad J, Cruz-Martins N, Nigam M, Mishra AP, et al. Phytosterols: From Preclinical Evidence to Potential Clinical Applications. *Frontiers in pharmacology*. 2020;11:599959. Epub 2021/02/02.
- [80] Bootter MB, Li J, Zhou W, Edwards D, Batley J. Diversity of Phytosterols in Leaves of Wild Brassicaceae Species as Compared to Brassica napus Cultivars: Potential Traits for Insect Resistance and Abiotic Stress Tolerance. *Plants*. 2023;12(9):1866.
- [81] Okoye NN, Ajaghaku DL, Okeke HN, Ilodigwe EE, Nworu CS, Okoye FBC. beta-Amyrin and alpha-amyrin acetate isolated from the stem bark of *Alstonia boonei* display profound anti-inflammatory activity. *Pharmaceutical Biology*. 2014;52(11):1478-86.
- [82] Okoye F, Osadebe P, Proksch P, Edrada-Ebel R, Nworu C, Esimone C. Anti-inflammatory and Membrane-stabilizing Stigmastane Steroids from *Alchornea floribunda* Leaves. *Planta medica*. 2009;76(02):172-7.
- [83] Papadopoulou K, Melton RE, Leggett M, Daniels MJ, Osbourn AE. Compromised disease resistance in saponin-deficient plants. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;96(22):12923-8. Epub 1999/10/27.
- [84] Vincken JP, Heng L, de Groot A, Gruppen H. Saponins, classification and occurrence in the plant kingdom. *Phytochemistry*. 2007;68(3):275-97. Epub 2006/12/05.
- [85] Juang YP, Liang PH. Biological and Pharmacological Effects of Synthetic Saponins. *Molecules*. 2020;25(21). Epub 2020/10/31.