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Secondary Metabolites: The Natural Remedies

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Abstract

The chapter discusses the meaning and origin of some important classes of secondary metabolites such as alkaloids, terpenoids, tannins, flavonoids, saponins, glycosides, and phenolic compounds, etc., produced by some bacteria, fungi, or plants. Very important drugs that are used clinically are derived from these secondary metabolites. Several reports obtained in scientific journals and books written by different scientists working or who have worked in the fields of natural products medicine were reviewed. These different classes of secondary metabolites have shown activity against varied diseases, and compounds that are of novel structure and activity have been isolated and characterized from them. The chapter highlights the economic impacts of these chemical compounds including their role in improving human and animal health and well-being by serving as sources of some antibiotics, anticancer, anti-inflammatory, antifertility, antidiabetics, analgesics, growth promoters, etc. Secondary metabolites are also used to enhance agricultural productivity, they find uses as pesticides, insecticides, and preservatives. Some folkloric uses of secondary metabolites chemical compounds based on reliable sources of information and genuine scientific investigations are highlighted.

Keywords: secondary metabolites, natural remedies, phytochemical constituents, bioactive compounds

1. Introduction

Metabolomics is the study of metabolites within biofluids, cells, tissues, or organisms [1]. Whereas collectively, metabolites and their interactions are known as metabolome [2].

Metabolites are small molecules produced by metabolic reactions; these molecules are intermediate or end products of metabolic reactions. The metabolic reactions are catalyzed by naturally occurring enzymes within the organisms' cells [3]. Compounds derived from primary and secondary metabolism are known as primary and secondary metabolites, respectively.

Primary metabolites are indispensable compounds used by organisms for their growth, development, and reproduction; these compounds are synthesized by the cells as a result of metabolism during the growth phase. Primary metabolites are referred to as central metabolites due to their key role in maintaining normal physiological

processes. Primary metabolites include vitamins (B2 and B12), lactic acid, amino acids, polyols, alcohols such as ethanol, nucleotides, organic acids, etc. [3, 4].

The current chapter discusses the meaning and origin or sources of some important classes of secondary metabolites such as alkaloids, terpenoids, tannins, flavonoids, saponins, cardiac glycosides, phenolic compounds, etc., the economic impacts of secondary metabolite compounds including their role in improving human and animal health and well-being (as antibiotics, anticancer, anti-inflammatory, antifertility, antidiabetics, pain relievers, growth promoters, etc.). The chapter addresses the role of secondary metabolites in enhancing agricultural productivity (as pesticides, insecticides, preservatives, etc.); it also discusses the important present-day drugs derived from secondary metabolites, as well as some important biological/pharmacological effects or activities of different classes of the secondary metabolites and their folkloric usage based on reliable sources of information and genuine scientific investigations.

1.1 The meaning and origin of important classes of secondary metabolites

Secondary metabolites also known as phytochemical constituents, bioactive compounds, specialized metabolites, secondary products, or toxins are organic compounds produced by organisms such as plants, fungi, or bacteria as a result of secondary metabolic processes that lead to production and accumulation of diverse chemical compounds known as secondary metabolites. These compounds are not required for primary metabolic processes by the organisms [3–5]. Secondary metabolites are formed toward the end of the growth phase; thus, they are not directly involved in the normal physiologic processes of the organism such growth and development as well as reproductive processes. Instead, they increase the organism's survivability through mediation of ecological interaction, to the organism, this serves as a selective advantage [4, 5]. Interspecies defenses such as defense against herbivory by plants are part of the important roles of secondary metabolites. However, humans use secondary metabolites as medicines, recreational drugs, flavorings, pigments, etc. [6].

Secondary metabolites are classified commonly based on their vast structural diversity, biosynthesis, and function. According to the literature, over 2140, 000 secondary metabolites are known; however, the main classes of secondary metabolites are five, which include alkaloids, terpenoids and steroids, nonribosomal polypeptides, polyketides and fatty-acid-derived substances, and enzyme cofactors [7].

1.2 The origin and sources of some important classes of secondary metabolites

Secondary metabolite is a term coined in 1910 by a Medicine and Physiology Nobel Prize laureate, Albert Kossel [8]. Friedrich Czapek, a Polish botanist, 30 years later described them as metabolic nitrogenous end products [9].

Secondary metabolites are produced by plants, fungi, or bacteria as well as many marine organisms such as snails, corals, tunicates, and sponges [10]. There are 150, 000–200, 000 bioactive compounds derived from the plant kingdom, 50, 000–100, 000 from animal kingdom, and 22,000–23, 000 from microbes [11].

1.3 Plant secondary metabolites

Plants are the major sources of secondary metabolites; they produced 80% of the known secondary metabolites occurring in nature [10]. Secondary metabolites are

used by carnivorous plants to attract, capture, digest, and assimilate the prey [12]. One of the early known plant secondary metabolites is morphine, isolated in 1804 [11].

1.4 Fungal secondary metabolites

In 1928, Alexander Fleming while working at St Mary's Hospital in London discovered the most known secondary metabolite, the penicillin. Penicillin was discovered experimentally from a mold, the *Penicillium notatum* [13, 14].

1.5 Bacterial secondary metabolites

Oligosaccharide, b-lactam, polyketide, non-ribosomal pathways, and shikimate are the main secondary metabolite production pathways in bacteria [15]. Although bacterial secondary metabolites have some beneficial effects, many are toxic to mammals through secretion of exotoxin, botulinum toxin secreted by *Clostridium botulinum* bacteria is a very good example [15].

1.6 The alkaloids

The name alkaloid was introduced by Carl Friedrich Wilhelm Meißner, in the year 1819. The name was derived from Latin root alkali, rooted from Arabic word al-qalwi meaning plants ashes. The wide usage of the word alkaloid came after J. Oscar's publication in the year 1880 in Albert Ladenburg, the chemical dictionary [16].

A large variety of organisms produced alkaloids; these chemical compounds are derived from plants, bacteria, fungi, and animals [17]. Morphine was the first individual alkaloid isolated in 1804 from the opium poppy plant (*Papaver somniferum*) [18].

1.7 The cardiac glycosides

The ancient Romans, Syrians, and Egyptians used cardiac glycosides contained in plant extracts for medicinal purposes, the plant extracts from *Urginea maritima* (Scilla), squill, or sea onion were used as emetics and heart tonics. African warriors in the medieval age used *Strophanthus* species as arrows head poison against their targets. Cardiac glycosides were established in the twentieth century as agent for the treatment of heart failure [19].

Early writings of 1250 BC mentioned *Digitalis purpurea*; digitalis was included in herbal collections used in prescription by the Welsh family physicians. The origin of digitalis was from the foxglove plant. A botanist and physician of English origin, William withering in the eighteenth century described the foxglove plant's clinical effects in a published monograph. He was the first investigator of the systemic bioactivity of digitalis. "An account of the Foxglove and some of its medical uses with practical remarks on dropsy, and other diseases" is a book authored by William Withering in 1785 reporting the toxicity and indications of digitalis [19].

Plant is main source of cardiac glycosides; however, bufadienolide was isolated from frogs and mammalian tissues that are rich sources of endogenous digitalis; this show that animal species are also good sources of cardiac glycosides [20].

1.8 The flavonoids

Flavonoids or bioflavonoids are yellow compounds derived from the Latin word Flavius, meaning yellow, their natural coloration [21]. Albert Szent-Györgyi and some

group of scientists in the 1930s discovered that crude yellow extracts from lemons, oranges, etc., were more effective at preventing scurvy than vitamin C. They referred to these compounds as citrin or vitamin P, which were later discovered to be hesperidin, neohesperidin, etc., belonging to flavonoids rather than the vitamins [22].

Flavonoids are compounds belonging to polyphenolic structural class of secondary metabolites. They are widely found in vegetables, fruits, flowers, wine, tea, grains, roots, bark, and stem [23, 24]. Flavonoid compounds are found in several parts of plants, they are products extracted from plants using various extraction techniques such as chromatography [25].

1.9 The phenolic compounds

Phenolic compounds are secondary metabolites produced by the secondary metabolic pathways of plants [26]. They are derived from pentose phosphate and shikimic acid of plants through metabolization of phenylpropanoid [27, 28]. The composition of phenolic substances or polyphenols includes tannins, flavonoids, lignans, coumarins, and phenolic acids [26], colored anthocyanins [29]; these compounds are naturally found in vegetables, fruits, leaves, and roots among other products of plant origin [26, 27].

1.10 The tannins

Tannins are group of astringent and complex polyphenolic compounds found in plants, which can bind and precipitate proteins; the word tannin was derived from the usage of this compound in tanning animal hides and skins to make leather [30]; the term was first introduced in 1796 [31]. Commonly, tannins are found in wood, buds, fruits, leaves, stems, roots, seeds, and in the bark of trees [32]. Condensed tannins are the most abundant polyphenols, which are virtually found in plant families [33].

1.11 The terpenoids

Terpenoids or isoprenoids are modified terpenes [34, 35]; terpenoids usually contain additional functional group and oxygen [35]. These chemical compounds are the largest class of secondary metabolites representing 60% of the natural products known [36].

2. The biological activities of secondary metabolites

Unique structural diversity is provided by natural products when compared with standard combinatorial chemistry; these give opportunities for discovering novel lead compounds with low molecular weight. The world's biodiversity evaluation of natural products for potential biological activity is less than 10%; thus, a lot of useful novel natural lead compounds await discovery [37].

Terrestrial plants are the major source of secondary metabolites; other sources include fungi, bacteria, as well as several marine organisms [10].

2.1 The pharmacological activity of plant-derived secondary metabolites

2.1.1 Antibacterial activity

Natural antibiotics are secondary metabolites produced by microbes that inhibit bacterial growth by targeting essential cellular processes such as the synthesis of the

bacterial cell wall, DNA/RNA, and proteins. They are not essential for the growth of the organism (and usually produce at the end of the exponential phase of their growth). They have diverse roles, such as in cellular differentiation, nutrient sequestration, metal transport, ecological interactions, and defense [38, 39].

Between 1935 and 1968, 12 classes of antibiotics were launched and approved for use as drugs. However, between 1969 and 2000, the number dropped markedly, with only two classes introduced. Out of the 30 antibiotics launched between the year 2003 and 2015, 16 belong to natural products and their derivatives. They include three new classes of natural antibiotics—two actinomycete: the lipopeptide daptomycin in 2003 and fidaxomicin (of the tiacumicin family) in 2010. The third is a fungal product: retapamulin derived from pleuromutilin and approved in 2007 for topical use [38, 40].

Newman and Cragg reported the introduction of several natural secondary metabolites that have been reported to possess potent antibacterial activity including: anthrasil, omadacycline, dalbavacin, plazomicin, ceftaroline fasamil acetate, lefamulin, sarecycline, eravacycline imi-cilast-relebactam, etc. [41].

2.1.2 Anti-inflammatory activity

Inflammation is a normal biological process that occurs as a response to microbial infection, chemical irritation, or tissue injury. It is usually initiated by moving the immune cells from blood vessels and release of mediators to the damage site. It is then followed by reinforcement with inflammatory cells, release of reactive oxygen species (ROS), reactive nitrogen species (RNS), and proinflammatory cytokines to fight the foreign pathogens and repairing the injured tissues. In general, normal inflammation is rapid and self-limiting, but unresolved and prolonged inflammation causes various chronic disorders. As a pathologic condition, inflammation can include a wide range of diseases such as rheumatic and immune-mediated conditions, diabetes, cardiovascular accident, etc. [38, 42]. Aswad and coworkers reported the use of moupinamide, capsaicin, and hypaphorine—natural products—with high scores in their indexing of potential anti-inflammatory drug candidates [43]. Mona et al. also reported more than 15 herbs, where their anti-inflammatory effects have been evaluated in clinical and experimental studies including *Curcuma longa*, *Zingiber officinale*, *Rosmarinus officinalis*, *Borago officinalis* [42].

2.1.3 Anticancer activity

Cancer is one of the leading causes of death (second to cardiovascular diseases) in the world, despite the availability of wide range of anticancer drugs. The estimated cancer burden in the world as reported by the World Health Organization (WHO) is 18.1 million new cases and 9.6 million deaths as at 2018 [38, 44]. Presently, research efforts are directed toward the discovery of natural products with anticancer potential [45]. Several secondary metabolites have been reported to possess anticancer potential; some of these compounds have the capacity to prevent oxidative stress and inflammation that causes damage to DNA, which in turn leads to carcinogenesis [45]. Natural products such as irinotecan, vincristine, vinblastine, etoposide, and paclitaxel from plants, actinomycin D and mitomycin C from bacteria as well as marine-derived bleomycin are widely used in the treatment of various cancers [44].

Also, fruits and vegetables are plant sources that are known to contain vitamins, minerals, folate, plant sterols, carotenoids, and various phytochemicals such as

flavonoid and polyphenols—natural product compounds that are associated with reduced cancer mortality and risk [46]. The critical relationship of fruit and vegetable intake and cancer prevention has been thoroughly documented. It has been suggested that major public health benefits could be achieved by substantially increasing consumption of these foods [38].

Herbs and spices such as ginger, capsicum, curcumin, clove, rosemary, sage, oregano, and cinnamon are very rich in antioxidants due to the high content of phenolic compounds and have been shown to counteract reactive oxygen species (ROS)-mediated damage in different human cancers [47]. Many cyclic peptides and their derivatives obtained from marine organisms have been shown to possess anticancer, antimicrobial, anti-inflammatory, antiproliferative, and antihypertensive properties [46]. Furthermore, lactoferrin, a multifunctional protein found in bovine and camel milk, has also been reported to possess anticancer effect [48].

2.1.4 Antiviral activity

Natural compounds are an important source for the discovery and the development of novel antiviral drugs because of their availability and expected low side effects. Naturally occurring compounds with antiviral activity have been recognized as early as 1940s. The search for effective drugs against human immunodeficiency virus (HIV) is the need of hour. Most of the work related with antiviral compounds revolves around inhibition of various enzymes associated with the life cycle of viruses. Structure-function relationship between secondary metabolites and the HIV enzyme inhibitory activity has been observed [38].

2.1.5 Hepatoprotective activity

Diseases of the liver have been classified as high priority areas of health care, as an estimate by the World Health Organization shows approximately 500 million people of the world are suffering from a severe form of liver disorders that may lead to chronic hepatitis. Hepatic disorders can be caused by exposure to agents such as drugs, viruses, parasites, and toxins. Such an exposure usually may result in degeneration and inflammation of the liver; furthermore, it results in fibrosis and cirrhosis [49]. In addition, different chronic diseases such as diabetes may lead to development of hepatic clinical manifestations.

Several flavonoids such as catechin, apigenin, quercetin, naringenin, rutin, and venoruton are reported for their hepatoprotective activities [38]. Muhammad and coworkers review studies conducted on the composition, pharmacology, and nature of some selected plants in the light of possible mechanism deduced from experimental trials [49]. Also, a comprehensive review by Meng et al. [50], listed several plants and products that have been used in the prevention and treatment of chemically induced liver damages [50].

2.1.6 Important present-day drugs derived from plants secondary metabolites

Many drugs with wide range of pharmacological activities were derived from alkaloids [51]. Some of the important drugs derived from alkaloids include:

1. Quinine—antimalaria [51]
2. Morphine—analgesic [52]

3. Codeine—analgesic, antitussive [53]
4. Ephedrine—antiasthma [51]
5. Galantamine—cholinomimetics [54]
6. Homoharringtonine—anticancer [50]
7. Quinidine—antiarrhythmic [52]
8. Vincamine—vasodilator [52]
9. Chelerythrine—antibacterial [55]
10. Piperine—antihyperglycemic [56]
11. Atropine—anticholinergic [57]
12. Pilocarpine—cholinergic agonist [58]
13. Paclitaxel—anticancer [59]
14. Ergotamine—anti-migraine [60]
15. Reserpine—antihypertensive [60]
16. Vinblastine and vincristine—anticancer [60]
17. Physostigmine—anti-mydriatic, etc. [60]

2.1.7 *The pharmacological activities of cardiac glycosides*

The effects of cardiac glycosides mainly for increasing heart muscle force of contraction and reducing heart rate are beneficial for treating cardiac arrhythmias and congestive heart failure; cardiac glycosides have long been used to manage these ailments. The commonest cardiac glycosides used clinically include digoxin, digitoxin, ouabain, and bufalin [61]. Other forms of cardiac glycosides are antiarin, thevetin A and B, peruvoside, neriifolin, thevetoxin, ruvoside, theveridoside, cerberin, convallarin, convallamarin, convallatoxin, glucoscillarene A, proscillaridine A, scillarene A, scilliglaucoside and scilliphaeoside, marinobufagenin, oleandrin, folineriin, adynerin, digitoxigenin, marinobufagenin, telocinobufagin [62]. Among these substances, literature has also reported the therapeutic uses of acetyldigoxin, digitoxin, digoxin, gitoformate, gitoxin, lanatoside C, metildigoxin (β -methyldigoxin), ouabain (strophanthin-g), peruvoside, proscillaridin, strophanthin-k [63], apart from digoxin, digitoxin, ouabain, and bufalin earlier mentioned [61].

2.1.8 *The pharmacological activities of flavonoids and phenolic compounds*

From plants, over 8000 phenolic compounds have been reported [64]. Interestingly, flavonoids make up half of these phenolic compounds [64]. Effectively,

flavonoids and several other phenolic compounds have been reported to possess antibacterial, anti-inflammatory, antioxidants, anticancer, cardioprotective, immunomodulatory, and skin radioprotective effects from UV light. More so, these compounds are good pharmaceutical candidates for medical application [65]. Several flavonoids including apigenin, galangin, flavone and flavonol glycosides, isoflavones, flavanones, and chalcones have been shown to possess potent antibacterial activity [38].

2.1.9 *The pharmacological activities of tannins*

Certain carcinogenic incidences, such as esophageal cancer, have been related to tannins-rich foods consumption, especially the herbal tea and betel nuts. However, several reports showed that tannins' carcinogenic effects are not due to tannins themselves but likely due to components associated with the tannins [66]. Many literatures revealed negative association between cancer incidences and consumption of tannins components and tea polyphenols, suggesting their anticarcinogenic effects [66].

The antimutagenic and antimicrobial activities of tannins have been documented. Tannins inhibit the growth of viruses, bacteria, yeast, and many fungi. It has also been reported that propyl gallate and tannic acid inhibit aquatic bacteria and food-borne bacteria; this action is not reported for gallic acid. In food processing industry, catfish fillets' shelf-life can be enhanced using the tannic acid antimicrobial property. The antihypertensive, hypolipidemic, coagulative, and immunomodulatory effects of tannins have been reported [66].

2.1.10 *The pharmacological properties of terpenoids*

Terpenoids being the most abundant compounds in natural products have been reported to possess antibacterial, antimalarial, antiviral, hypoglycemic, neuroprotective, and anti-inflammatory activities. Furthermore, literatures have also documented the effects of terpenoids in treating and preventing cardiovascular diseases, antioxidation, immunoregulation, and promotion of transdermal absorption of substances [67].

2.2 **The pharmacological activities of fungal-derived secondary metabolites**

2.2.1 *Some important drugs of fungal origin*

2.2.1.1 *Antibiotics*

The beginning was the discovery of penicillin by Alexander Fleming from penicillium mold; penicillin is one of the most known antibiotics in use, and the beta lactam antibiotics penicillin and cephalosporin were all derived from fungus [68]. Other antibiotics derived from fungus include alamethicin, brefeldin A, aphidicolin, citromycin, fumagillin, cerulenin, eupenifeldin, fusidic acid, fusafungine, itaconic acid, usnic acid, helvolic acid, nigrosporin B, verrucarins A, vermiculine, etc. [68]. Tiamulin, retaparmulin, and valnemulin are antibiotics derived from pleuromutilin [68].

2.2.1.2 *Antifungal agents*

Antifungal griseofulvin is a derivative of penicillium species [69], azoxystrobin, echinocandins, strobilurin, micafungin, anidulafungin, and caspofungin are all antifungal agents originally derived from fungus [70].

2.2.1.3 Immunosuppressive agents

Bredinin, cyclosporin, mycophenolic acid, myriocin, endocrocin, and gliotoxin are all immunosuppressants isolated from fungus [71].

2.2.1.4 Potential antiviral agents

Compounds from several mushrooms such as *Ganoderma lucidum*, *Grifola frondosa*, *Ganoderma colossus*, *Lentinus edodes*, *Hypsizygus marmoreus*, *Scleroderma citrinum*, *Cordyceps militaris*, *Trametes versicolor*, *Flammulina velutipes*, *Fomitopsis officinalis* are under research for potential antiviral activities validations [72, 73].

2.2.1.5 Potential antidiabetic and antimalarial agents

Ternatin and many other fungal isolates have potential hypoglycaemic effects [74]. Potential antimalarial agents of fungal origin under scientific elucidations include antiamebin, codinaeopsin, zervamicins, and efraeptins [75].

2.3 The pharmacological activities of bacterial-derived secondary metabolites

Pharmaceutical agents of bacterial origin include antibiotics, immunomodulators, nematicides, antitumor agents, coccidiostatic agents, enzyme inhibitors, and insecticides. Interestingly, *Escherichia coli* is used as a host in molecular biology for synthesis of recombinant proteins [76]. Selman Abraham Waksman, the father of antibiotics, discovered actinomycin; this effort was followed by the discovery of streptomycin in 1944 [77]. Other clinically important antibiotics derived from bacteria include bacitracin [78], polymyxin B [79], gentamicin [80], amphotericin b [81], tetracycline [82], erythromycin [83], rifamycin [84], vancomycin [82], neomycin [85], streptomycin [86], and chloramphenicol [87]. Etc.

3. The role of secondary metabolites in enhancing agricultural productivity

The resistance against herbivores and pathogens is a role played decisively by the chemical protection nature of plants, the secondary metabolites; they are plant features important especially for protection against a wide range of microorganisms such as bacteria, viruses, fungi, arthropods, herbivores, and vertebrates [88]. Soil decomposition is influenced by plant secondary metabolites by increasing nitrogen immobilization in the soil; cycling of carbon (C) and nitrogen (N) is affected by terpenes and tannins [89].

Exudates from plants roots contain secondary metabolites that can attract, kill, or deter underground microbes, herbivorous insects, and nematodes, competing plants and underground injuries are also inhibited [90]. Plants secondary metabolites contain potential toxic substances used for defense against insects; these chemical compounds can be utilized for design of future insecticides with multiple or specific targets [91]. A good example of an insecticidal compound of such nature is pyrethrin derived from the flowers of *Pyrethrum cinerariaefolium* plant; pyrethroids are the synthetic analogs of pyrethrin [92].

In terms of animals' productivity, animals that ingest forages containing different plants secondary metabolites get their meat and dairy products enhanced in terms of biochemical richness making them good for human consumption [93].

In today's food industries, plants secondary metabolites are used extensively as flavoring, coloring, and texturizing agents. Preservation and anti-browning are done with metabolites possessing antioxidative properties [94].

4. Folkloric usage of secondary metabolites based on reliable sources of information and genuine scientific investigations

The fact that animals and humans have been in existence before the advent of orthodox medicine is a proof that plants have been quite effective in treating diseases. The folkloric use of plant medicine has a long history [95]. From the earliest times, man acquired knowledge of the adverse and beneficial effects of plants from observations on animals. To distinguish edible from poisonous plants, grazing animals were observed and the plants not eaten were considered poisonous [96]. About 80% of the rural population today depends largely on medicinal plants for primary health care [97]. About 25% of all prescription drugs in developed countries are obtained directly or indirectly from plants [98].

Plants produce valuable organic compounds, some of which have potentials in treating ailments in both animals and humans [99]. Of the 252 drugs considered as basic and essential by the WHO, 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors [100]. In 1997, the world market for phytomedicinal products was estimated at US\$10 billion [101]. This prompted the WHO to consider phytotherapy in its alternative or complementary health program. Locally produced plant medicines can be cheaper than imported synthetic drugs. One striking example is an herbal wound powder (Himax®) in Sri Lanka that was found to be as effective as an imported powder (Neomex®) and comparatively 80–90% cheaper [102].

The most easily accessible, affordable, and inexpensive sources of treatment in the primary healthcare system throughout the world are medicinal plants; there is a long history for the therapy of various disease conditions traditionally in various regions of the world [103].

Natural products' earliest records were depicted on clay tablets from Mesopotamia (2600 BC) in cuneiform; there are documented evidences of the folkloric use of oils derived from *Commiphora species* and *Cupressus sempervirens* that are still in use today to treat inflammation, coughs, and colds [104]. The Egyptian pharmaceutical record "the Ebers Papyrus" (2900 BC) documented over 700 drugs of plant origins; these agents include infusions, gargles, ointments, and pills. The Chinese folkloric record books such as the *Materia Medica* (1100 BC) with 52 prescriptions, the *Tang Herbal* (659 AD) with 850 drugs, and the *Shennong Herbal* (100 BC) with 365 drugs provide records of natural products' uses [104]. Theophrastus (300 BC), the Greek natural scientist and philosopher, is an expert in dealing with medicinal herbs, while Dioscorides (100 AD), the Greek physician, documented the uses and storage of medicinal herbs [104]. The monasteries in Germany, England, France, and Ireland preserved this knowledge during the Dark and Middle Western Ages. Preservation of the Greek and Roman knowledge was done by the Arabs. They also expanded of their own resources; this is done with the Indian and Chinese unfamiliar herbs to the Greek and Roman world [104]. In the eighth century, it was the Arabs who privately

own pharmacies. Avicenna, a Persian physician, pharmacist, poet, and philosopher, contributed a lot to the science of medicine and pharmacy through his notable work such as the “Canon Medicine” [104].

4.1 Some reported medicinal uses of secondary metabolites

4.1.1 Alkaloids

Alkaloids have a wide range of pharmacological effects including antimalarial (quinine), antiasthma (ephedrine), anticancer (homoharringtonine), vasodilatory (vincamine), antiarrhythmic (quinidine), analgesic (morphine), antibacterial (chelerythrine), and antihyperglycemic activities (e.g., piperine) [37].

4.1.2 Anthraquinones

Huang et al. [105] and other teams clearly demonstrated that anthraquinones, such as emodin, aloe-emodin, and rhein, inhibit the growth and proliferation of various cancer cells, such as lung adenocarcinoma, myelogenous leukemia, neuroblastoma, hepatocellular carcinoma, bladder cancer, and others through cell death and survival's modulation. Several anthraquinones are able to inhibit the replication of viruses or even directly kill enveloped or unenveloped strains [106]. Senna, cascara, frangula, rhubarb, and aloe are commonly used for their laxative effects [107].

4.1.3 Flavonoids

Flavonoids have various health-promoting effects such as antioxidative, anti-inflammatory, anticarcinogenic, and antimutagenic. Flavonoids have antioxidant effects associated with various diseases such as Alzheimer's disease, cancer, atherosclerosis [108].

4.1.4 Cardiac glycosides

The most important use of the cardiac glycosides is its effects in treatment of cardiac failure. In cardiac failure, or congestive heart failure, heart cannot pump sufficient blood to maintain body needs. During each heart contraction, there is an influx of Na^+ and an outflow of K^+ . Before the next contraction, Na^+ , K^+ -ATPase must reestablish the concentration gradient pumping Na^+ into the cell against a concentration gradient. This process requires energy, which is obtained from hydrolysis of ATP to ADP by Na^+ , K^+ -ATPase. Cardiac glycosides inhibit Na^+ , K^+ -ATPase, and consequently increase the force of myocardial contraction [109].

4.1.5 Saponins

Saponins exhibit a biological role and medicinal properties such as anti-inflammatory [110], antibacterial, antifungal, antiviral, insecticidal, anticancer, cytotoxic, and molluscicidal action [111].

4.1.6 Terpenes and steroids

Terpenes include substances such as floral fragrances, which serve as insect attractants, pine oil, growth inhibitors, plant hormones (gibberellic acid and abscisic acid),

and some of which are insecticidal. About 30,000 terpenes have been identified; they all possess repeating five-carbon isoprene units (a five-carbon ring) [112].

Artemisinin is a sesquiterpene, which originated from the Chinese medicinal plant Quinhao (*Artemisia annua*). It was used to treat fever medicine for over two millennia. It was mentioned in the 52 Remedies recovered from the Mawangdui Tomb dating from the Han Dynasty 206 BC – 221 BC located in Henan Province [113]. Placitaxol (a diterpene) is quite effective in treating against ovarian, breast, colon, non-small-cell lung cancer, and malignant melanoma [114]. Terpenoids (diterpenoids, sesquiterpenoids, triterpenoids) and lignoids also have antiviral activities. A number of them inhibit replication of inhibit coronaviruses, including SARS-Corona Virus. Betulinic acid and savinin are competitive inhibitors of a protease (an enzyme that breaks down proteins) produced by the SARS-CoV 3CL virus [114]. It will be worthwhile testing the effect of these terpenoids on SARs-CoV 2, the cause of recent Covid-19 pandemic.

4.1.7 Alkylresorcinols

Secondary metabolites are known for their angiogenic or wound healing activity, new compounds such as the new alkylresorcinols isolated from the lipophilic extract of *Urginea indica* L. bulbs have been reported to possess wound healing activity following experimental trauma [115].

Conflict of interest

Authors declare no conflict of interest.

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