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Frontiers in Natural Product Chemistry

Editor:
Atta-ur-Rahman, *FRS*

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PREFACE

Frontiers in Natural Product Chemistry presents recent advances in the chemistry and biochemistry of naturally occurring compounds. It covers a range of topics including important researches on natural substances of plants, microbes and animals. The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information in natural product chemistry. The chapters are written by authorities in the field and are mainly focused on isolation, structure, biosynthesis, biological activity, and chemistry of the major groups of natural products. The contents of the present volume represent exciting recent researches ranging from horizontal gene transfer (HGT) for the production of secondary metabolites to natural products used against neglected tropical diseases.

I hope that the readers will find these reviews valuable and thought provoking so that they may trigger further research in the quest for the new and novel therapies against various diseases. I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), and Mr. Shehzad Naqvi (Senior Manager Publications) at Bentham Science Publishers.

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CHAPTER 1

The Implications of Horizontal Gene Transfer for Access to Secondary Metabolites

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Abstract: Comparative analysis of archaeal, bacterial, and eukaryotic genomes indicates the occurrence of horizontal gene transfer (HGT) in many genomes. Although widely studied in prokaryotic systems, eukaryotes, which were thought to evolve principally through reproduction and mutation (vertical gene transfer), also acquire novel genes and pathways through the acquisition of sequences from distantly related species. HGT is a notable phenomenon that allows the sharing of genetic information among members of most or all kingdoms. HGT leads to extremely dynamic genomes, which have the potential to effectively change the type and presence of secondary metabolites in an organism. HGT is documented in fungi, bacteria, animals, and plants - when viral mechanisms are included, all organisms likely are subject to HGT. The quantities of genetic material that are horizontally transferred range from small gene fragments to groups of genes, including whole operons that encode complex biochemical pathways. Examples of HGT that contribute to novel or expanded ranges of secondary metabolite products include filamentous and unicellular fungi, actinomycetes and other bacteria, and plants. In this chapter we will discuss several examples of secondary metabolite production that occur as a consequence of HGT, the study of natural products acquired through HGT processes and the ramifications of HGT for biosynthesis and exploitation of natural products that arise from horizontally-transferred pathways. We have focused primarily on the literature published from 2000 to 2015.

Keywords: Bioinformatics, Eukaryotes, Evolution, Horizontal gene transfer, Lateral gene transfer, Natural products, Prokaryotes, Secondary metabolites.

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INTRODUCTION

Horizontal gene transfer (HGT) is particularly widespread and well-documented in prokaryotes, especially bacteria, where it serves as a major driver of genetic innovation and niche adaptation [1]. There is an increasing awareness that HGT is equally important in eukaryotic systems [1b] although somewhat more difficult to document. Because many of the genes transferred by these HGT mechanisms encode enzymes [2] and are associated with metabolic pathways, within and outside of gene clusters [3], these processes are of interest to the researcher focused on the production of secondary metabolites in a wide variety of organisms.

There are two major hypotheses developed to explain HGT: the gene ratchet [4] and the weak-link model [1b]. In the gene ratchet, engulfment, phagocytosis, or invasion of cells into eukaryotic hosts leads to break-down of the internalized cell, with a release of the nucleic acid contents into the surrounding cytoplasm. This genetic material is an opportunity to acquire new genes, and takes into account the propensity for cell nuclei, at least in some cases, to take up linear cytoplasmic DNA [5]. In the weak-link model, DNA can be acquired through a variety of mechanisms (infection, invasion, engulfment) by whatever stage of the reproductive life cycle is most exposed to the external environment (the weak link). In this hypothesis, single-celled organisms would be most subject to HGT, since the reproductive entity is also the vegetative entity. Even well-protected reproductive cells (mammals, angiosperms) would still be susceptible to infection, symbiotic transfer, or transfer from surrounding non-reproductive cells of horizontally-acquired genes.

In this chapter, we will provide definitions of terms less familiar to many in the natural products community, the mechanisms of HGT processes, methods to determine whether HGT has occurred, examples of HGT in various organisms, and the implications of HGT for those interested in discovery of new secondary metabolites and additional producers of known metabolites.

I. DEFINITIONS

I.a. Horizontal Gene Transfer

The traditional assumption of biological evolution is modification of existing heritable information (genes) by passage of genetic material from the parent to offspring and ancestor to descendant (genealogical or **vertical gene transfer-VGT**). The exchange of genetic information by VGT can occur only between sexually-reproductive members of the same species. However, there is widespread understanding of genetic information shared among prokaryotes outside species boundaries [6]. Prokaryotes frequently engage in cross-species exchange of genetic material by the acquisition of sequences from distantly related species (**HGT**, also known as lateral gene transfer). Eukaryotes appear to use HGT to a lesser extent, although the frequency of this exchange is under intensive study. HGT, by both sexual and asexual mechanisms, increases the genetic diversity of the recipient, sometimes conferring selective or adaptive advantage, pathogenic potential, or symbiotic outcome.

HGT events are known within and among all three domains of life (Archaea, Bacteria, and Eukarya); HGT was first noticed due to incongruities in phylogenetic trees. Often considered to be a driving force in the innovation of genomes, particularly in prokaryotes [1, 7], the extent and impact of HGT on the evolution of diverse organisms is controversial [8]. Of interest to the natural products researcher, HGT leads to a broader range of producer organisms for particular secondary metabolites than would be suggested by phylogeny.

I.b. Variation in HGT Histories

The simplest form of HGT mechanistically is acquisition of foreign DNA from the external environment. More complex are acquisitions following ingestion or phagocytosis of unrelated organisms. These can lead to **intracellular or internal gene transfer (IGT)**. If the engulfed organism becomes an internal symbiont (plastid, mitochondrion, or other organelle), subsequent transfer of genetic material from the genome of the symbiont into the host genome can be referred to as **endosymbiotic gene transfer (EGT)** or **organellar gene transfer (OGT)** [1b]. As we will show, even more complex histories are known; some of the most

CHAPTER 2

Polyphenols: From Wastes to High added Value Bio-products

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Abstract: Over the past two decades, biotechnologies have provided a motor for innovation and sustainability in many economies all around the world by developing new processes and products in a *bio-economy* approach. Besides food and feed, increasing interest on biomass derived fuels, chemicals and materials, sustainably sourced and produced, has raised, providing an alternative to heavy reliance on finite fossil fuel resources. One of the most innovative and promising sectors of the bio-economy is related to bio-based products, obtained in part or entirely from organic biomass, which account for about 16% of world production of bio-economy's products. Plant biomass is rich in high added value compounds; mainly antioxidants and fibres, which once extracted can serve as green fine chemicals or can be used in food supplements and/or nutraceutical sector.

A great deal of evidence has established that the secondary compounds of higher plants (*i.e.* polyphenols) inhibit and/or quench free radicals and reactive oxygen species (ROS) thus protecting against oxidative damage. These compounds can therefore be exploited as additives in a large number of different commodities, such as plastics and nanomaterials.

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This chapter gives an insight into the relevant research results regarding the valorization of polyphenol fractions extracted from agricultural wastes, focusing on those derived from fruit production and transformation. Structure-activity relationships will be discussed in view of their use in the field of innovative materials.

Keywords: Bio-economy, Bio-materials, Plant wastes, Polyphenols.

INTRODUCTION

New discoveries in life sciences and the societal challenges, such as climate change, population growth, pollution, and unsustainable consumption patterns, are leading to a crucial change that involves long-term approaches and interactions that occur at all levels of society [1]. Besides, the rising price of essential inputs has led to an increasing emphasis towards the development of those technologies that are perceived as renewable and sustainable. In this scenario, the emergence of a novel model of economy, the "bio-economy", which utilizes new biology-based technologies for commercial and industrial purposes and for the improvement of the human welfare, appears essential [2, 3].

According to the Organisation for Economic Co-operation and Development (OECD), bio-based material production (*e.g.* bio-based chemicals and plastics) is widely viewed as a central manufacturing element of the next bio-economy, after the explosion of worldwide interest in biofuels production that took place in early 2000s [4 - 6].

According to the "European Standard EN 16575:2014", the term "bio-based product" refers to a product "wholly or partly derived from biomass", whereas the product can be an intermediate, material, semi finished or final product.

Residues generated along the agro-food pipeline represent a valuable biomass resource that, if optimally utilized, would provide high added value compounds before being converted into biofuels.

In fact, agricultural wastes contain a variety of biologically active species, such as antioxidants (*e.g.* phenolics, thiols, carotenoids…) and natural colorants, which currently are discarded with no revenue. Consequently, apart from being a serious environmental problem, agro-food wastes can also represent a precious resource of potentially valuable molecules.

The society may derive environmental and economic benefit through better utilization of these resources. Since the industrial revolution, the main pattern in developed societies has been based on a 'take-make-consume and dispose' growth. In the last few decades the unsustainability of this model has been fully demonstrated since it is clear that the current population growth cannot afford the up-to-now used linear model based on the assumption that resources are abundant, available, and cheap to be disposed. All these effects represent a threat to competitiveness and sustainability in the global world economy. Circular economy systems keep the added value in products for as long as possible, proceeding to erase the waste. Transition to circular economy requires, however, changes throughout the value chain, from product design to new business models and markets, up to new ways of turning waste into a resource for a new type of consumer. The use of bio-based materials in these new paradigms for the global economy is a first-class challenge for society. Therefore, improvements in sustainability will be necessary in the short term to improve the citizen´s quality of life. In fact, some market drivers have been drawn to promote the change of these paradigms to a sustainable and environmentally friendly society:

1. ***Valorization of agricultural residues.*** There is a clear tendency in developed countries to eliminate agricultural residues by using environmentally friendly procedures to avoid incineration and waste accumulation. In addition, if these residues acquire value by getting chemicals, monomers and building blocks to further produce valuable natural products this will close the circle to give value to current residues.
2. ***Use of non-food competitive feedstock.*** Companies and consumers are today reticent to use bio-based materials when they are made from food competitive feedstock (*e.g.* decrease of poly(lactic acid) (PLA) market in France partially because of the use of corn starch as raw material).
3. ***Increasing bio-based contents of technical compounds with the use of bio-based additives and solid fraction of the biomass.*** It could allow end-users to obtain eco-labels to increase the use of ameliorate products' environmental efficiency, which could lead to satisfy the market demands.
4. ***Cost efficient technology and feedstock for bio-products production.*** Price is

CHAPTER 3

The Role of Natural Products in Tropical Diseases

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Abstract: Tropical diseases are largely prevalent in the tropics and they are a significant cause of morbidity and mortality. Tropical diseases refer to infectious diseases such as malaria, leishmaniasis, lymphatic filariasis, American trypanosomiasis (Chagas disease), African trypanosomiasis, and dengue that thrive in relatively hot and humid conditions. This chapter presents an overview of recent developments on the use of various natural products active against malaria, leishmaniasis, lymphatic filariasis, American trypanosomiasis (Chagas disease) and African trypanosomiasis.

Keywords: African Trypanosomiasis, American Trypanosomiasis (Chagas Disease), Leishmaniasis, Lymphatic Filariasis, Malaria, Natural Products, Tropical Diseases.

1. TROPICAL DISEASES

Tropical diseases encompass all diseases that are largely prevalent in the tropics causing a significant number of morbidity and mortality. Practically, the term is often taken to refer to infectious diseases such as malaria, Chagas disease, leishmaniasis, lymphatic filariasis, African trypanosomiasis, and dengue *etc.* that thrive in hot, humid conditions. Unlike in tropics, cold season in temperate climates, by forcing hibernation, regulates the population of insect's population. Most common diseases carriers or vectors are insects: mosquitoes and flies. These

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insects might contain a parasite (*e.g.*, virus or bacterium) that could be infectious to other living beings. Mostly, the disease transmission is by insect "bite".

Generally a parasite will not kill its host instantly, as by an evolutionary manner this would be a dead end for it. Nevertheless, some parasitic infections for instance malaria, trypanosomiasis or Chagas can be deadly if the patients are not provided with proper therapies on time.

Historically, plants have an extraordinary medicinal importance since ancient times – having been used as the most valued source of medicines [1], and they continue to serve as the basis for development of a great number of pharmaceuticals. This chapter presents an overview of recent developments in the use of natural products and their synthetic derivatives active against malaria, leishmaniasis, lymphatic filariasis, American trypanosomiasis (Chagas disease) and African trypanosomiasis.

2. MALARIA

2.1. Introduction

Malaria is a one of the serious global health challenge, with a large number of new infections and deaths reported annually. It is one of the major child killer diseases, especially in those parts of the world where the health facilities are inadequate and those having under-developed medical systems [2]. A recent report from WHO (December, 2014), stated that there were about 198 million documented cases of malaria around the world in 2013 which caused 584,000 deaths [3]. Africa remains the worst-hit continent as every 60-second, a child dies from malaria – though this is preventable and the disease is curable. However, since 2000, malarial mortality rates have reduced by 47% worldwide, with a decrease of 54% in the WHO African region [4].

Malaria is an infectious health care problem caused by a protozoan parasite (*Plasmodium*) which is transmitted by the bite of the specific female anopheles mosquito. Five species of the genus *Plasmodium* may transmit the malarial parasite in the human body: *Plasmodium malariae*, *Plasmodium vivax, Plasmodium falciparum*, *Plasmodium ovale* and *plasmodium knowlesi*. Among these four species, *P. vivax* and *P. ovale* are the more virulent. This is because even after the treatment of malaria the parasites may remain dormant in the liver cells of the infected person, as hypnozoites, for several months, or even years [4]. The two phases for malarial infection growth involve liver (exo-erythrocytic phase) and red blood cells (erythrocytic phase) [3]. Sporozoites present in the saliva of infected mosquito enter the blood stream as these mosquitoes feed on human blood and then they migrate in to the liver and cause infection. Once in the liver, the sporozoites undergo an incubation period of 8 to 30 days for asexual multiplication before the full-blown infection develops.

2.2. Different Classes of Natural Products and their Anti-malarial Activity

Historically anti-malarial chemotherapy is closely associated with the traditional knowledge of herbal medicinal products preparation. Quinine and artemisinin are the outstanding examples of anti-malarial natural products. Quinine remained in use as a standard drug to treat malaria for decades but, in 1930, it was replaced by a sequence of synthetic drugs [4].

2.2.1. Alkaloids

Alkaloids are natural compounds which contain nitrogen atom/s. The alkaloid quinine (**1**) used as an anti-malarial drug was obtained from the bark of cinchona tree, and purified as the major alkaloid in 1820 by French scientists Pelletier and Caventou. It is a drug of choice to treat fatal and complicated falciparum malaria [5]. A Bolivian plant, *Pogonopus tubulosus* K. Schum. (Rubiaceae), was found to contain tubulosine (**2**), a β-carboline-benzoquinolizidine alkaloid derivative. It exhibited an IC_{50} value of 0.012 μM against *P. falciparum* (a chloroquine-sensitive strain) [5]. Naturally occurring bisbenzylisoquinoline alkaloids, penduline (**3**) and tetrandrine (**4**) showed good activity as anti-plasmodium agents [5]. The isoquinoline alkaloids, augustine (**5**), crinamine (**6**), and lycorine (**7**) isolated from *Crinum amabile*, belonging to family Amaryllidaceae, showed a broad range of biological activities. Augustine and crinamine were found to be effective inhibitors of *P. falciparum in vitro* [5]. Compound **5** exhibited anti-malarial activity with IC_{50} value 0.46-0.60 μM against chloroquine sensitive and chloroquine resistant strains of *P. falciparum*, respectively. Compound **6** showed

CHAPTER 4

Corrinoids in Food and Biological Samples

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Abstract: Vitamin B_{12} is synthesized by only certain bacteria but not by plants. Thus, foods derived from animals, namely meat, milk, fish, and shellfish, are major dietary sources of vitamin B_{12}. Intestinal bacteria have the ability to synthesize various corrinoid compounds carrying different base moieties in the lower ligand. Thus, animal manures and human feces contain substantial amounts of various cobamides with different bases. When food corrinoids were purified and characterized, certain food items unexpectedly contained pseudovitamin B_{12}, in which adenine replaces 5,6-dimethylbenzimidazole as the base. Cyanobacteria used as human health supplements provide substantial amounts of pseudovitamin B_{12}, which functions as a cofactor for cobalamin-dependent methionine synthase in these organisms. Oral administration of pseudovitamin B_{12} to mammals suggests that this cobamide does not act as a vitamin B_{12} antagonist in the gastrointestinal absorption of vitamin B_{12} and cobalamin-dependent enzyme systems. Furthermore, vitamin B_{12} is converted into an inactive analogue vitamin B_{12}[*c*-lactone] by the treatment with chloramine-T, which is used as a disinfectant. The unnatural vitamin B_{12} analogue was found in certain dried mushroom fruiting bodies.

Keywords: Benzimidazoles, Biosynthesis of corrinoids, Cyanocobalamin, Food, Phenolic compounds, Pseudovitamin B_{12}, Purines, Vitamin B_{12}.

INTRODUCTION

Vitamin B_{12}, also known as cyanocobalamin, a member of corrinoids that contain the macrocyclic corrin ring (Fig. **1**). Among them, cyanocobalamin ($C_{63}H_{88}CoN_{14}$

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$O_{14}P$; molecular weight 1355.3651 g/mol; monoisotopic mass 1345.5674 g/mol; CAS registry number 68-19-9) is stable in neutral pH solution and autoclaving for short periods at 121°C [1]. Hydroxocobalamin, methylcobalamin, and 5′-deoxyadenosylcobalamin are chemically more labile than cyanocobalamin. In particular, coenzyme forms of cobalamin, methylcobalamin and 5′-deoxyadenosylcobalamin are highly light sensitive compounds. Methylcobalamin is the cofactor of methionine synthase (EC 2.1.1.13), and 5′-deoxyadenosylcobalamin functions as the coenzyme of methylmalonyl-CoA mutase (EC 5.4.99.2) that catalyzes the conversion of (*R*)-methylmalonyl-CoA to succinyl-CoA in the catabolic pathway of amino acids and odd-chain fatty acids in mammals [2, 3].

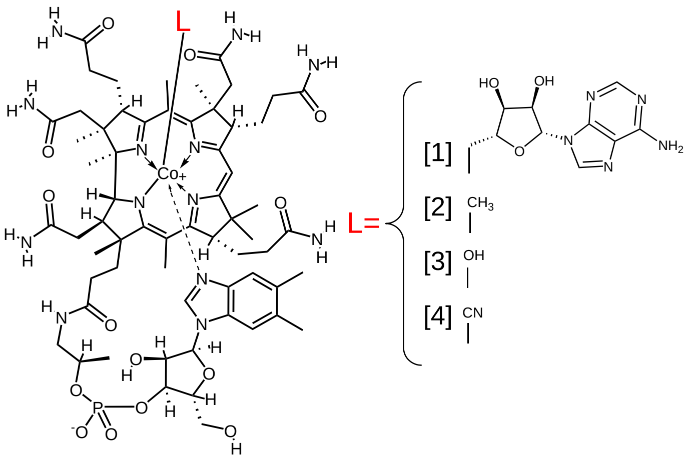


Fig. (1). Structural formula of vitamin B_{12} and partial structures of vitamin B_{12} related compounds. [1] 5′-Deoxyadenosylcobalamin; [2] Methylcobalamin; [3] Hydroxocobalamin; and [4] Cyanocobalamin (vitamin B_{12}).

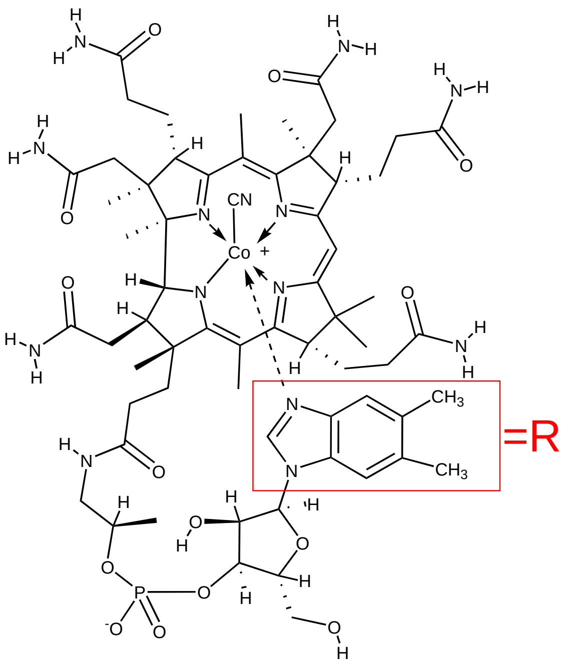
Vitamin B_{12} is only synthesized by certain bacteria [4] and concentrated in predators higher up in the natural food chain. Thus, food items derived from animals (fish, shellfish, and milk) are considered major dietary sources of vitamin B_{12} [5].

BIOSYNTHESIS OF VARIOUS CORRINOIDS CARRYING DIFFERENT BASE MOIETIES

The metabolic pathways of aerobic [6] and anaerobic [7] corrinoid biosynthesis have been elucidated. The lower ligand is attached to the cobalt-ordinated corrin ring *via* the nucleotide loop and 5,6-dimethylbenzimidazole (DMB) is usually found as a base. The aerobic and anaerobic pathways of DMB biosynthesis have been characterized [8]. DMB is synthesized from flavin mononucleotide (FMN) in various aerobic microorganisms [8]. In *Sinorhizobium melilote*, *bluB* gene is necessary for DMB biosynthesis and the gene product forms DMB from FMN in an O_2-dependent manner [9].

Anaerobic microorganisms synthesize DMB from the building blocks glycine, glutamine, formate, erythrose, and methionine [8]. Corrinoids carrying bases other than DMB are also found in anaerobic microorganisms [8]. These bases are divided into purines, phenols, and benzimidazoles. The pathway of anaerobic DMB biosynthesis was suggested to branch off the biosynthetic pathway of purines, similar to the pyrimidine ring of thiamin pyrophosphate [10]. 5-Aminoimidazole ribotide is an intermediate compound between the biosynthesis of purines, benzimidazoles, and thiamin. An anaerobic bacterium *Eubacterium limosum* expresses the *bzaABCDE* genes, which support the DMB production. The expression experiments of these genes revealed that the lower ligands of cobamides, namely 5-hydroxybenzimidazole, 5-methoxybenzimidazole, and 5-methoxy-6-methylbenzimidazole, are intermediates in the DMB biosynthesis pathway [11].

OCCURRENCE OF VARIOUS CORRINOIDS CARRYING DIFFERENT BASE MOIETIES IN FOOD AND BIOLOGICAL SAMPLES



CHAPTER 5

Bioactive Phenols in Small Fruits and Berries

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Abstract: Bioactive compounds are extra nutritional constituents occurring naturally in plant foods in small amounts, however in quantities enough to produce bioactive effects. Among bioactive compounds the phenolic compounds are a very large set of molecules, which include several groups such as for example flavonoids, phenolic acids or tannins. Small fruits and berries include a wide diversity of fruits, like grapes, strawberries, blackberries, blueberries, raspberries, cherries, hardy kiwi, gooseberries, cranberries, currants (black, white, red), physalis, crowberries, açaí, elderberries, dates or goji berries, and these have frequently been reported as having particularly high concentrations of phenolic compounds with antioxidant activity. Hence, the objective of this chapter is to review the literature about the type and content of different phenolic compounds present in small fruits and berries, as well as their bioactive properties, including antioxidant capacity. All the fruits and berries investigated in this chapter were particularly rich in bioactive compounds, including phenolic compounds that provide the fruits with high antioxidant properties. The most relevant health promoting effects include anti-cancer, anti-inflamatory, neuro protective, cardio protective or anti-diabetes, thus indicating that these foods are a valuable resource to prevent and treat diseases.

Keywords: Anthocyanins, Antioxidant activity, Flavonoids, Health, Phenolic acids, Phenolic compounds.

INTRODUCTION

Currently there is great interest in studying antioxidant compounds, since they are substances that in small quantities can prevent and treat diseases caused by free

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radicals [1]. Free radicals of oxygen or, more generally, reactive oxygen species (ROS) are products of the normal metabolism of the cells that are associated with processes such as power generation, phagocytosis, regulation of cell growth, intracellular signalling and synthesis of important biological substances. However, when in excess, they have harmful effects, such as peroxidation of membrane lipids and attack to tissues and membranes proteins, enzymes, carbohydrates and DNA [2 - 4].

The most common ROS include superoxide anion, hydrogen peroxide (H_2O_2), peroxyl (ROO—) radical and reactive hydroxyl (OH—) radicals [3]. These reactive species play an important role in pathogenesis of diverse diseases related to oxidative stress, such as carcinogenesis, cardiovascular diseases, rheumatoid arthritis, ulcerative colitis and neurological degenerative diseases. The reduction of the risk of developing chronic diseases and the prevention of disease progression is possible by either enhancing the body's natural antioxidant defenses or by supplementing with dietary antioxidants. Antioxidants offer resistance against oxidative stress by scavenging the free radicals, inhibiting the lipid peroxidation and by many other mechanisms and thus prevent disease progression [3, 5].

Among the various types of natural antioxidants, phenolic compounds are those who have received more attention. The phenolic compounds are very abundant in the plant kingdom and correspond to simple or more complex structures. Up to the present about 10000 phenolic structures have been identified, thus evidencing their number and variety. These compounds are represented in almost all classes of secondary metabolites, being of considerable importance in physiology and morphology of plants. They are essential in growth and reproduction, in addition to being responsible for defense mechanisms of the plant against external stress factors, such as infections, injuries, ultraviolet radiation, among others. Additionally, they contribute to pigmentation and sensory characteristics such as flavour and astringency of fruits and vegetables [6 - 11].

The phenolic compounds are the major class of antioxidants found in plants, and in particularly high concentrations in fruit and vegetables [12, 13]. They inhibit lipid oxidation and, because of their capacity to neutralise free radicals, they offer protection against oxidative stress-related diseases, fighting cellular aging [13 - 15]. Moreover, phenolic compounds have demonstrated an extensive variety of physiological properties such as anti-diabetic, anti-allergic, antifungal, anti-inflammatory, anticancer, antimicrobial, cardioprotective and vasodilator effects [6, 16 - 18]. There have also been reported protective effects on osteoporosis, degenerative diseases and central nervous system diseases [15, 19].

Structurally phenolic compounds comprise one or more aromatic rings with hydroxyl groups originating a wide variety of chemical structures, from simple molecules to highly polymerized compounds [9]. This complex group of molecules can be divided into non-flavonoids or flavonoid compounds [20, 21]. The group of flavonoid compounds comprises flavanols, flavonols, isoflavones, flavones, flavanas, flavanones, proanthocyanidins and anthocyanins [22, 20, 23]. In turn, the non-flavonoid compounds are part tocopherols, phenolic acids (benzoic acid, cinnamic acid and its derivatives), hydrolysable tannins, stilbenes, coumarins and lignans. Phenolic acids, flavonoids and tannins are regarded as important dietary phenolic compounds. In this diversity, polyphenols can be found associated with various carbohydrates and organic acids [21, 22].

Methods of Extraction and Analysis of Phenolic Compounds

The analysis of phenolic compounds is influenced by many factors, such as: the nature of the compounds, the extraction method, the sample size, storage time and conditions, the standard used and the presence of interfering agents such as waxes, fats, terpenes and chlorophylls [24]. The solubility of the phenolic compounds is variable deending on the the polarity of the solvent used, the degree of polymerization of the phenols and their interactions with other constituents of food. The most widely used solvents for extraction of these compounds are methanol, ethanol, acetone, water, ethyl acetate, propanol, dimethylformaldehyde and diverse combinations of these solvents in variable proportions [25].

Various methods for spectrophotometric quantification of phenolic compounds in foods have been developed. These methods are based on different principles and are used to quantify total phenols, specific classes of phenolic compounds (*e.g.*, anthocyanins, ortho-diphenols, tannins) or a specific phenolic compound. Alternatively, identification of single compounds is also achieved by specific methods, like chromatographic techniques [26 - 30].

CHAPTER 6

Sambucus nigra L.: A Potential Source of Health-promoting Components

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Abstract: European elder plant, *Sambucus nigra* L., has been used since ancient times in folk medicine, and more recently in nutraceutical formulations, being considered the medicine "chest" from the days of Hippocratic medicine. This chapter aims at giving a general perspective of *S. nigra* L. berries and flowers potential as sources of health-promoting compounds, covering first aspects ranging from its taxonomic classification and geographic distribution, current applications from food products to traditional medicine. Then, a detailed overview of berries and flowers chemical composition, specially focused on sterols, terpenic and phenolic components, and important factors that have impact on their biosynthesis and preservation are presented. Finally, the main findings regarding the potential health benefits of *S. nigra*-based preparations, namely antimicrobial, anti-viral, antioxidant, anti-inflammatory, anti-cancer, and antidiabetic are also described, and special focus is devoted to diabetes mellitus and related complications, as it is a disease of a major threat to human health due to its alarming incidence growth.

Keywords: Chemical composition, Diabetes mellitus, Elderberries, Elderflowers, Health benefits, *Sambucus nigra* L.

INTRODUCTION

Sambucus nigra L. is a plant whose berries and flowers are widely used on diverse formulations that range from food products to formulations that are applied on folk medicine, and more recently on supplements and nutraceuticals.

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The current market trends on agro-industries follow the consumers' desire for added value products, convenience, and foods which assist in disease prevention and healthy ageing, in response to the social and lifestyle changes [1, 2]. These trends, allied with the fact that people can optimize the health-promoting capabilities of their diet though the consumption of foods that have been formulated or fortified to include health-promoting factors or by supplementation [1], reinforce the interest on studying plants that might contribute to the health status of an individual. Despite the interest of several macro and micronutrients, in the last decades, *Sambucus nigra* flowers and berries secondary metabolites composition received increased attention due to presence of phytochemicals, with many health benefits that include monoterpenic, sesquiterpenic and triterpenic compounds, sterols and phenolic compounds. Considering that a wide range of biological properties have been reported for these secondary metabolites, in other matrices or using standards, this chapter unveils the high interest in systematizing the information available related to *S. nigra* secondary metabolites composition, both in terms of their potential health benefits but also of their role in the plant metabolism and protection.

Among secondary metabolites the key families worth of consideration in the present context are mono and sesquiterpenes, sterols, triterpenes and phenolic compounds. Mono and sesquiterpenes play an important role in plant defense mechanisms being often reported as toxic to some microorganisms and are also involved in plant-insect interactions, such as pheromones, attractants and as feeding deterrents [3]. These compounds are also involved in the plant protection against oxidative stress, namely as thermo-tolerance mediators [4]. Beyond their protection and communication roles in plants, and their pleasant aroma properties, diverse potential health benefits are documented, namely their hepatoprotection [5], anti-inflammatory [6], analgesic [7] and antioxidant [8] properties. Sterols contribute to the regulation of the fluidity and permeability of cell membranes in plant cells. They are also substrates for the synthesis of numerous secondary plant metabolites and act as biogenic precursors of other compounds involved in plant growth [9]. Plant sterols are well known, since 1953, for their role in lowering the absorption of the low-density lipoprotein-cholesterol (LDL-cholesterol) in humans, which led to the development of several food supplements and nutraceuticals [10]. Triterpenic compounds have been described as plant defense agents against pathogens and herbivores [11, 12], and exhibit anti-inflammatory, antimicrobial [13] and hepatoprotective potential [14], among others [15]. Finally, plant phenolic compounds have interested scientists for decades, as, on the one hand they are essential to plant physiology, contributing *e.g.* to plant pigmentation, and they are also involved in growth, reproduction and provide plants resistance for pathogens and predators [16]. On the other hand, phenolic compounds exhibit a wide range of health benefits [17], such as anti-allergenic, anti-artherogenic, anti-inflammatory, antimicrobial, antioxidant, antithrombotic and cardioprotective effects. Within phenolic compounds, phenolic acids act as signaling molecules in plant-microbe symbioses, and are involved in the plant defense mechanisms when exposed to biotic and abiotic stress [18]. Regarding to their effects in human health, phenolic acids are often linked to potential antioxidant and anti-cancer activities [19]. On the other hand, flavonoids are involved on electron and proton transport, ion exchange and membrane potential, radicals formation; as regulators (inhibitors or activators in enzyme reactions) [20]; protection of the plant against the harmful effects of oxidative processes [19]; plant-microorganism communication; and attractants [19]. The potential health benefits of flavonoids are vast, although the interest is mainly associated with their antioxidant and anti-carcinogenic activities [19]. These compounds may also play important roles in the control of other human diseases, such as, among other, diabetes and cardiovascular diseases [19], being their activity deeply dependent of their structural features [21].

This chapter aims at giving a general perspective of *S. nigra* L. berries and flowers potential as sources of health-promoting compounds. This will cover aspects that range from its taxonomic classification and geographic distribution, current applications, a detailed overview of berries and flowers chemical composition, mainly focused on sterols, terpenic and phenolic components, and important factors that have impact on their biosynthesis and preservation. Finally, the main findings regarding their potential health benefits with special focus on diabetes mellitus and related complications.

Sambucus nigra L. Taxonomic Classification and Geographic Distribution

Elderberries belong to genus *Sambucus* being often included with the Caprifoliaceae family, but more recently, studies associate this plant to the Adoxaceae family [22, 23]. Since no definitive taxonomic DNA-based studies have been conducted, and because species of this genus are difficult to delimit

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CHAPTER 7

Flavonoid Variations in Pathogen-Infected Plants

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Abstract: Flavonoids are polyphenolic secondary metabolites with various *in vivo* and *in vitro* structure-related benefits that are ubiquitously found in plants. In addition to their role in many physiological activities, flavonoids play major roles as phytoalexins and phytoanticipins in protecting plants from potent pathogens. Since the first discovery of such defense roles, their routes of biosynthesis induced upon pathogen infection and mechanisms of action have attracted the attention of researchers in various fields. The ultimate goal of the study of plant-pathogen interactions is to develop biotechnological applications that enhance crop production in an environmentally friendly manner, with the outcome of engineering highly pathogen-

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resistant genotypes. Steady progress has been made previously in this regard. Inoculation of potential pathogens in plant tissues, followed by the systematic analysis of various targeted biochemical changes, including investigations into flavonoid variations, has become an appealing methodological approach. In this chapter, the role of flavonoids as defense mechanisms in plant-pathogen interactions is discussed with respect to the latest findings. In addition, we emphasize research trends observed in this regard. In light of the most recent studies, including those conducted by some of the authors of this chapter, key findings in flavonoid variations upon pathogen infection are highlighted comprehensively, focusing on fungal inoculation and liquid chromatography-tandem mass spectrometry analysis for reasons described in later sections.

Keywords: Defense, Flavonoid, Flavonoid variation, Liquid chromatography, Pathogen, Phytoalexin, Phytoanticipins, Tandem mass spectrometry.

INTRODUCTION

Flavonoids comprise a diverse class of polyphenolic compounds in plants. They have a wide range of biological activities that make them beneficial to human health. For example, high consumption of flavonoid-rich fruits and vegetables is associated with a lower risk of cardiovascular disease, diabetes, and cancer; the most deadly diseases of modern times. Recent systematic reviews and meta-analysis studies have been reported in this regard [1 - 6]. In addition, many studies have supported the *in vivo* and *in vitro* anti-inflammatory [7 - 9], antiviral [10, 11], antimicrobial [12, 13], and antidepressant [12, 14] properties of flavonoids. These diverse biological activities of flavonoids are highly correlated with their structures [15 - 17] and a number of research studies have focussed on their detection and structural elucidations using chromatographic techniques, and separation and hyphenated spectroscopic techniques [18 - 23]. Such investigations form part of the major efforts being made for wild edible plants to serve as functional foods. In addition, these investigations have contributed and will continue to contribute to the advancement of flavonoid applications in agriculture, the cosmetic industry, and drug discovery [24, 25]. For example, flavopiridol (L86-8275, HMR1275), a flavonoid-derived drug, is undergoing clinical trials for approval for its use in cancer therapy. Studies that show the positive implications of flavonoid applications in insect and pest management are also being conducted [26 - 28].

The differences in the structure and state of oxidation have formed the basis of flavonoids classification into flavanones, flavones, flavonols, flavanols, isoflavones, anthocyanins, and biflavonoids. Some of these classes also have subdivisions. For example isoflavanes, pterocarpans, coumestans and isoflavanones are the most common isoflavonoids [29]. Except for biflavonoids, the skeleton structure of flavonoids contains two aromatic rings designated as A- and B-rings that are bridged by another C-ring. The three carbon containing C-ring consists of an oxygen atom and two carbons from the A ring [30] (Fig. **1**). The degree of saturation and availability of substituents on this ring plays a major role in the structural classification of flavonoids. Biflavonoids, as the name implies, are flavonoid dimers comprising various combinations, in which the two components are connected either through a C-C or C-O-C bond [31]. Despite their role as key intermediates in flavonoid biosynthesis, it is unclear whether of chalcones (with an open C-ring) should be labelled as flavonoids or a distinct class of polyphenols [30, 32].

Generally, the diverse structural variation in flavonoids contributes to their role in defense, pigmentation, cell growth, scent, pollen fertility, transport, taste, and allelopathy of plants [33, 34]. Over the past few years, the role of flavonoids as defense molecules against pathogens has attracted the attention of researchers. Flavonoids are also involved in plant protection from abiotic stresses, such as unfavourable UV-light, drought, temperature, and soil-related trauma [35, 36].

A number of organisms that interact with plants in various ways can create a hostile environment. Hence, both the mechanisms of action and the type of chemicals involved in the defense of plant species also vary. Such variation can be observed at the various stages of colonization by pathogens [37]. In pre-invasion defense that involves the response upon first contact with pathogens, physical actions usually dominate, which guard the epidermal wall and stomata. When a potential invader by-passes the pre-defense barriers, plants undergo transcriptional and metabolic reprogramming that induces the synthesis and/or release of late post-invasive defense molecules [37, 38]. Flavonoids are among such post-invasive defense molecules, the synthesis of which is associated with the

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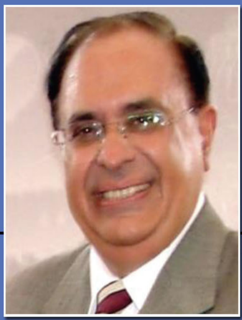

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