Journal of Pharmacy and Pharmacology 2 (2014) 377-392

Plant Secondary Metabolites: Biosynthesis, Classification, Function and Pharmacological Properties

Justin N. Kabera[1], Edmond Semana[1], Ally R. Mussa[1] and Xin He[1, 2]

1. Department of Pharmacology, School of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China

2. Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin 300193, China

Abstract: Secondary metabolites, also known as phytochemicals, natural products or plant constituents are responsible for medicinal properties of plants to which they belong. The role they play in the plant is not, to date, well known or understood, but it may be beyond the protection. Their classification is based on chemical structure, composition, their solubility in various solvents, or the pathway by which they are synthesized. The main classification system includes three major groups: terpenoids, alkaloids and phenolics. For each one, we find subclasses with complexity in structure. In this review, we deal with the description of second metabolites, their biosynthesis, function, and the current pharmacological findings. Natural products are an important source of drug candidates in pharmaceutical industry, more deeply we understand them, the easier it is for scientists to intervene in alleviating different kind of diseases. The recent references have been consulted for presenting updated information, but also showing the new potentialities of plant second metabolites in drug research and development.

Key words: Secondary metabolites, biosynthesis, terpenoids, alkaloids, phenolics, pharmacological activities.

1. Introduction

Humans have used medicinal plants throughout their history life, and long time before, good records were kept about herbs use [1]. Texts from ancient China and India provide a good example of very early use of medicinal herbs. They contain prescriptions of countless plant-derived medicines [2, 3]. In modern times, natural products from plants have been isolated for drug discovery and development. During the last 20 to 30 years, the analysis of secondary plant products has progressed a lot [4]. The use of modern analytical techniques like chromatography, electrophoresis, isotope techniques and enzymology have succeeded in the elucidation of exact structural formulas and the most important biosynthetic pathways [5, 6].

The secondary metabolites from plants, which are distinguished from primary metabolites such as nucleic acids, amino acids, carbohydrate, fat, etc. [7] are extremely diverse; thousands of them have been identified in several classes. Each plant family, genus, and species produce a characteristic mix of these chemicals, and they can sometimes be used as taxonomic characters in classifying plants [8].

Many scientific sources state that their role is not crucial for living cells in normal growth, development, and reproduction [9], but they act in defense purposes to protect a plant from any possible harm in the ecological environment [10] and other interspecies protection [11]. Therefore, they are usually synthesized in plants for particular needs, while the primary metabolites have generally the shared biological purposes across all species. Secondary metabolites may often be created by modified synthetic pathways from primary metabolite, or share substrates of primary metabolite origin. Plants have been evolving to adapt the environment with genetic encoding of useful and diverse synthases for secondary metabolites [12]. In human life, these compounds are used as medicines, flavorings, or relaxing drugs, especially essential oils.

Corresponding author: Xin He, Ph.D., professor, research field: pharmacology (pharmacokinetic and pharmacodynamic). E-mail: hexintn@163.com.

In most references, it is stated that the secondary metabolites extracted from plants are subdivided in three major classes: terpenoids, alkaloids and phenolics. They contain numerous natural products with interesting pharmacology activities [13, 14].

In this review, we highlight the secondary metabolites classified in three main groups mentioned above, showing pharmacological activities leading to drug discovery and development. Plant constituent should be regarded as a complex mixture of several unwanted chemicals, refined of the objective of identifying and isolating an active principle. In order to study the activity of a given medicinal plant, it is often necessary to purify it or to isolate a specific compound [15]. However, some drug resistance cases observed in infectious diseases or cancer, the approach of synergy therapy is applied to overcome the challenge and improve the treatment [16].

2. Biosynthesis

The pathways of biosynthesis are responsible for the occurrence of both primary and secondary metabolites [17, 18]. Biosynthetic reactions are energy consuming, fuelled by the energy released by glycolysis of carbohydrates and through the citric acid cycle. Oxidation of glucose, fatty acids and amino acids results in ATP (adenosene triphosaphate) formation, which is a high-energy molecule formed by catabolism of primary compounds. ATP is recycled in fuel anabolic reactions involving intermediate molecules on the pathways. Whereas, catabolism involves oxidation of starting molecules, biosynthesis or anabolism involves reduction reaction. Hence, the need of reducing agent or hydrogen donor, which is usually the NADP (nicotinamide adenine dunucleotide phosphate). These catalysts are known as coenzymes and the most widely occurring is CoA (coenzyme A) made up of ADP (adenosine diphosphate) and pantetheine phosphate [19].

The most common pathways taken for biosynthesis are performed through the pentose for glycosides, polysaccharides; shikimic acid for phenols, tannins, aromatic alkaloids; acetate-malonate for phenols and alkaloids and mevalonic acid for terpenes, steroids and alkaloids [20]. As showed in the Fig. 1, the scheme outlines how metabolites from the process of photosynthesis, glycolysis and Krebs cycle are tapped off from energy-generating process to provide biosynthetic intermediates. By far, the important building blocks employed in the biosynthesis of secondary metabolites are derived from acetyl-CoA (acetyl coenzyme A), shikimic acid, mevalonic acid and 1-deoxylulose 5-phosphate [21].

3. Structure and Classification

As said previously, the classification of secondary metabolites consists of terpenoids, alkaloids and phenolics [13]. Glycosides, tannins and saponins are part of them according their specific structure.

3.1 Terpenoids

Terpenoids constitute a large family of phytoconstituents of little functional and structural common ground. Steroids, carotenoids, and gibberelic acid are just some of its members. They are composed by the most important group of active compounds in plants with over than 23,000 known structures. They are polymeric isoprene derivatives and synthesized from acetate via the mevalonic acid pathway. During their formation, the isoprene units are linked in head and tail fashion. The number of units incorporated into a particular terpene serves as a basis for their classification. Many of them have pharmacological activity and are used for diseases treatment both in humans and animals. According to Tada et al. cited by Ref. [22], diterpenes tend to be most abundant in Lamiaceae family and have antimicrobial and antiviral properties.

Some interesting compounds are extensively used in the industry sector as flavors, fragrance, spices [23, 24]. Several thousand different types of molecules from very different plant groups have been isolated and

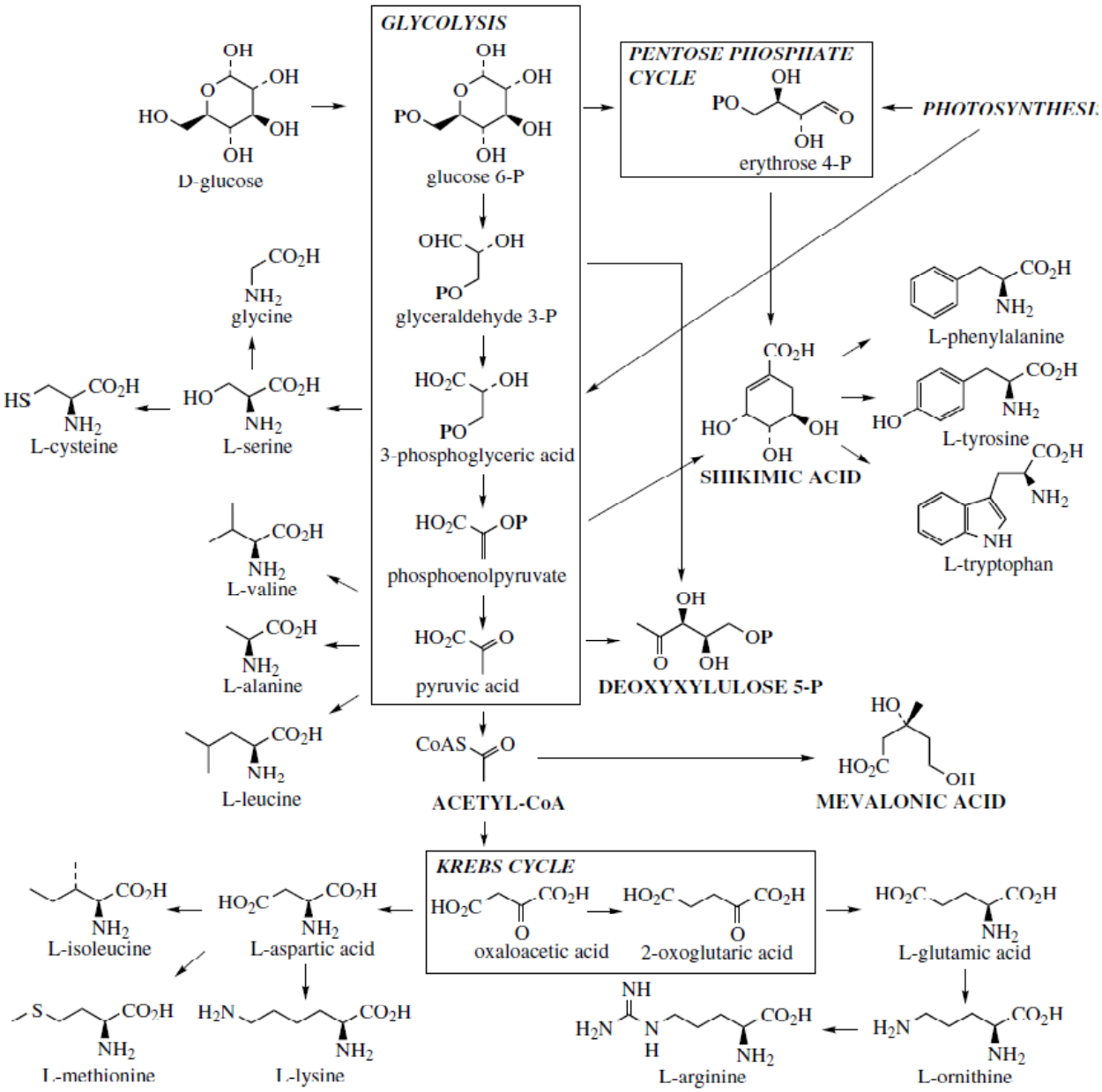

Fig. 1 Biosynthesis scheme of plants secondary metabolites [21].

characterized. Despite their varied structures, all of them are synthesized by only a few pathways as shown below in Fig. 2.

3.1.1 Functions

Plants tissues are related to adaptation to both abiotic and biotic stressors such herbivores and pathogens. However, the high volatility and reactivity of some terponoids may also affect the atmosphere composition [25]. Volatility of terpenoids provides, for sessile plants, a tool for communication with other organisms such as neighboring plants, pollinators and foes of herbivores, via air-bone infochemicals. From a physiological standpoint, briefly, plant volatiles are involved in three critical processes, namely plant—plant interaction, the signaling between symbiotic organisms, and the attraction of pollinating insects. Their role in these "housekeeping" activities underlies agricultural applications that range from the search for sustainable methods for pest control to the production of flavors and fragrances [26].

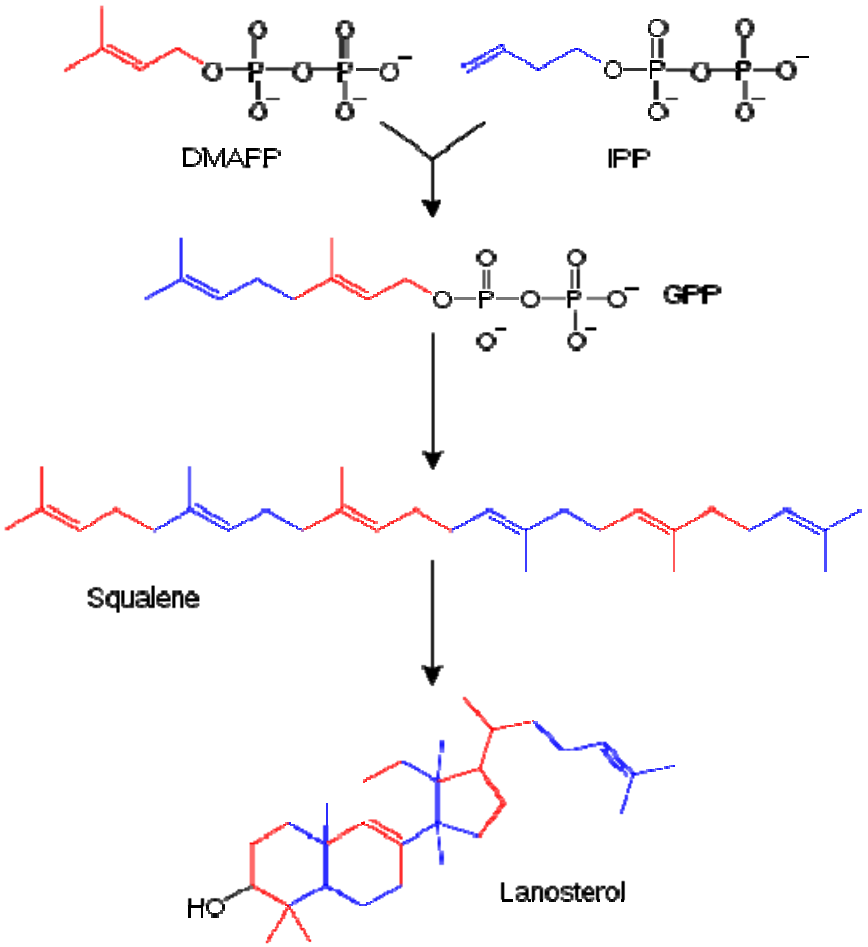

Fig. 2 Example of sterol synthesis (source: weekpedia, February 13, 2014).

3.1.2 Pharmacological Activities

Extensive biological investigations have been carried out within the group and these studies have revealed a broad spectrum of pharmacological and physiological properties. Some of them have led to a number of terpenoids gaining medicinal applications [26]. The recent findings demonstrate that certain nitrogenous terpene derivatives possess the potent anti-hypertensive activity and may indicate a new era in medicine through the synthetic terpenoids path. The antimicrobial and insecticidal properties of other terpenoids have led to their utilization as pesticides and fungicides in agriculture and horticulture [27, 28].

3.2 Essential oils

Essential oils are natural aromatic and volatile compounds found in the parts of plants. Interest in essential oils has revived in recent decades with the popularity of aromatherapy, a branch of alternative medicine that claims that essential oils and other aromatic compounds have curative effects. According several findings of research, they are reputed to have various pharmacological effects such as antibacterial, antifungal and antiviral [29].

They are known to be characterized by both beautifully and powerfully fragrant. Thus, they provide protection to the plants against predators and disease and play a role in plant pollination [30]. Although they are fat soluble, they do not include fatty lipids or acids found in vegetables and animal oils. Single or combined extract stimulate the olfactory nerve, sending messages to the brain's limbic system (the seat of memory, learning, and emotion) that are said to trigger physiological responses (e.g., *eucalyptus*

relieves congestion, lavender promotes relaxation, and *menthe piperita* promote exercise performance) [31, 32]. The use of oils and their solutions have been shown to have certain effects but are not standardized. The few risks involved include allergic reactions [33, 34].

3.3 Alkaloids

The alkaloids present the group of secondary metabolites that contain basic nitrogen atoms. Some related compounds with neutral and weakly acid properties are also included in the alkaloids. In addition to carbone, hydrogen and nitrogen, this group may also contain oxygen, sulfur and rarely other element such as chlorine, bromine and phosphorus [18]. Alkaloids are produced by a large variety of organisms, such as bacteria, fungi, animals but mostly by plants as secondary metabolites. Most of them are toxic to other organisms and can be extracted by acid-base. They have diverse pharmacological effects [48], and have a long history in medication [49].

The boundary between alkaloids and other nitrogen-containing natural compounds is not clear-cut [21]. Compounds like amino acids, proteins, peptides, nucleotides, nucleic acid, and amines are not usually called alkaloids.

Compared with most other classes of secondary metabolites, alkaloids are characterized by a great structural diversity and there is no uniform classification of them [13]. First classification was based on the common source because no information about chemical structure was yet available. Recent classification is based on similarity of the carbon skeleton [14]. Alkaloids are biosynthesized from amino acids such as tyrosine [50]. The typical example is the biosynthesis of morphine that includes a phenol coupling reaction involving a benzylisoquinoline alkaloid.

Table 1 Important molecules of terpenoids [35].

Number of carbone	Name	Example
C_5	Hemiterpene	Isoprene, prenol, isovaleric acid
C_{10}	Monoterpene	Limonene, eucalyptol, pinene
C_{15}	Sesquiterpene	ABA (abscisic acid)
C_{20}	Diterpene	Gibberellin
C_{25}	Sesterterpenes	
C_{30}	Triterpene	Brassinosteroids, squalen, lanosterol
C_{40}	Tetraterpene	Carotenoids, lycopen
$C_{>40}$	Polyterpenes	Ubuquinones, rubber, cytokonines, vitamine E

Table 2 Summary of some terpenoids properties.

Name of terpenoid	Location	Pharmacological activity	References
Isoprenol	Synthesis	Act as alcohol	[36]
Isovaleric acid	Essential oils	Anticonvulsant agent in valeria, used largely in perfumery	[37, 38]
Limonene	Essential oils	Fragrant, botanical insecticide, anti carcinogenic, anti bacterial	[39, 40]
Linalool	Essential oils	Antibacterial, exert effect on CNS (centre nervous system)	[41, 42]
ABA		Anti transpirant	[43]
Phytoalexins	Synthesized plants at areas of pathogen infection	Anti oxidative effects, antimicrobial, anti tumor and neurotrophic effects	
Gibberlin	*Gibberella fujikuroi*	Promoting growth and elongation of plant cells	[44, 45]
Brassinosteroids	*Lychnis viscaria*, *Brassica napus*	Involved in plant protection	[46, 47]
sterols	Natural in plants, animals and fungi	Nutritional supplements and medicinal	
Carotenoids	Carrots, chloroplasts and chromoplasts of plants	Antioxidants, sunlight protection, immune function	

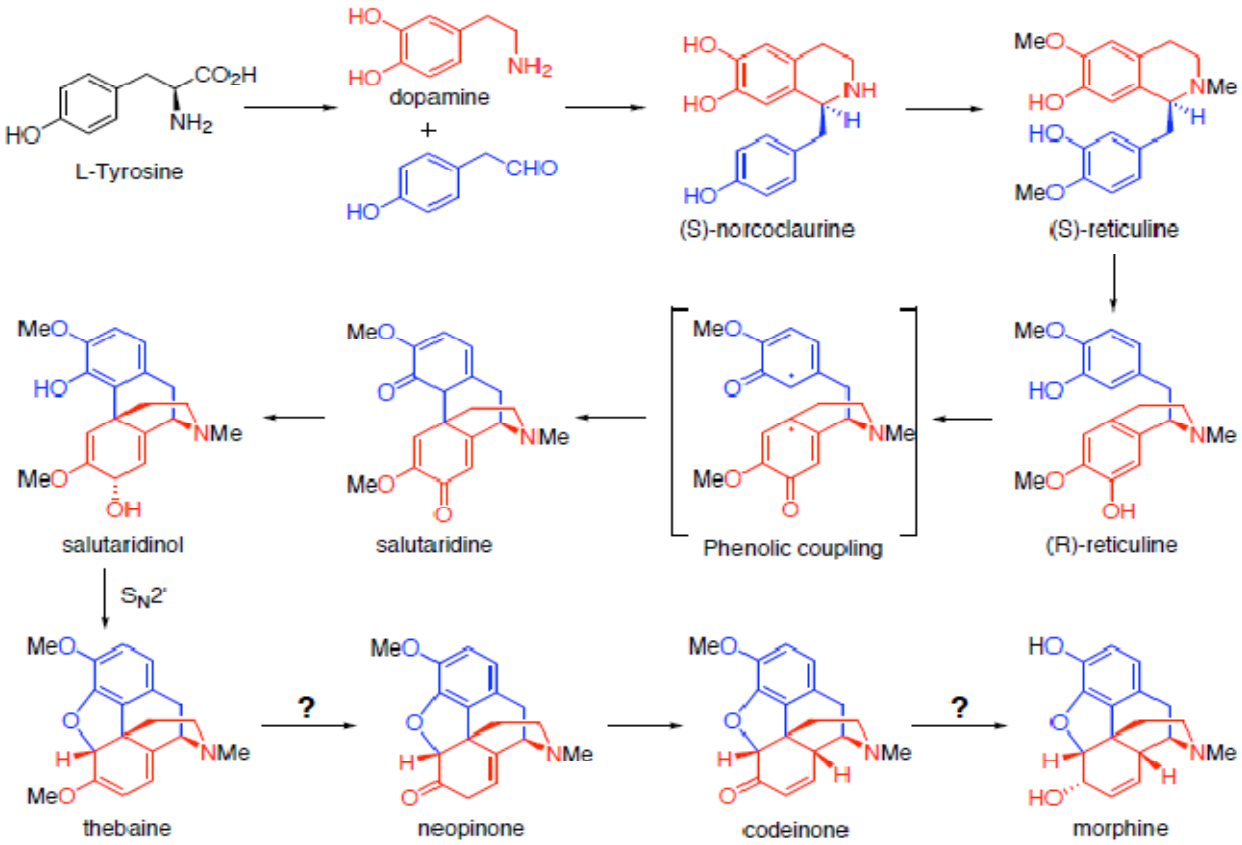

Fig. 3 The Biosynthesis of morphine [51, 52].

Table 3 Pharmacological effects of some well known alkaloids.

Alkaloid name	Source	Pharmacological activity	References
Atropine	*Atropa belladonna, Darura stramonium, Mandragora officinarum*	Competitive antagonist of muscarinic acetylcholine receptors, anti cholinergic, anti myopia effects	[53, 54]
Berberine	*Berberis* species, *Hydrastis, Canadensis, Xanthorhiza simplicissima*, *Phellodendron amurense*, *Coptis chinensis*, *Tinospora cordifolia*, *Argemone mexicana* and *Eschscholzia californica*	Anti inflammatory, anti bacterial/viral, recently experiments showed anti diabetic and beneficial effects on cardiovascular system and anti cancer and others disorders such as intestinal	[55-58]
Codeine	*Papaver somniferum*	Analgesic, antitussive, anti diarrheal, antidepressant, sedative and hypnotic properties	[59-62]
Coniine	*Conium macularum, Sarracenia flave*	Neurotoxin, poisonous	[63, 64]
Cytisine (baptitoxine, sophorine)	*Labum* and *cytisus* of Fabaceae family, most extracted from seeds of *Cytisus laborinum*	Acetylcholine agonist, smoking cessation drug	[65, 66]
Morphine	*Papaver somniferum* and poppy derivatives	Act on CNS (central nervous system), on myenteric plexus, acute pulmonary edema and reduce the shortness of breath	[67-69]
Nicotine	Solanaceae plants family	Stimulant, antiherbivore, insectide, anti inflammatory	[70-73]
Quinine	*Cinchona succirubra, C. calisya, c. ledgeriana*, plants of Rubiaceae family.	Antimalarial, antpyretic, analgesic, anti-inflammatory, antiarrhythmic, bacteriostatic	[74-77]
Solanine	*Solanum tuberosum, s. lycopersiam, s. igrum*, plants of Solanaceae family	Antifungal, antipesticide, sedative, anticonvulsant, anticarcinogenic, anti inflammatory	[78-81]
Strychnine	*Strychnos nux-vomica*, loganiaceae plants family	Persticide, strong poisonous, Convulsant	[82-85]
Thebaine (paramorphine)	*Papaver bracteatum*	Analgesic, not therapeutically used.	[86-89]
Tomatine	Green parts of tomato plants	Immune effects, anticancer, antifungal, poisonous	[90-92]

3.4 Phenolics

Phenolic compounds from plants are one of largest group of secondary plants constituents synthesized by fruits, vegetables, teas, cocoa and other plants that possess certain health benefits. They are characterized by the antioxidant, anti-inflammatory, anti-carcinogenic and other biological properties, and may protect from oxidative stress and some diseases [93]. Simple phenolics are bactericidal, antiseptic and anthlemintic. Phenol itself is a standard for other antimicrobial agents [94]. They are distributed in almost all plants and subject to a great number of chemical, biological, agricultural, and medical studies [95, 96].

They are diverse in structure, and present in common the hydroxylated aromatic rings (e.g., flavan-3-ols). Most of phenolic compounds are polymerized into larger molecules such as the PA (proanthocyanidins; condensed tannins) and lignans. Furthermore, phenolic acids may occur in food plants as esters or glycosides conjugated with other natural compounds such as flavonoids, alcohols, hydroxyfatty acids, sterols, and glucosides [95]. Hydroxybenzoic and hydroxycinnamic acids present two main phenolic compounds found in plants. In tea, coffee, berries and fruits, the total phenolic comounds could reach up to 103 mg/100 g fresh weigh [97].

3.3.1 Classification and Structure

The approach to classifying plant phenolics are based on: (1) a number of hydroxylic groups. So, they may be divided on 1-, 2- and polyatomic phenols. Phenolic compounds containing more than one OH-group in aromatic ring are polyphenols; (2) chemical composition: mono-, di, oligo- and polyphenols; (3) substitutes in carbon skeleton, a number of aromatic rings and carbon atoms in the side chain. According to the latter principle, phenolic compounds are divided into four main groups: phenolics with one aromatic ring, with two aromatic rings, quinones and polymers.

Phenolic compounds with one aromatic ring: a large number of compounds, among them are simple phenols (C_6), phenol with attached one (C_6-C_1), two (C_6-C_2) and three (C_6-C_3) carbon atoms.

Phenolic compounds with two aromatic rings: this group includes benzoquinones and xanthones (C_6-C_1-C_6) containing two aromatic rings which are linked by one carbon atom; stylbenes (C_6-C_2-C_6) which are linked by two carbon atoms; and flavonoids, containing three carbon atoms (C_6-C_3-C_6). Flavonoids, depending on the structure of propane unit and an attaching place of side chain B, are divided into flavonoids in strict sense, which are derived from chromane or chromone, isoflavonoids and neoflavonoids.

Polyphenolics are more than 8,000 different compounds identified to date. That is why the terminology and classification of polyphenols is complex and confusing. Although all polyphenols have similar chemical structures, there are some distinctive differences. Based on these differences, polyphenols can be subdivided into two classes: flavoinoids and non flavonoids, like tannins [98].

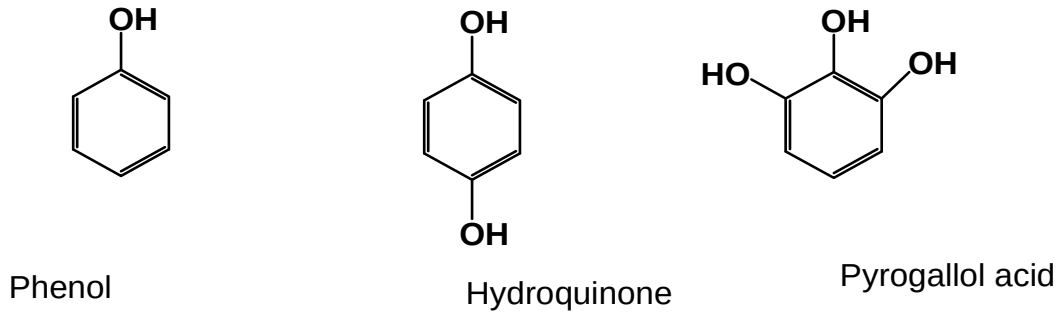

Fig. 4 Examples of simple phenolics, C_6 (phenol, hydroquinone and pyrogallol acid).

Fig. 5 Examples of C_6-C_1 phenolics: gallic acid and salicylic acid.

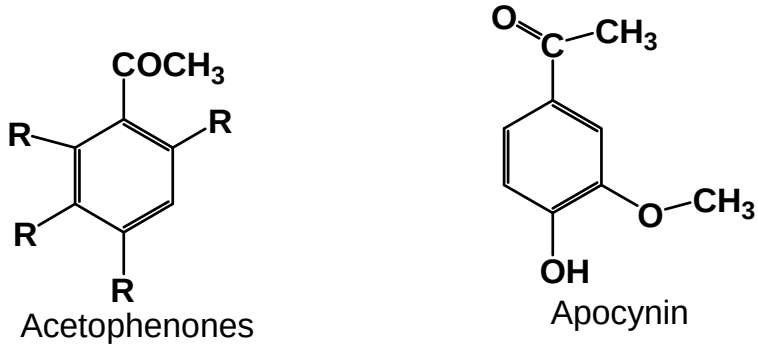

Fig. 6 Examples of C_6-C_2: acetophenones, apocynin.

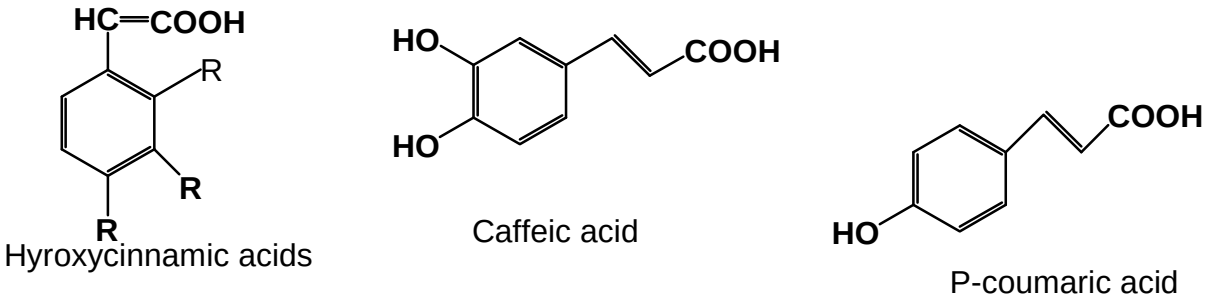

Fig. 7 Phenolics with C_6-C_3 (phenylpropanoids): hydroxycinnamic acid, ferulic acid and sinapic acid.

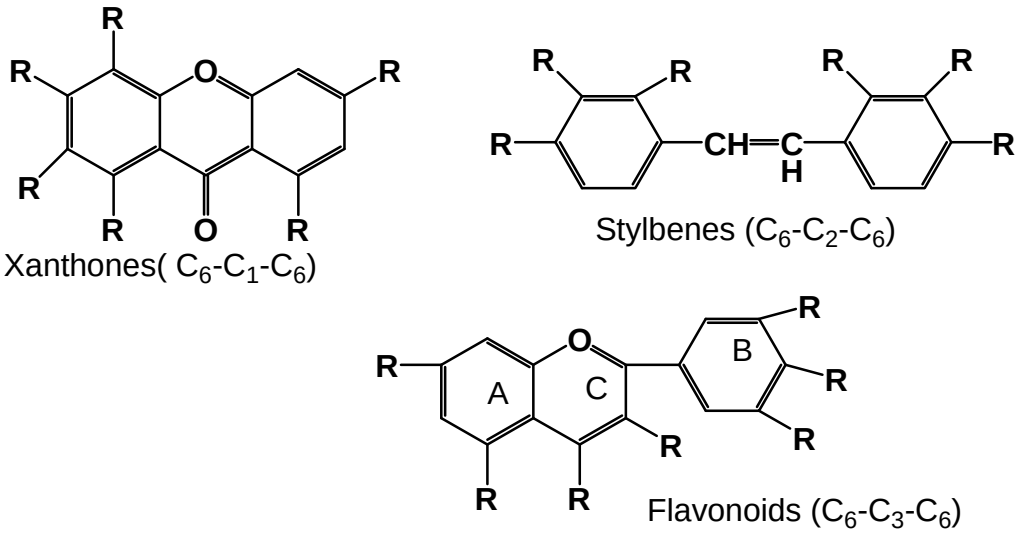

Fig. 8 Some phenolics with two aromatic rings (xanthones: C_6-C_1-C_6; stylbenes: C_6-C_2-C_6 and flavonoids: C_6-C_3-C_6).

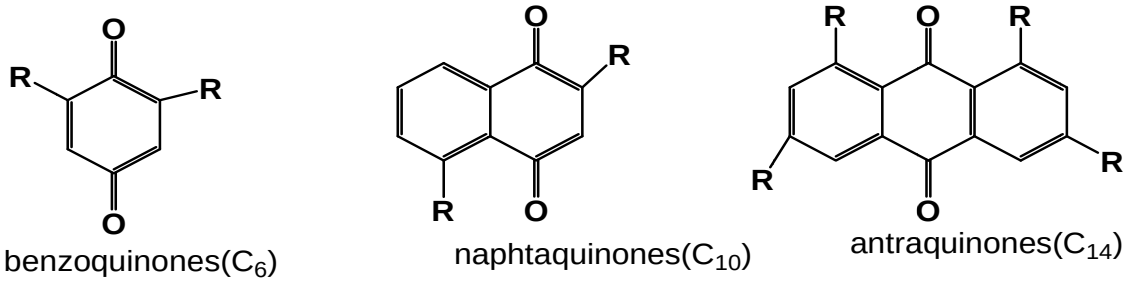

Fig. 9 Main groups of quinines: benzoquinones, naphtoquinones, and anthraquinones polyphenolics (flavonoids, tanins, glycosides, saponins).

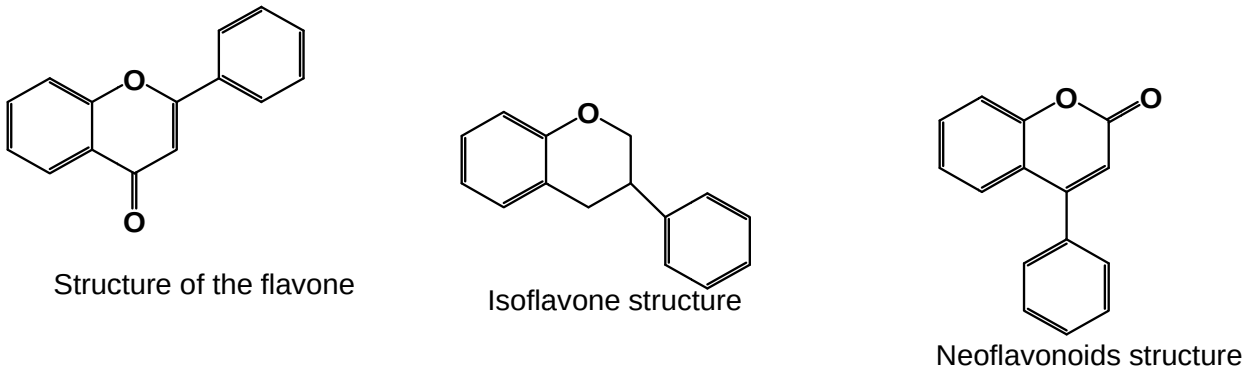

Fig. 10 Basic structures of flavonoids.

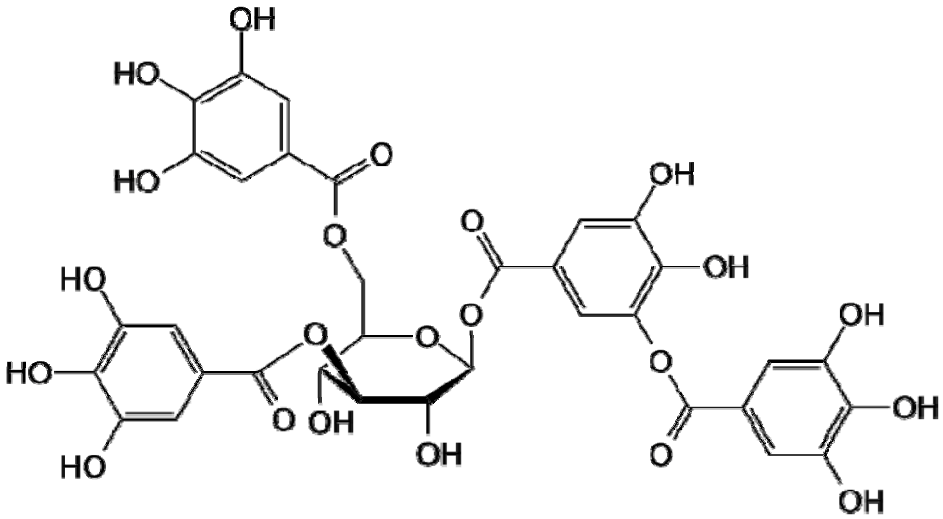

Fig. 11 Tannic acid, type of tannins.

3.4 Flavonoids

Flavonoids stand as the first class of polyphenols. They are water-soluble pigments found in the vacuoles of plant cells. They can also be divided into three groups: anthocyanins, flavones and flavonols. They are widely distributed in plants, fulfilling many functions such as flower coloration, producing yellow, red or blue pigmentation in petals designed to attract pollinator animals. In higher plants, flavonoids are involved in UV (ultraviolet) filtration, symbiotic nitrogen fixation and floral pigmentation. They may also act as chemical messengers, physiological regulators, and cell cycle inhibitors. Flavonoids are secreted by the root of their host plant *Rhizobia* help in the infection stage of their symbiotic relationship with

legumes like peas, beans, clover, and soy [99]. *Rhizobia* living in soil are able to sense the flavonoids and this triggers the secretion of nod factors, which in turn are recognized by the host plant and can lead to root hair deformation and several cellular responses such as ion fluxes and the formation of a root nodule. Some flavonoids have inhibitory activity against organisms that cause plant disease, for example, *Fusarium oxysporum* [100].

They have become very popular because their health benefits. Some of the activities attributed to them include: anti-allergic, anti-cancer, antioxidant, anti-inflammatory and anti-viral [101, 102]. The flavonoids quercetin is known for its ability to relieve high fever, eczema, asthma and sinusitis. Epidemiological studies have illustrated that heart diseases are inversely related to flavonoid intake. Studies have shown that flavonoids prevent the oxidation of low-density lipoprotein thereby reducing the risk for the development of atherosclerosis [103, 104]. The contribution of flavonoids to the total antioxidant activity of components in food can be very high; for instance red wine contains high levels of flavonoids, mainly quercetin and rutin. The high intake of it by the French might explain why they suffer less from coronary heart disease than other Europeans, although their consumption of cholesterol rich foods is higher (French paradox) [105]. Many studies have confirmed that one or two glasses of red wine daily can protect against heart disease [106]. Their antioxidant activities in chemical and biological assays are undisputed, and many are associated with the health-promoting effects of fruits and vegetables. However, extending these effects to entire organisms, and clinical outcomes in human disease in particular, remains a controversially discussed topic in nutrition science and disease prevention [107]. Recently, it has been mentioned that growing consensus for the hypothesis that the specific intake of food and drink containing relatively high concentrations of flavonoids may play a meaningful role in reducing the risk of CVD (cardiovascular disease). The reviewers stated that research to date has been of poor quality. The large and rigorous trials are needed to better investigate the possible adverse effects associated with excessive polyphenol intake. Currently, a lack of knowledge about safety suggests that polyphenol levels should not exceed that which occurs in a normal diet [108].

3.5 Tannins

Tannin is the name derived from French "Tanin" (tanning substance) and used for a range of natural polyphenols. The tannins are the phenolic compounds that precipitate proteins. They are composed by a very diverse group of oligomers and polymers. They can form the complex with proteins, starch, cellulose and minerals. They are synthesized via shikimic acid pathway, also known as the phenylpropanoid pathway. The same pathway leads to the formation of other phenolics such as isoflavones, coumarins, lignins and aromatic aminoacids. Tannins are water soluble compounds with exception of some high molecular weight structures. They are usually subdivided in two groups: HT (hydrolysable tannins) that include gallotannins, elligatannins, complex tannins, and PA, also known as condensed tannins [16].

The tannins also constitute the active principles of plant-based medicines. According the literature, the tannins containing plants are used as astringents against diarrhea [109], adiuretic against stomach and duodenal tumors [110], and anti-inflammatory [111].

3.6 Glycosides

Glycosides may be phenol, alcohol or sulfur compounds. They are characterized by a sugar portion or moiety attached by a special bond to one or non-sugar portions. Many plants store chemicals in the form of inactive glycosides, which can be activated by enzyme hydrolysis [112]. For this reason, most glycosides can be classified as prodrugs since they remain inactive until they are hydrolyzed in the large bowel leading to the release of the aglycone, the right

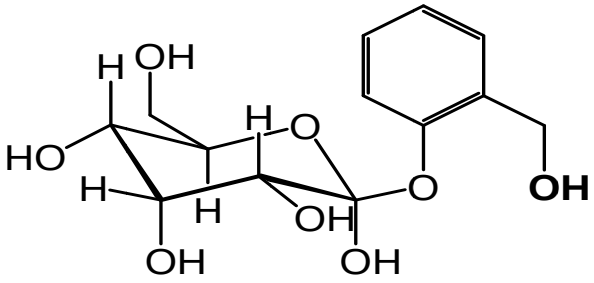

Fig. 12 Salicin, a glycoside type related to aspirin.

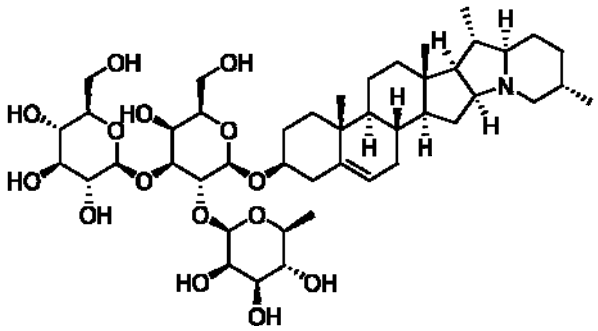

Fig. 13 Type of saponin: solanine chemical structure.

active constituent.

The classification of glycosides is based on the nature of aglycone, which can be any of a wide range of molecular types including phenols, quinines, terpenes and steroids. They are heterogeneous in structure, therefore, they are not easy to learn as specific group and are described here in this review for the convenience. Glycosidic bonds are of great significance, since they link monosaccarides together to form oligosaccharides and polysaccharides [113, 114]. Concerning the therapeutic actions in different studies, it has been shown that glycosides are anticancer [115], expectorant [116], sedative and digestives properties [117, 118].

3.7 Saponins

Saponins are compounds whose active portions form colloidal solutions in water, which produce lather on shaking and precipitate cholesterol. They occur as glycosides whose aglycone is tripenoid or steroidal structures. The combination of lipophilic sugars at the end gives them the ability to lower surface tension, producing the detergent characteristic or soap-like effect on membranes and skin [119].

They are largely distributed in plant kingdom, which have many physicochemical (foaming, emulsification, solubilization, sweetness and bitterness) and biological properties (haemolytic, antimicrobial, antioxidant, moluscacide, insecticide and ichthyocide), exploited in many applications in food, cosmetics, pharmaceutical industries and soil bioremediation. Among the saponins properties, CMC (critical mi cellar concentration), maximum surface density and aggregation number (number of monomers in a micelle) are of great importance for application as surfactants and foaming agents. These are influenced by variables such as temperature, salt concentration, aqueous phase pH, solvent concentration and type, such as ethanol or methanol.

4. Conclusions

Investigating the secondary metabolites remains the largest area of research where a lot of work related to their functions, pharmacological properties must be and will still be carried out. Skills, knowledge embedded in the natural sciences such as botany, chemistry or biochemistry and pharmacology is required. The knowledge of individual class constituents is essential for developing assurance quality methods, extraction procedures, understanding of pharmacological activity, pharmacokinetics and most importantly the potential toxicity and interactions with pharmaceutical drugs. As this review summarized the complexity of second metabolites, each group or class, may have a specific study for more information in order to preview the perspectives in new drugs research and development. Therefore, for some, such as glycosides, they seem to present difficulties in learning them specifically because of heterogeneity and complexity in their structure. In addition, the functions of second metabolites on plants are not well understood, but at least people such as scientists and herbalists still appreciate how much they contribute to relief and heal human and animal ailments.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (81373890); the Research Fund for the Doctoral Program of Higher Education (20121210110011), and the Natural Science Foundation of Tianjin (No. 12JCZDJC26100).

References

[1] Petrovska, B. B. 2012. "Historical Review of Medicinal Plants' Usage." *Pharmacognosy Reviews* 6 (11): 1-5.

[2] Kirtikar, K. R., and Basu, B. D. 1918. *Indian Medicinal Plants*. Bahadurganj: Sudhindra Nath Basu, 72.

[3] Tang, W., and Eisenbrand, G. 1992. *Chinese Drugs of Plant Origin, Chemistry, Pharmacology and Use in Traditional and Modern Medicin*. Berlin: Springer Verlag, 1065.

[4] Okada, T., Afendi, F. M., Altaf-Ul-Amin, M., Takahashi, H., Nakamura, K., Kanaya S. 2010. "Metabolomics of Medicinal Plants: the Importance of Multivariate Analysis of Analytical Chemistry Data." *Current Computer-Aided Drug Design* 6 (3): 179-96.

[5] Harborne, J. B. 1998. *Phytochemical Methods A Guide to Modern Techniques of Plant Analysis*, London: Springer.

[6] Balunas, M. J., and Kinghorn, A. D. 2005. "Drug Discovery from Medicinal Plants." *Life Sciences* 78 (5): 431-41.

[7] Weinberg, E. D. 1971. "Secondary Metabolism: Raison d'etre." *Perspectives in Biology and Medicine* 14 (4): 565-77.

[8] Thrane, U. 2001. "Development in the Taxonomy of Fusarium Species Based on Secondary Metabolites." In *Fusarium: Paul E. Nelson memorial symposium*, edited by B. A. Summerell. St.Paul, Minnesota: APS Press, 29-49.

[9] Fraenkel G. S. 1959. "The Raison d'Être of Secondary Plant Substances These Odd Chemicals Arose as a Means of Protecting Plants from Insects and Now Guide Insects to Food." *Science* 129 (3361) 1466-1470.

[10] Stamp N. 2003. "Out of the Quagmire of Plant Defense Hypotheses." *The Quarterly Review of Biology* 78 (1) 23-55.

[11] Samuni-Blank, M., Izhaki, I., Dearing M. D., Gerchman, Y., Trabelcy, B., Lotan, A., Karasov, W. H., and Arad, Z. 2012. "Intraspecific Directed Deterrence by the Mustard Oil Bomb in a Desert Plant." *Current Biology* 22 (13) 1218-1220.

[12] P.G. Waterman 1992. "Roles for secondary metabolites in plants." In P*roceedings of the 171st Ciba Foundation Symposium on Secondary Metabolites: Their Function and Evolution,* 255-75.

[13] Verpoorte, R. 1998, "Exploration of Nature's Chemodiversity: The Role of Secondary Metabolites as Leads in Drug Development." *Drug Discovery Today* 3 (5): 232-8.

[14] Savithramma, N., Linga Rao, M., and Suhrulatha, D. 2011. "Screening of Medicinal Plants for Secondary Metabolites." *Middle-East J. Sci. Res.* 8: 579-84.

[15] Koehn, F. E., and Carter, G. T. 2005. "The Evolving Role of Natural Products in Drug Discovery." *Nature Reviews Drug Discovery* 4 (3): 206-20.

[16] Lancini, G., and Lorenzetti, R. 1993. *Biosynthesis of Secondary Metabolites, in Biotechnology of Antibiotics and Other Bioactive Microbial Metabolites.* New York: Springer Science + Business, 95-132.

[17] Herbert, R. B. 1989. *The Biosynthesis of Secondary Metabolites.* London: Springer, 200.

[18] Nicolaou, K. C., Jason S. Chen, and Elias James Corey. 2011. *Classics in Total Synthesis. Further Targets, Strategies, Methods III III*. Weinheim: Wiley-VCH.

[19] Michal, G., and Schomburg, D. 2013. *Biochemical Pathways: An Atlas of Biochemistry and Molecular Biology*. 2nd ed. Wiley, 416

[20] Dewick, P.M. 2002. *Medicinal Natural products*. New York: Jonh Wiley & Sons Ltd, 495.

[21] Giweli, A. A., Džamić, A. M., Soković, M., Ristić, M., Janaćković, P., and Marin, P. 2013. "The Chemical Composition, Antimicrobial and Antioxidant Activities of the Essential Oil of Salvia fruticosa Growing Wild in Libya." *Archives of Biological Sciences* 1 (65): 321-9.

[22] Beaulieu, J. C. and Baldwin, E. A. 2002. *Flavor and Aroma of Fresh-Cut Fruits and Vegetables, Fresh-Cut Fruits and Vegetables: Science, Technology, and Market*. CRC Press, 391-425.

[23] Styger, G., Prior, B., and Bauer, F.F. 2011."Wine flavor and Aroma." *Journal of Industrial Microbiology and Biotechnology* 38 (9): 1145-59.

[24] Gershenzon, J., and Dudareva, N. 2007. "The Function of Terpene Natural Products in the Natural World." *Nature Chemical Biology* 3 (7): 408-14.

[25] Maffei, M. E., Gertsch, J., and Appendino, G. 2011. "Plant Volatiles: Production, Function and Pharmacology." *Natural Product Reports* 28 (8): 1359-80.

[26] Maffei, M. 2010. "Sites of Synthesis, Biochemistry and Functional Role of Plant Volatiles." *South African Journal of Botany* 76 (4): 612-31.

[27] Kataev, V. E., Strobykina, I. Yu., Andreeva, O. V., Garifullin, B. F., Sharipova, R. R., Mironov, V. F., and Chestnova, R.V. 2011. "Synthesis and Antituberculosis Activity of Derivatives of Stevia Rebaudiana Glycoside Steviolbioside and Diterpenoid Isosteviol Containing Hydrazone, Hydrazide, and Pyridinoyl Moieties." *Russian Journal of Bioorganic Chemistry* 37 (4): 483-91.

[28] Böhme, K. Velázquez, J. B., and Calo-Mata., P. 2014. "Antibacterial, Antiviral and Antifungal Activity of Essential Oils: Mechanisms and Applications." In *Antimicrobial Compounds.* Berlin: Springer, 51-81.

[29] Schnaubelt, K., and Beasley, J. M. 1998. *Advanced Aromatherapy: The Science of Essential Oil Therapy*. Vermont: Healing Arts Press Rochester.

[30] Angelucci, F. L., Silva, V. V., Dal Pizzol, C. L., Spir, G., Praes, C. E. O., and Maibach, H. 2014. "Physiological Effect of Olfactory Stimuli Inhalation in Humans: An Overview." *Internatioanal Journal of Cosmetic Science* 36 (2): 117-23.

[31] Meamarbashi, A. 2014. "Instant Effects of Peppermint Essential Oil on the Physiological Parameters and Exercise Performance." *Avicenna Journal of Phytomedicine* 4 (1): 72-8.

[32] Tan, C. H., Rasool, S., and Johnston G. A. 2014. "Contact Dermatitis: Allergic and Irritant." *Clinics in Dermatology* 32 (1): 116-24.

[33] Conti, B., Flamini, G., Cioni, P. L., Ceccarini, L., Macchia, M., and Benelli, G. 2014. "Mosquitocidal Essental Oils: Are They Safe against Non-target Aquatic Organisms?" *Parasitology Research* 113 (1): 251-9.

[34] Leandro, L. M., Vargas, Fde S., Barbosa, P. C., Neves, J. K., da Silva, J. A., and da Veiga-Junior, V. F. 2012. "Chemistry and Biological Activities of Terpenoids from *Copaiba (Copaifera spp.) oleoresins*." *Molecules 17* (4): 3866-89

[35] Kogan S. B., Kaliya, M., and Froumin, N. 2006. "Liquid Phase Isomerization of Isoprenol into Prenol in Hydrogen Environment." *Applied Catalysis A: General* 297 (2): 231-6.

[36] Eadie, M. J. 2004. "Could Valerian Have Been the First Anticonvulsant?" *Epilepsia* 45 (11): 1338-43.

[37] Ara, K., Hama, M., Akiba, S., Koike, K., Okisaka, K., Hagura, T., and Tomita, F. 2006. "Foot Odor Due to Microbial Metabolism and Its Control." *Canadian Journal of Microbiology* 52 (4): 357-64.

[38] Elson, C. E., Maltzman, T. H., Boston, J. L., and Tanner, M. A. 1988. "Anti-carcinogenic Activity of d-limonene during the Initiation and Promotion/Progression Stages of DMBA-Induced Rat Mammary Carcinogenesis." *Carcinogenesis* 9 (2): 331-2.

[39] Espina, L., Gelaw, T. K., de Lamo-Castellví, S., Pagán, R., and García-Gonzalo, D. 2013. "Mechanism of Bacterial Inactivation by (+)-limonene and Its Potential Use in Food Preservation Combined Processes." *PloS one* 8 (2): e56769.

[40] Coelho, V., Mazzardo-Martins, L., Martins, D. F., Santos, A. R., da Silva Brum, L. F., Picada, J. N., and Pereira, P. 2013. "Neurobehavioral and Genotoxic Evaluation of (−)-linalool in Mice." *Journal of Natural Medicines* 67 (4) 1-5.

[41] Taniguchi, S., Miyoshi, S., Tamaoki, D., Yamada, S., Tanaka, K., Uji, Y., and Gomi, K. 2014. "Jasmonate Induction of the Monoterpene Linalool Confers Resistance to Rice Bacterial Blight and Its Biosynthesis is Regulated by JAZ Protein in Rice." *Plant, Cell and Environment* 37 (2): 451-61.

[42] Zhang, J., Schurr, U., and Davies, W. 1987. "Control of Stomatal Behaviour by Abscisic Acid Which Apparently Originates in the Roots." *Journal of Experimental Botany* 38 (7): 1174-81.

[43] Hakoshima, T., Murase, K., Hirano, Y., and Sun. T. P. 2011. "Gibberellin Perception by the Gibberellin Receptor and Its Effector Recognition." *Nihon Kessho Gakkaishi* 52: 37-41.

[44] Sun, T. P. 2010. "Gibberellin-GID1-DELLA: A Pivotal Regulatory Module for Plant Growth and Development." *Plant Physiology* 154 (2): 567-70.

[45] Krishna, P. 2003. "Brassinosteroid-mediated Stress Responses." *Journal of Plant Growth Regulation* 22 (4): 289-97.

[46] Hacham, Y., Holland, N., Butterfield, C., Ubeda-Tomas, S., Bennett, M. J., Chory, J., and Savaldi-Goldstein, S. 2011. "Brassinosteroid Perception in the Epidermis Controls Root Meristem Size." *Development* 138 (5): 839-48.

[47] Iwu, M. M. 2014. *Handbook of African Medicinal Plants.* CRC Press.

[48] Aniszewski, T. 2007. *Alkaloids-Secrets of Life: Aklaloid Chemistry, Biological Significance, Applications and Cological Role*. Elsevier.

[49] Clarke, E. G. C. 1970. *The Forensic Chemistry of Alkaloids, in the Alkaloids.* Vol. XII. Edited by Manske, H. F. New York: Academic Press, 514-590.

[50] Evans, D., and Mitch, C. 1982. "Studies Directed towards the Total Synthesis of Morphine Alkaloids." *Tetrahedron Letters* 23 (3): 285-8.

[51] Zezula, J., and Hudlicky, T. 2005. "Recent Progress in the Synthesis of Morphine Alkaloids." *Synlett* 03: 388-405.

[52] Holmstedt, B., Lundgren, G., and Sundwall, A. 1963. "Tremorine and Atropine Effects on Brain Acetylcholine." *Life Sciences* 2 (10): 731-6.

[53] McBrien, N. A., Stell, W. K., and Carr. B., 2013. "How does Atropine Exert Its Anti-myopia Effects?" *Ophthalmic and Physiological Optics* 33 (3): 373-8.

[54] Gu, L., Li, N., Gong, J., Li, Q., Zhu, W., and Li., J. 2011. "Berberine Ameliorates Intestinal Epithelial Tight-Junction Damage and Down-Regulates Myosin Light Chain Kinase Pathways in a Mouse Model of Endotoxinemia." *J. Infect Dis.* 203 (11): 1602-12.

[55] Kim, J. B., Yu, J. H., Ko, E., Lee, K. W., Song, A. K., Park S. Y., Shin, I., Han, W., and Noh, D. Y. 2010. "The

Alkaloid Berberine Inhibits the Growth of Anoikis-resistant MCF-7 and MDA-MB-231 Breast Cancer Cell Lines by Inducing Cell Cycle Arrest." *Phytomedicine* 17 (6): 436-40.

[56] Zha, W., Liang, G., Xiao, J., Studer, E. J., Hylemon, P.B., Jr. Pandak, W. M., Wang, G., Li, X., and Zhou, H. 2010. "Berberine Inhibits HIV Protease Inhibitor-Induced Inflammatory Response by Modulating ER Stress Signaling Pathways in Murine Macrophages." *PLoS One* 5 (2): e9069.

[57] Zhang, Q., Cai, L., Zhong, G., and Luo, W. 2010. "Simultaneous Determination of Jatrorrhizine, Palmatine, Berberine, and Obacunone in Phellodendri Amurensis Cortex by RP-HPLC]." *Zhongguo Zhong Yao Za Zhi* 35 (16): 2061-164.

[58] Agyapong, V. I. O., Singh, K., Savage, M., Thekiso, T. B., Finn, M., Farren, C. K., and McLoughlin, D. M. 2013. "Use of Codeine-Containing Medicines by Irish Psychiatric Inpatients before and after Regulatory Limitations on Their Supply." *Irish Journal of Psychological Medicine* 30 (01): 7-12.

[59] Simera, M., Poliacek, J., and Jakus, J. 2010. "Central Antitussive Effect of Codeine in the Anesthetized Rabbit." *European Journal of Medical Research* 15: 184-8

[60] Smith, J., Owen, E., Earis, J., and Woodcock, A. 2006. "Effect of Codeine on Objective Measurement of Cough in Chronic Obstructive Pulmonary Disease." *Journal of Allergy and Clinical Immunology* 117 (4): 831-5.

[61] Vree, T., Van Dongen, R., and KoopmanKimenai, P. 2000. "Codeine Analgesia is Due to Codeine-6-glucuronide, not Morphine." *International Journal of Clinical Practice* 54 (6): 395.

[62] Mody, N. V., Henson, R., Hedin, P. A., Kokpol, U., and Miles, D. H. 1976. "Isolation of the Insect Paralyzing Agent Coniine from *Sarracenia flava*." *Experientia* 32 (7): 829-30.

[63] Panter, K. E., Welch, K. D., Gardner D. R., and Green, B. T. 2013. "Poisonous Plants: Effects on Embryo and Fetal Development." *Birth Defects Research Part C: Embryo Today: Reviews* 99 (4) : 223-34.

[64] Hajek, P., McRobbie, H., and Myers, K. 2013. "Efficacy of Cytisine in Helping Smokers Quit: Systematic Review and Meta-analysis." *Thorax*. 68 (11): 1037-42.

[65] West, R., Zatonski, W., Cedzynska, M., Lewandowska, D., Pazik, J., Aveyard, P., and Stapleton, J. 2011. "Placebo-Controlled Trial of Cytisine for Smoking Cessation." *New England Journal of Medicine* 365 (13): 1193-200.

[66] Porreca, F., Cowan, A., Raffa, R. B., and Tallarida, R. J. 1983. "Ketazocines and Morphine: Effects on Gastrointestinal Transit after Central and Peripheral Administration." *Life Sciences* 32 (15): 1785-90.

[67] Rozov-Ung, I., Mreyoud, A., Moore, J., Wilding, G. E., Khawam, E., Lackner, J. M., and Sitrin, M. D. 2014. "Detection of Drug Effects on Gastric Emptying and Contractility Using a Wireless Motility Capsule." *BMC Gastroenterology* 14 (1): 2.

[68] Takita, K., Herlenius, E., Yamamoto, Y., and Lindahl, S. G. 2000. "Effects of Neuroactive Substances on the Morphine-Induced Respiratory Depression; an *in vitro* Study." *Brain Research* 884 (1): 201-5.

[69] Clarke, P. B., Fu, D. S., Jakubovic, A., and Fibiger, H. C. 1988. "Evidence that Mesolimbic Dopaminergic Activation Underlies the Locomotor Stimulant Action of Nicotine in Rats." *Journal of Pharmacology and Experimental Therapeutics* 246 (2): 701-8.

[70] Gandhi, P.T. 2013. Novel nicotine derivatives, US Patent, 20130123106

[71] Melton, L. 2006. "Body Blazes." *Sci. Am.* 294 (6): 24.

[72] Rhoades, D. F., Cates, R. G. 1976. *Toward a General Theory of Plant Antiherbivore Chemistry, in Biochemical Interaction between Plants and Insects*. US: Springer. 168-213.

[73] Achan, J., Talisuna, A. O., Erhart, A., Yeka, A., Tibenderana, J. K., Baliraine, F. N., and D'Alessandro, U. 2011. "Quinine, an Old Anti-malarial Drug in a Modern World: Role in the Treatment of Malaria." *Malar. J.* 10 (144): 1475-2875.

[74] Adnyana, I. K. 2013. "Efficacy and Safety o-desmethyl Quinine Compare to Quinine for Nocturnal Leg Cramp." *Journal of Medical Sciences* 13 (8): 819-23.

[75] El-Tawil, S., Al-Musa, T., Valli, H., Lunn, M. P., El-Tawil, T., and Weber, M. 2010. "Quinine for Muscle Cramps." *Cochrane Database Syst. Rev.* 12: CD005044. DOI: 10.1002/14651858.

[76] Mwita, C., Mwai, L., and Newton, C. 2012. "Antiepileptic Properties of Quinine: A Systematic Review." *Annals of Neurosciences* 19 (1): 14-20

[77] Fewell, A. M., and Roddick, J. G. 1993. "Interactive Antifungal Activity of the Glycoalkaloids α-solanine and α-chaconine." *Phytochemistry* 33 (2): 323-8.

[78] Lu, M. K., Shih, Y. W., Chang Chien, T. T., Fang, L. H., Huang, H. C., and Chen, P. S. 2010. "ALPHA.-Solanine Inhibits Human Melanoma Cell Migration and Invasion by Reducing Matrix Metalloproteinase-2/9 Activities." *Biological and Pharmaceutical Bulletin* 33 (10): 1685-91

[79] Kenny, O. M., McCarthy, C. M., .Brunton, N. P., Hossain, M. B., Rai, D. K., and Collins, S. G. 2013. "Anti-inflammatory Properties of Potato Glycoalkaloids in Stimulated Jurkat and Raw 264.7 Mouse Macrophages." *Life Sciences* 92 (13): 775-82.

[80] Mohsenikia, M., Alizadeh, A. M., Khodayari, S., Khodayari, H., Karimi, A., and Zamani, M. 2013. "The Protective and Therapeutic Effects of Alpha-solanine on

Mice Breast Cancer." *European Journal of Pharmacology* 718 (1): 1-9.

[81] Bonjoch, J., and Solé, D. 2000. "Synthesis of Strychnine." *Chemical Reviews* 100 (9): 3455-82.

[82] Buckingham, J., and Nemesis, B. 2010. *The Intimate History of Strychnine*. CRC Press.

[83] Jensen A. A., Gharagozloo, P., Birdsall N. J., and Zlotos, D. P. 2006. "Pharmacological Characterisation of Strychnine and Brucine Analogues at Glycine and α7 Nicotinic Acetylcholine Receptors." *European Journal of Pharmacology* 539 (1): 27-33.

[84] Umukoro, S., Adrian Omogbiya, I., Taghogho Eduviere, A. 2013. "Evaluation of the Effect of Jobelyn® on Chemoconvulsants-Induced Seizure in Mice." *Basic and Clinical Neuroscience* 4 (2): 19-23.

[85] Do Pham, D. D., Kelso, G. F., Yang, Y., and Hearn, M. T. 2014. "Studies on the Oxidative N-demethylation of Atropine, Thebaine and Oxycodone Using a Fe III-TAML Catalyst." *Green Chemistry* 16 (3): 1399-409.

[86] Fist, A. J., Byrne, C. J., and Gerlach, W. L. 2000. Papaver somniferum strain with high concentration of thebaine and oripavine, Google Patents, US6067749 A.

[87] Jeong, I. H., Kim, Y. S., Cho, K. Y., and Kim, K. J. 1990. "Unexpected Effect of Fluorine in Diels-Alder Reaction of 2-Fluoroacrolein with Thebaine." *Bulletin* of *Korean Chemical Society* 11 (3): 178-9.

[88] Lee, S., Park, Y., Han, E., Choi, H., Chung, H., Oh, S. M., and Chung, K. H. 2011. "Thebaine in Hair as a Marker for Chronic Use of Illegal Opium Poppy Substances." *Forensic Science International* 204 (1): 115-8.

[89] Heal, K. G., Taylor Robinson, A. W. 2010. "Tomatine Adjuvantation of Protective Immunity to a Major Pre-erythrocytic Vaccine Candidate of Malaria is Mediated via CD8+ T Cell Release of IFN-gamma." *J. Biomed. Biotechnol.* Article ID 834326, 7 pages, doi:10.1155/2010/834326.

[90] Morrow, W. J., Yang, Y. W., and Sheikh, N. A. 2004. "Immunobiology of the Tomatine Adjuvant." *Vaccine* 22 (19): 2380-4.

[91] Tomsik, P., Micuda, S., Sucha, L., Cermakova, E., Suba, P., Zivny, P., and Rezacova, M. 2013. "The Anticancer Activity of Alpha-tomatine against Mammary Adenocarcinoma in Mice." *Biomed. Pap. Med. Fac. Univ. Palacky. Olomouc. Czech. Repub.* 157 (2): 153-61.

[92] Gao, S., and Hu. M. 2010. "Bioavailability Challenges Associated with Development of Anti-cancer Phenolics" *Mini Reviews in Medicinal Chemistry* 10 (6): 550-67.

[93] Park, E. S., Moon, W. S., Song, M. J., Kim, M. N., Chung, K. H., and Yoon, J. S. 2001. "Antimicrobial Activity of Phenol and Benzoic Acid Derivatives." *International biodeterioration and biodegradation* 47 (4): 209-14.

[94] Pengelly, A. 2004. *The Constituents of Medicinal Plants: An Introduction to the Chemistry and Therapeutics of Herbal Medicine*, CABI Publishing.

[95] Dai, J., Mumper, and R.J. 2010. "Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties." *Molecules* 15 (10): 7313-52.

[96] Herrmann, K., and Nagel, C. W. 1989. "Occurrence and Content of Hydroxycinnamic and Hydroxybenzoic Acid Compounds in Foods." *Critical Reviews in Food Science & Nutrition* 28 (4): 315-47.

[97] Manach, C., Scalbert, A., Morand, C., Rémésy C., and Jiménez, L. 2004. "Polyphenols: Food Sources and Bioavailability." *The American Journal of Clinical Nutrition* 79 (5): 727-47.

[98] Somasegaran, P., and Hoben, H. J. 1994. *Handbook for Rhizobia: Methods in Legume-Rhizobium Technology*. New York: Springer-Verlag.

[99] Galeotti, F., Barile, E., Curir, P., Dolci, M., and Lanzotti, V. 2008. "Flavonoids from Carnation (Dianthus caryophyllus) and Their Antifungal Activity." *Phytochemistry Letters* 1 (1): 44-8.

[100] Middleton, E., Kandaswami, C., and Theoharides, T. C. 2000. "The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer." *Pharmacological Reviews* 52 (4): 673-751.

[101] Guardia, T., Rotelli, A. E., Juarez, A. O., and Pelzer, L. E. 2001. "Anti-inflammatory Properties of Plant Flavonoids. Effects of Rutin, Quercetin and Hesperidin on Adjuvant Arthritis in Rat." Farmaco. 56 (9): 683-7.

[102] Hertog, M. G., Kromhout, D., Aravanis, C., Blackburn, H., Buzina, R., and Fidanza, F. 1995. "Flavonoid Intake and Long-Term Risk of Coronary Heart Disease and Cancer in the Seven Countries Study." *Archives of Internal Medicine* 155 (4): 381-6.

[103] McCullough, M. L., Peterson, J. J., Patel, R., Jacques, P. F., Shah, R., and Dwyer, J. T. 2012. "Flavonoid Intake and Cardiovascular Disease Mortality in a Prospective Cohort of US Adults." *The American Journal of Clinical Nutrition* 95 (2): 454-64.

[104] Lippi, G., Franchini, M., Favaloro, E. J., and Targher, G. 2010. "Moderate Red Wine Consumption and Cardiovascular Disease Risk: Beyond the "French paradox"." *Semin.Thromb. Hemost.* 36 (1): 59-70.

[105] Wu, J. M., Wang, Z. R., Hsieh, T. C., Bruder, J. L., Zou, J. G., and Huang, Y. Z. 2001. "Mechanism of Cardioprotection by Resveratrol, a Phenolic Antioxidant Present in Red Wine (Review)." *International Journal of Molecular Medicine* 8 (1): 3-17.

[106] Halliwell, B. 2007. "Dietary Polyphenols: Good, Bad, or Indifferent for Your Health?" *Cardiovasc. Res.* 73 (2): 341-7.

[107] Habauzit, V., and Morand, C. 2012. "Evidence for a Protective Effect of Polyphenols-Containing Foods on

Cardiovascular Health: an Update for Clinicians." *Ther. Adv. Chronic. Dis.* 3 (2): 87-106.

[108] Loeb, H., Vandenplas, Y., Würsch, P., and Guesry, P. 1989. "Tannin-rich Carob Pod for the Treatment of Acute-onset Diarrhea." *Journal of Pediatric Gastroenterology and Nutrition* 8 (4): 480-5.

[109] Fujiki, H., Imai, K., Nakachi, K., Shimizu, M., Moriwaki, H., and Suganuma, M. 2012. "Challenging the Effectiveness of Green Tea in Primary and Tertiary Cancer Prevention." *Journal of Cancer Research and Clinical Oncology* 138 (8): 1259-70.

[110] Trouillas, P., Calliste, C. A., Allais, D. P., Simon, A., Marfak, A., Delage, C., and Duroux, J. L. 2003. "Antioxidant, Anti-inflammatory and Antiproliferative Properties of Sixteen Water Plant Extracts Used in the Limousin Countryside as Herbal Teas." *Food Chemistry* 80 (3): 399-407.

[111] Brito Arias, M., *Synthesis and Characterization of Glycosides*. Springer, ISBN 9780387262512 (2007).

[112] Polt. R.L. 1995. Method for Making Amino Acid Glycosides and Glycopeptides, U.S. Patent No. 5,470,949. Washington, DC: U.S. Patent and Trademark Office

[113] Levy, D. D. E., and Tang. P. C. 1995. *The Chemistry of C-glycosides*. Vol. 13. Elsevier.

[114] Newman, R. A., Yang, P., Pawlus, A. D., and Block, K. I. 2008. "Cardiac Glycosides as Novel Cancer Therapeutic Agents." *Molecular Interventions* 8 (1): 36-49.

[115] Zhou, Q., Liang, D., Deng, A., Zhang, J., Wu, C., Nie, Z., and Wang, Y. 2013. "Antitussive, Expectorant and Bronchodilating Effects of Ethanol Extract of< i> *Sorghum bicolor*</i>(L.) Moench Roots." *Journal of Ethnopharmacology* 149 (1): 297-302.

[116] Fernández, S. P., Wasowski, C., Loscalzo, L. M., Granger, R. E., Johnston, G. A., Paladini, A. C., and Marder, M. 2006. "Central Nervous System Depressant Action of Flavonoid Glycosides." *European Journal of Pharmacology* 539 (3): 168-76.

[117] Galvano, F., La Fauci, L., Lazzarino, G., Fogliano, V., Ritieni, A., Ciappellano, S., and Galvano, G. 2004. "Cyanidins: Metabolism and Biological Properties." *The Journal of Nutritional Biochemistry* 15 (1): 2-11.

[118] Güçlü-Üstündağ, Ö., and Mazza., G. 2007. "Saponins: Properties, Applications and Processing." *Critical Reviews in Food Science and Nutrition* 47 (3): 231-58.