Chapter 5

Coumarins — An Important Class of Phytochemicals

Maria João Matos, Lourdes Santana,
Eugenio Uriarte, Orlando A. Abreu,
Enrique Molina and Estela Guardado Yordi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/59982

1. Introduction

Phytochemicals are chemical compounds that occur naturally in the plant kingdom. Some are responsible for the organoleptic properties of the natural sources in which they are present. The term is generally used to refer to those chemicals that may have biological significance, for example carotenoids, flavonoids, coumarins, or chromones, but not all are established as essential nutrients. There may be as many as 4,000 different phytochemicals having potential activity against several diseases such as cancer and metabolic or degenerative diseases.

Among them, coumarins are a family of benzopyrones (1,2-benzopyrones or 2H-1-benzopyran-2-ones) widely distributed in the nature. They represent an important family of naturally occurring and/or synthetic oxygen-containing heterocycles, bearing a typical benzopyrone framework (Figure 1) [1].

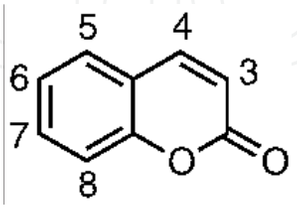

Figure 1. Chemical structure of coumarin and the IUPAC numeration of this scaffold.

The name coumarin comes from a French term for the Tonka bean, *coumarou*, seeds of *Dipteryx odorata* (*Coumarouna odorata*) (*Fabaceae/Leguminosae*), one of the sources from which coumarin was first isolated as a natural product in 1820. It has a sweet odor, easy to be recognized as the

scent of new-mown hay; because of that, coumarin has been used in perfumes since 1882. It is presumed to be produced by plants as a chemical defense to discourage predation [2, 3].

Coumarinic compounds are a class of lactones structurally constructed by a benzene ring fused to α-pyrone ring, and essentially possess - conjugated system with rich electron and good charge-transport properties [4, 5]. The simplicity and versatility of the coumarin scaffold make it an interesting starting-point for a wide range of applications [6-8]. There are coumarins as perfumes, cosmetics, and industrial additives. Some of its derivatives have been used as aroma enhancers in tobaccos and certain alcoholic drinks [9, 10]. But their most relevant role is described in natural products, organic chemistry, and medicinal chemistry [11, 12]. The extraction, synthesis, and evaluation of coumarins have become an extremely attractive and rapidly developing topic [13, 14]. Moreover, a lot of coumarin compounds as medicinal candidates for drugs with strong pharmacological activity, low toxicity and side effects, fewer drug resistance, high bioavailability, broad spectrum, better curative effects, etc., to treat various types of diseases are being actively studied [15]. Several efforts have been made mainly in developing coumarin-based anticoagulant, antioxidant [16], antimicrobial (anti-viral, antifungal, and anti-parasitic) [10, 17], anticancer [18-20], anti-diabetic, analgesic, anti-neurodegenerative, and anti-inflammatory agents [10, 21]. Moreover, the unique and versatile oxygen-containing heterocyclic structure makes coumarin compounds occupy an important place in medicinal chemistry [22, 23]. In addition, studies have been done regarding coumarins as bioactive agents [24], as well as supramolecular medicinal drugs, diagnostic agents and pathologic probes, and biological stains [25]. Particularly, the large - conjugated system in the coumarinic ring, with electron-rich and charge-transport properties, is important in the interaction of this scaffold with molecules and ions. Coumarin-based ion receptors, fluorescent probes, and biological stains are growing quickly and have extensive applications to monitor timely enzyme activity, complex biological events, as well as accurate pharmacological and pharmacokinetic properties in living cells [26, 27].

Coumarin was first synthesized in 1868, and it was used in the pharmaceutical industry as a precursor in the synthesis of a number of synthetic anticoagulant pharmaceuticals, starting with dicoumarol (removed from the current therapy) [28]. So far, some interesting coumarin-based anticoagulant drugs have extensively been used in clinics [29]. Coumarins are a type of vitamin K antagonists [30]. The most notable ones are warfarin, acenocumarol, and phenprocoumon, currently in use in several countries [31, 32]. Warfarin is employed more frequently than acenocoumarol because of its longer half-life (36 h), theoretically providing more stable anticoagulation and avoiding factor VII fluctuations that potentially occur during acenocoumarol treatment (half-life 10 h) [33]. Nowadays, some coumarins proved to be enzymatic inhibitory agents [monoamine oxidase (MAO) inhibitors, acetylcholinesterase (AChE) inhibitors, and butyrylcholinesterase (BuChE) inhibitors] with great potential in neurodegenerative diseases (ND) [34-38]. These studies represent an important tendency in the coumarin's chemistry and biological evaluation [39-41].

Therefore, the coumarin ring is prevalently applied to construct several functional molecules in the medicinal field. A great deal of work has been done directed towards the separation and purification of naturally occurring biological coumarins from a variety of plants, animals, and

http://dx.doi.org/10.5772/59982

microorganisms, as well as towards the artificial synthesis of coumarin compounds with novel structures and properties [42]. Coumarin compounds as medicinal drugs have been increasingly attracting special interest due to their underlying outstanding contributions in the prevention and treatment of diseases, and the related researches and developments have become an extremely attractive highlighted area.

In this context, an overview of the role of coumarins as important phytochemicals and their interesting applications will be presented and discussed. The origin, natural sources, biosynthesis, and applications are going to be presented in this chapter.

2. Natural occurring coumarins

Coumarin (Figure 1) and its derivatives are an important group of natural compounds widely distributed in the natural kingdom [43]. They can be found in the integument of seeds, fruits, flowers, roots, leaves, and stems, although the largest concentration is generally in fruits and flowers [44]. Originally, coumarin was isolated from the seed of *D. odorata*. Coumarins are secondary metabolites of higher plants, few microorganisms (bacteria and fungi), and sponges [45]. The function of this type of end product of secondary metabolism is related to defense mechanisms against herbivores and attacks by microorganisms. These compounds are biosynthesized from phenylalanine via the shikimic acid [46]. Natural coumarins are generally unsaturated lactones and comprise another class of compounds C_6C_3. Almost all the natural coumarins have an oxygenated substituent at position 7 [47], either free as in hydroxylated umbelliferone, or combined (methyl, sugars, etc.) in other derivatives. Structurally, they are considered derivatives of the *ortho*-hydroxy-cinnamic acid.

There are different classifications for the coumarin derivatives. Generally, they can be chemically classified according to the most common cores: simple coumarins, complex coumarins, and various coumarins. More complex coumarins are generally fused with other heterocycles [3]. Therefore, they can be classified as: simple coumarins, furocoumarins, dihydrofurocoumarins, pyranocoumarins (linear and angular), phenylcoumarins, and biscoumarins [1]. As said before, hundreds of coumarins have been identified in natural sources, especially plants [48, 49]. Major coumarin constituents isolated from plants include: simple hydroxycoumarins, furocoumarins and isofurocoumarins, pyranocoumarins, biscoumarins, and dihydroisocoumarins (Figure 2) [1].

Coumarins have been isolated from hundreds of plants species distributed in more than 40 different families. There were isolated more than different 1300 coumarins, well distributed in *Angiospermae*, *Monocotyledoneae* and *Dicotyledoneae* families. Orders with occurrence numbers > 100 are *Araliales*, *Rutales*, *Asterales*, *Fabales*, *Oleales*, *Urticales*, and *Thymelaeales*. Families with occurrence numbers > 100 are *Apiaceae* (*Umbelliferae*), *Rutaceae*, *Asteraceae* (*Compositae*), *Fabaceae* (*Leguminosae*), *Oleaceae*, *Moraceae*, and *Thymelaeaceae*, respectively (Figure 3) [50]. The best known and researched coumarins in the field of phytochemistry, pharmacology, medicinal chemistry, and the food science can be found in these families. Therefore, these are the coumarins that are going to be further addressed in the next sections of this chapter.

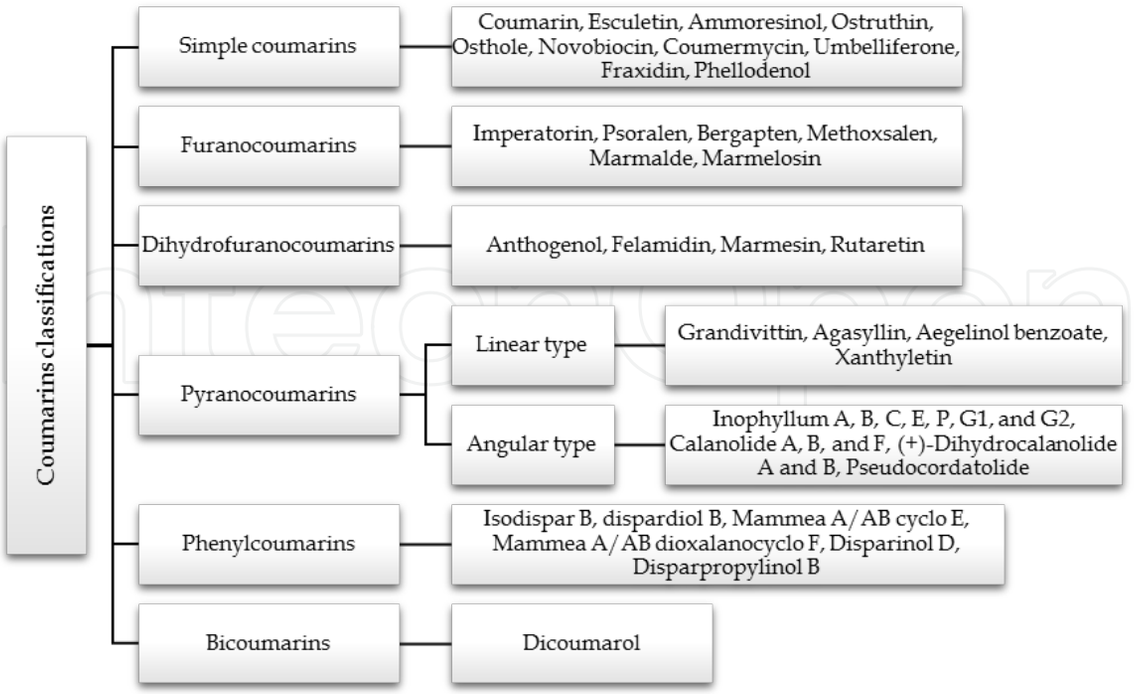

Figure 2. Principal types of coumarins isolated from plants.

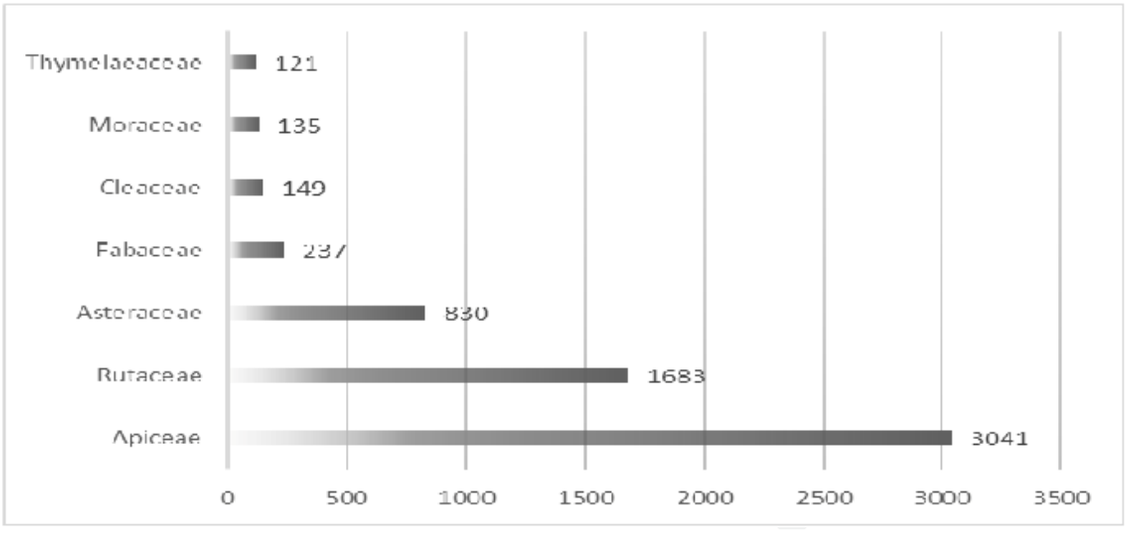

Figure 3. Number of coumarins presented in seven different families of plants[50].

Coumarins usually are in the free state in plants as they are polar structures, and many of them can sublimate. They might also be found in the form of glycosides, including psoralen core-related structures [44]. They are characterized by UV light absorption, resulting in a very characteristic blue fluorescence; they are also very photosensitive as they can be altered by natural light [44]. These features are used in the isolation and analysis, as well as in unusual therapies such as photochemotherapy and the industry of chemical sensors [51, 52].

http://dx.doi.org/10.5772/59982

3. Biosynthesis of coumarins

Simple coumarins are biogenetically derived from shikimic acid, via cinnamic acid. The specificity of the process is the C-2 hydroxylation, producing a break (*β*-oxidation) of the side chain (i.e. *Salix* spp.), or chain isomerization and subsequent lactonization, generating the umbelliferone. Figure 4 explains the entire process [46, 53].

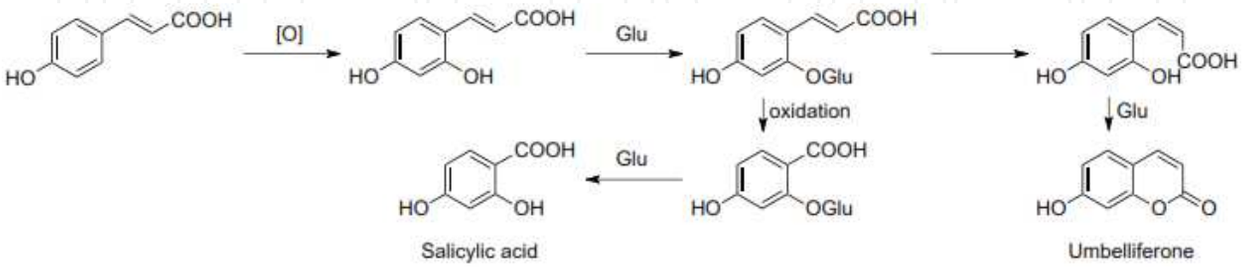

Figure 4. Biosynthesis of simple coumarins.

Pyrano and furocoumarins (Figure 2) are also biogenetically derived from shikimic acid. These coumarins could be divided in two groups—lineal and angular—depending on the position where the isopentenyl pyrophosphate is condensed to further cyclize and form the heterocycle. The biosynthesis of these complex coumarins could also be the result of the cyclization of a simple coumarin previously prenylated [53].

Among the coumarins classified as "various" is the dicoumarol, which is formed by bacterial fermentation of Yellow Sweet Clover, and was isolated for the first time from decomposed leaves of *Melilotus albus* (*Fabaceae/Leguminosae*).

An approximation for the dicumarol biogenesis is the hydroxylation of the 4-position of the coumarin, that then captures a molecule of formaldehyde and is condensed with another molecule of 4-hydroxycoumarin, and finally enolize the keto group forming the dicumarol [46].

From a chemotaxonomic approach, Ribeiro & Kaplan (2002) evidenced that the diversity and structural complexity of the coumarins constitute an example of higher plant evolution. Simple coumarins are the most common in all angiosperms, especially in *Oleaceae* and *Asteraceae*, and their occurrence is of 100% and 98, 68%, respectively [50]. The second most prevalent coumarins are furocoumarins and pyranocoumarins. Coumarin in some families are high (*Thymelaeaceae*, *Rutaceae*, *Apiaceae*, *Fabaceae*, and *Moraceae*). In the case of well-diversified structural types in *Apiaceae* and *Rutaceae*, coumarins are considered as chemotaxonomic markers [50].

Apiaceae is the major source of coumarins (Figure 3) and one of the more diverse, containing five different types of coumarin derivatives (simple coumarins, lineal furocoumarins, angular furocoumarins, lineal pyranocoumarins, and angular pyranocoumarins) [50, 54]. *Rutaceae* is also highlighted in both occurrence and diversification. Generally, the division *Angiospermae* is preferably rich in simple coumarins, followed by the furo and pyranocoumarins [50].

4. Coumarins in medicinal plants

A large number of valuable species used commonly as medicinal plants, aromatic plants, and edible plants for human and animal feeding belongs to coumarin-rich plant families. Among them are species with well-documented biological activity, in which coumarins are part of the active principles. Table 1 shows a selection of plants of these families (first listed seven families with number of occurrence > 100) and some other families with species of particular pharmacological interest on chronic diseases. Coumarins presenting great pharmacological interest have been isolated in different geographical regions from other botanical families. Also shown are the coumarin compounds having species and their yield (if available).

Most of these plants are well known by people and scientists as part of herbal medicine repertories in Europe, Asia, or the Americas [55-58]. From the list, several coumarin-containing species or genera have also ethnomedical records in Cuba and the Caribbean Basin [59, 60]. Among of plant included are species with a great historical record of ethnomedicinal uses, and are present in *traditional medicine systems*: Ayurveda Medicine, Traditional Chinese Medicine and Unani Medicine, or in other recent cultures. Also, renowned species used on conventional therapeutics and modern herbal medicine are included, ie. *Aesculus hippocastanum* (Horsechestnut), *Passiflora incarnata* (Passion Flower), *Lawsonia inermis* (Henna), *Hypericum perforatum* (Saint John Wort), *Tilia cordata* (Lime Tree) and *Uncaria tomentosa* (Cat's Claw).

Coumarins are also present in several species belonging to different botanical families, which are widespread in the northeastern region of Brazil [61]. Some of them are reported in folk medicine as traditional remedies drugs for the treatment of respiratory diseases [55]. Many pharmacological activities have been ascribed to coumarins such as anticlotting, hypotensive, antimicrobial, anti-inflammatory, and antitumor activities [61].

Recent studies and review manuscripts regarding the coumarin scaffold describe the huge variety of biological activities that may be present in the natural coumarins [8, 18, 62-64]. Venugopala et al. (2013) presented several coumarins displaying activities such as anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer, anti-hypertensive, antitubercular, anticonvulsant, anti-adipogenic, Cytochrome P450 inhibiting, anti-hyperglycemic, antioxidant, and neuroprotective. Several recent reviews summarize and highlight advances in the application of coumarins, especially concerning their antioxidant and anticancer properties [62-70].From *Calophyllum* spp., it is remarkable the antiviral activity of calanolides and other related pyranocoumarins on Epstein-Barr virus and HIV [56]. As active compound of molluscicidal effects on *Biomphalaria glabrata* of *C. brasiliense* extracts were determined (-) mammea A/BB, also found in *C. Verticillatum* [71].

It is the great structural diversity of coumarinic compounds that allows for their several applications, and also allows for the high interest of these derivatives as phytochemicals. The pharmacological and biochemical properties and therapeutic applications of simple coumarins depend upon the pattern of substitution [68].

http://dx.doi.org/10.5772/59982

Family-specie (vernacular name)	Coumarin	Use*	Reference
Apiaceae/ Umbelliferae			
Ammi majus (*Bishop's flower*)	Imperatorin, bergapten, oxypeucedanin, pabulenol, marmesin, xanthotoxin, isopimpinellin and heraclenin.	M	[72]
A. visnaga (Pick-tooth, Toothpickweed)	PyranoCoumarins	M	[58, 73]
Anethum graveolens (Dill)	Aesculetin, bergapten, scopoletin	M, F	[60]
Angelica archangelica (Angelica)	Angelicin, osthol (major constituent in rhizome/ root at 0.2%), bergapten, imperatorin, isoimperatorin (major constituent in fruit), oreoselone, oxypeucedanin, umbelliferone, xantonin, xanthotoxin, xanthotoxol	M, F	[57, 58]
Apium graveolens (Celery)	Apigravin, apiumetin, apiumoside, bergapten, celerin, celereoside, isoimperatorin, isopimpinellin, osthenol, rutaretin, seselin, umbelliferone, 8-hidroxy-5-methoxypsoralen.	M, F	[57, 58]
Coriandrum sativum (Coriander)	Umbelliferone,	M, F	[58]
Cuminum cyminum (Cumin)	Escopoloetina, bergapten	M, F	[58]
Daucus carota subsp. *carota* (Wild Carrot)	8-methoxypsoralen, 5-methoxypsoralen (0.01–0.02 ug/g) in fresh plant, concentration increased in the disease plant.	M	[57]
Foeniculum vulgare (Fennel)	Umbelliferone, esculetin, bergapten, seselin, psoralen	M, F	[58]
Ferula assafoetida (Asafoetida)	Umbelliferone, coumarin-sesquiterpene complexes e.g. asacoumarin A and asacoumarin B.	M	[57]
Petroselinum crispum (Parsley)	Bergapten and oxypeucedanin as major constituent (up to 0.02% and 0.01%, respectively); also 8-metoxypsoralen, imperatorin, isoimperatorin, isopimpinellin, psoralen, xanthotoxin (up to 0.003%).	M, F	[57, 58]
Pimpinella anisum (Aniseed)	Scopoletin, umbelliferone, umbelliprenine, bergapten	M, F	[57, 58]
Trachyspermum ammi /Carum copticum (Ajwain)	Coumarins	-	[74]
Rutaceae			

Family-specie (vernacular name)	Coumarin	Use*	Reference
Aegle marmelos (Bael fruit)	Sesquiterpenic coumarin ethers, diterpenic coumarin ethers, triterpenic coumarin ethers, sesterterpenic coumarin ethers, auraptene, epoxyauraptene, marmin.	M, F	[75-77]
Citrus aurantium (Bitter Orange tree)	Volatile Coumarins (0.09%): aurapteno, auraptenol, bergapteno, bergaptol, escoparona, citropteno.	M, F	[58]
C. limonum (Lemon tree)	Escopoletin, umbelliferone, bergamotin, bergapten, bergaptol, citropten	M, F	[58]
C. sinensis (Orange tree)	Herniarin, scopoletin	M, F	[60]
Melicope spp.	Coumarins, chromones, dichromones	M	[56]
Murraya paniculata (*M. exotica*)(Orange Jessamine, Chinese box)	Coumarins	M	[74]
Paramygnya monophylla	Poncitrin, nordentatin	M	[56]
Stauracanthus perforates	Coumarins	M	[78]
Tetradium daniellii (*Euodia daniellii*)	Coumarins	M	[79, 80]
Toddalia aculeata (*T. asiatica*) (Orange climber)	Ulopterol	M	[74, 81]
Zanthoxilum americanum (Northern Prickly Ash)	Xanthyletin, xanthoxyletin, alloxanthoxyletin, 8-(3,3-dimethylallyl)-alloxanthoxyletin.	M	[57]
Z. syncarpum	Coumarins	M	[82]
Asteraceae/Compositae			
Achillea millefolium (Yarrow)	Coumarins (0.35%)	M	[58]
Ageratum conyzoides (Mexican ageratum)	1-2 benzopirone	M	[83]
Arnica montana (Arnica)	Scopoletin, umbelliferone	M, F	[57, 58]
Chamaemelum nobile (Roman Chamomile)	Scopoletin-7-glucoside	M, F	[57, 58]
Cichorium intybus (Chicory)	Coumarins	M, F	[73]
Conyza sumatrensis (Fleabane)	Osthol	M	[56]
Eupatorium triplinerve (White Snakeroot)	Coumarins	M	[84]

http://dx.doi.org/10.5772/59982

Family-specie (vernacular name)	Coumarin	Use*	Reference
Hieracium pilosela (Mouse Ear)	Coumarins (0.2–0.6%): 7-glucosil- umbeliferone	M	[58]
Lactuca virosa (Wild Lactuce)	Aesculin, cichoriin	M	[58]
Matricaria recutita (Chamomille)	Umbelliferone and its methyl ether, heniarin.	M, F	[57, 58]
Mikania glomerata (Guaco)	Coumarins	M	[85]
Mikania hirsutissima	Coumarins	M	[86]
Fabaceae/Leguminosae			
Dipteryxodorata (*Coumarouna odorata*)(Tonka Bean, Coumaru)	Coumarins (35,000 ppm)	M	[84]
Euchresta formosana	Coumarins	M	[87]
Medicago sativa (Lucerne)	Cumestrol, medicagol, sativole, trifoliole, lucernole, dafnoretin.	M, F	[57, 58]
Melilotus officinalis (Yellow Sweet Clover)	Coumarins (0.4–1%)	M	[84] [58]
Glycyrriza glabra (Liquorice)	Glycyrin, heniarin, liqcoumarin, umbelliferone, GU-7 (3-arylcoumarin derivative)	M, F	[57, 58]
Myroxylon balsamum (Balsam Tolu)	Coumarins	M	[58]
Trigonella foenum-graecum (Fenugreek)	Coumarins	M, F	[57, 58]
Moraceae			
Dorstenia brasiliensis	Coumarins	M	[88]
Morus alba (White Mullberry)	Coumarins	M	[89]
Oleaceae			
Fraxinus excelsior (Common ash)	Fraxoside, esculoside, fraxinol, escopoletoside	M	[57]
Oleae europaea (Olive)	Coumarins	M, F	[90]
Thymelaeaceae			
Daphne feddei	feddeiticin (dicoumarinolignoid), dicoumarin glucosides	-	[91]
D. gnidium (Flax-leaved daphne)	daphnetin, daphnin, acetylumbelliferone, daphnoretin	-	[92]

Family-specie (vernacular name)	Coumarin	Use*	Reference
D. odora (Winter daphne)	daphnetin	-	[93]
D. oleoides	dimeric coumarin glycoside, trimeric coumarin fucosides, daphnetin,	-	[94, 95]
D. pedunculata	3-[(3-hydroxy-4-ethylpropanpicatephenyl)oxy]-6-methoxy-7-hydroxycoumarin	-	[96]
Achanthaceae			
Justicia pectoralis (Tilo)	Coumarin, umbelliferone	M	[97]
Araliaceae			
Eleutherococcus senticosus (Eleutherococcus)	Coumarins	M	[58]
Brassicacae/Cruciferae			
Radicula armoracia (Horseradish root)	Aesculetin	M, F	[57, 58]
Caryophylacae			
Herniaria glabra (Rupture wort)	(0.1-0.4%) umbelliferone, herniarin	M	[58]
Caprifoliaceae			
Vivurnum prunifolium (American black haw)	Scopoletin (7-hidroxy-6-methoxicoumarin), scopolin, sculetin	M	[58]
Clusiaceae/Guttiferae			
Calophyllum brasiliense (Guanandi, Ocuje)	volatile Coumarins, (-) mammea A/BB, brasimarins A, B, and C		[71, 98]
C. cerasiferum	(-) calanolide B	M	[56]
C. cordato-oblongum	Coumarins	M	[56]
Calophyllum inophyllum (Borneo mahogany)	Coumarins		[56]
Calophyllum lanigerum var *austrocoriaceum*	(+)- calanolide A	M	[56]
C. teysmannii var *inophylloide*	(-) calanolide B, sonlattrolide	M	[56]
C. verticillatum	mammea A/BB		[71]
Connaraceae			
Connarus monocarpus	Bergenin1.5%	M	[56]
Cupresaceae			

Family-specie (vernacular name)	Coumarin	Use*	Reference
Juniperus communis (Common Juniper)	Umbeliferone	M	[58]
Hippocastanacae			
Aesculus hippocastanum (Horse-chestnut)	Aesculetin, fraxin, scopolin, aesculetosides (glucosides)	M	[57, 58]
Hypericaceae			
Hypericum perforatum (Saint John Wort)	Umbelliferone, escopoletin,	M	[58]
Lamiaceae/Labiadae			
Lavandula angustifolia (Lavender)	Coumarins: 1,500 ppm, 0.25%: hernairin, santonin	M	[58, 84]
L. latifolia (Aspic)	Coumarins: 22 ppm	M	[84]
Lycopus europeus (European Bugle)	Coumarins: 1,200 ppm	M	[84]
Ocimum basilicum (Basil)	Aesculetin, aesculin	M, F	[60]
Salvia officinalis (Garden Sage)	Esculetin	M	[58]
Lauraceae			
Cinnamomum cassia (C. aromaticum) (Chinese cinnamon)	Coumarins	M, F	[57]
C. verum (*C. zeylanicum*) (Cinnamon)	Coumarins (0.65%)	M, F	[57, 58]
Laurus nobilis (laurel, sweet bay)	Coumarins	M, F	[57]
Persea americana (Avocado)	Scopoletin	M	[60]
Lytraceae			
Lawsonia inermis (Henna)	Coumarins	M	[58]
Meliaceae			
Trichilia hirta (Guabán)	Coumarins	M	[99]
Menianthaceae			
Menyanthes trifoliata (Buckbean)	Scoparone, brailin, scopoletin	M	[58]
Monimiaceae			

Family-specie (vernacular name)	Coumarin	Use*	Reference
Peumus boldus (Boldus)	Coumarins 125 ppm	M	[84]
Passifloraceae			
Passiflora incarnate (Passion Flower)	Scopoletin, umbelliferone	M, F	[57, 58]
Plantaginaceae			
Plantago major (Large Plantain)	Esculetin	M	[58]
Poaceae (Graminae)			
Zea mays (Corn)	Coumarins: 2,000 ppm	F	[84]
Rhamnaceae			
Zizyphus jujube (Jujube)	Coumarins: 3,000 ppm	M, F	[84]
Rubiaceae			
Galium odoratum (*Asperula odorata*) (Woodruff)	Coumarins: 13,000 ppm	M	[84]
Uncaria tomentosa (Cat's Claw)	Coumarins	M	[100]
Tiliaceae			
Tilia cordata (Lime tree)	Fraxosides, sculosides	M	[58]
Urticaceae			
Urtica dioica (Nettle)	Scopoletin	M, F	[57, 58]

* M: Medicine, F: Food.

Table 1. Medicinal and food plant uses of some species from major coumarin-containing families.

5. Natural coumarins, non-nutrients presented in the food

Phytochemicals are defined as bioactive non-nutrient plant compounds presented in fruits, vegetables, grains, and other food plants that have been linked to reducing the risk of major chronic diseases. It is estimated that > 5,000 individual phytochemicals have been identified in fruits, vegetables, and grains, but a large percentage still remain unknown and need to be identified before we can fully understand the health benefits of phytochemicals in whole foods [101].

Phenolics are compounds possessing one or more aromatic rings with one or more hydroxy groups, and generally are categorized as phenolic acids, flavonoids, stilbenes, coumarins, and tannins [102]. Phenolics are the products of secondary metabolism in plants, providing

http://dx.doi.org/10.5772/59982

essential functions in the reproduction and the growth of the plants, acting as defense mechanisms against pathogens, parasites, and predators, as well as contributing to the color of plants [103]. In addition to their roles in plants, phenolic compounds in our diet may provide health benefits associated with reduced risk of chronic diseases. Among the 11 common fruits consumed in the United States, cranberry has the highest total phenolic content, followed by apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit [104]. Some of these fruits as important antioxidant and antiproliferative activities [104]. Among the 10 common vegetables consumed in the United States, broccoli possesses the highest total phenolic content, followed by spinach, yellow onion, red pepper, carrot, cabbage, potato, lettuce, celery, and cucumber [105]. Some of these vegetables proved to display interesting antioxidant and antiproliferative activities [105]. It is estimated that flavonoids account for approximately two thirds of the phenolics in our diet and the remaining one third are from phenolic acids [106].

Epidemiological studies have consistently shown that a high dietary intake of fruits and vegetables as well as whole grains is strongly associated with reduced risk of developing chronic diseases, such as cancer and cardiovascular disease [107-109]. Even if it is not so described in the bibliographic sources, most of the food plants, spice plants, and culinary herbs used regionally or worldwide are coumarin-containing plants, thus its effect on health cannot be ignored. For example, the potentially health-promoting role of popular vegetables and spices proved to be derived from *Apiaceae* [110]. Additionally, the above vegetables and spices also contain several bioactive phytochemicals such as flavonoids (quercetin, rutin) and coumarins (bergapten, isopimpinellin, xanthotoxin), which are reported to have curative, preventive, or nutritive value [84]. The above coumarins have also been found to inhibit multiplication of bacteria, fungi, and viruses [111] and demonstrated anti-allergy [112], anti-inflammation [113], and immunosuppression activities [114].

Table 1 also shows the importance of a number of families containing coumarins in human nutrition. Among other species of interest, the *Apiaceae* family is a prominent food source of coumarins: carrots, celery, parsley, coriander, cumin, fennel, and aniseed are present in the culinary practice around the world and in the food industry (fixative) [110]. *Rutaceae* also proved to contain a great number of coumarins with nutritional and economic interest, particularly the c*itrus* and some other fruits such as Bael [115]. Besides fruits and vegetables, olive oil and beverages such as coffee, wine, and black and green tea are also important dietary sources of coumarins [73].

It is also known that essential oils derived from some plants also contain coumarin derivatives and are used as flavoring in foods. Some essential oils such as Chinese cinnamon oil [116], cinnamon bark oil [117], and lavender oil [118] have important amounts of coumarins. Coumarin's aroma has been described as sweet, aromatic, creamy vanilla bean odor with nut-like tones that are heavy, but not sharp or brilliant [119]. A major source in alcoholic beverages is *Hierochloe odorata*, which is used to flavor a special kind of vodka, produced mainly in Eastern Europe [120].

According to Lake (1999), the main source of coumarin in human diet is the cinnamon. Cinnamon comes from the dried bark of *Cinnamomum verum* and *C. cassia*/*C. aromaticum*, and

is considered a spice. Cinnamon is widely used in various cultures in preparation of desserts, cakes, candy, etc., to decorate and some flavoring dishes. It is also used in some places as a beverage or tea. It is also an ingredient in many curries and other dishes Eastern. Intake levels [tolerable daily intake (TDI)] of coumarin derivatives are 0.1 mg/kg bw [121]. For food and beverages in general, the maximum permissible level is 2 mg/kg [122.

It has been estimated that human exposure to coumarins diet is approximately 0.02 mg/kg/day (Lake, 1999). The theoretical maximum daily intake (TAMDI) of coumarin via food was estimated to be 4.085 mg/day (0.07 mg/kg bw/day) [123].

Evidence has suggested that coumarin is not a genotoxic agent [121, 124]. The International Agency for Research on Cancer [125] has classified coumarin as belonging to group 3 (''not classifiable as to its carcinogenicity in humans''). No epidemiological data relevant to the carcinogenicity of coumarin were available and there was only limited evidence in experimental animals for the carcinogenicity of coumarin [125].

The field of food science is of great interest to develop research related to consumer safety and also those designed to elucidate the potentially health-promoting capacity and biological activity of bioactive components that are part of so-called functional foods. However, the beneficial role of these phytocompounds when in synergy on the original food matrix or when isolated (nutraceutics or food supplement) is currently a hot topic [126].

Due to the structural diversity and versatility of applications of coumarins, not only in food sciences (including diet supplements), it is necessary to continue research related to the safety, and also its bioavailability, interactions with other dietary compounds, and therapeutic and environmental components. It is also important to amplify omics techniques, including epigenetic studies.

Different environmental insults can influence epigenetics and nutrition is one of the major factors that contribute to epigenetic regulation of diseases. Particularly, non-communicable diseases phenotypes can be determined by the role of prenatal or early-age nutrition and epi-mutations can have transgenerational effects, while some "epi-nutrients" and food products can also stabilize the genome [127, 128]. Therefore, the role of food-based "epi-bioactive" compounds has become an emerging field. Nutri-epigenomics is part of this new era too, since this approach on research has been carried out on chronic or degenerative diseases [129-133].

Besides micronutrients (folate, selenium, retinoic acid, and vitamins D and E) effects on epigenome, investigations on dietary phytochemicals has been carried out to determine their ability to reverse adverse epigenetic marks, mainly in cancer, for instance: polyphenols (resveratrol, curcumin, catechin, ellagitannin); genistein and soy isoflavones; sulfur-containing compounds (sulforaphane, phenylethyl isothiocyanat, phenylhexyl isothiocyanate, diallyldisulfide, allyl mercaptan) from *Allium* spp. (*Alliaceae*); and cruciferous (*Brassicaceae*) vegetables [129, 133].

Histone modifications are one of the major epigenetic mechanisms and its acetylation is mediated by the interplay of histone acetyltransferases (HATs) and histone deacetylases (HDACs). The class III HDACs, called sirtuins (SIRT), has been shown to deacetylate the

transcription factor p53. Given the regulatory functions of p53 in cell metabolism, inhibition of SIRT1 might contribute to inhibition of glycolysis and inhibit cell proliferation and the apoptosis [129, 133, 134].

Dihydrocoumarin (DHC), which is found in *Melilotus officinalis* (*Fabaceae*) (sweet clover) or synthetized, is commonly added as flavoring agent to food and cosmetics. This compound was studied by Olaharski et al. (2005), on different assays to evaluate it as an "epi-bioactive" agent and resulted that DHC inhibited the deacetylase activities of yeast SIRT2p and human SIRT1. DHC exposure in the human TK6 lymphoblastoid cell line also caused concentration-dependent increases in p53 acetylation, cytotoxicity, and flow cytometric analysis, demonstrating that DHC increased apoptosis more than 3-fold over controls [135].

Authors also stated that these findings on DHC could be potentially worrisome, since SIRT1 inhibition may lead to epigenetic alterations, as well as possible stem cell depletion and early tissue senescence, a phenotype associated with senescence and aging. However, on the possibility of deleterious human exposition to epigenetic toxicants that inhibit SIRT deacetylases, this effect can be desirable in cancer treatment mediated chemopreventive potential epigenetic mechanism [36, 129].

6. Extraction techniques and identification of coumarins

There have been a variety of methods described for extraction of coumarins. Generally, coumarins extraction can be performed either on dry or fresh material, with solvents of different polarities, depending on the type of structure. Some coumarins are sparingly soluble in apolar solvents and often they can be crystallized directly by cooling or concentrating the solvent.

Miranda and Cuéllar (2001), in their book entitled "Farmacognosia y Productos Naturales ", raised the possibility of following four variants using the Soxhlet method:

- Soxhlet extracts the dry powdered material with petroleum ether continuously for 3 days. The ether extract is concentrated until 1/5 of the original volume and it is cooled to obtain the crystallization of the extract. Coumarins are presented in the obtained solid.
- The dry material is removed and sprayed with ethanol, continuously using the Soxhlet for 2–3 days, at least. The extract is concentrated under vacuum to an oily residue. This residue is repeatedly washed with portions of hot water. The aqueous washings are combined and concentrated to the minimum volume, acidifying with hydrochloric acid solution 10%. The mixture is refluxed for 30 minutes. If some precipitate appears, it is filtered (hot filtration) and the solution is allowed to cool. The crystals are collected by filtration and found therein the coumarins.
- Available materials are extracted with ethyl ether or by successive macerations with the Soxhlet apparatus. The extract is concentrated to dryness and the residue contains the coumarins.

- The dried and ground plant material is extracted with acetone continuously in a Soxhlet apparatus, for at least 3 days, and the extract is concentrated to dryness giving a residue that contains the coumarins.

Purification and separation of coumarins contained in various extracts could be performed by using chromatographic columns, using as a carrier aluminum oxide and as solvent the eluotropic series: benzene-hexane (1:2.5); benzene; chloroform; chloroform-acetone, in proportions of a linear gradient to pure acetone [44]. For recognition of the described structures some trials were described, within which there are:

- Those that recognize coumarin's phenolic substitutions where Emerson's Reagent is used, developing color.
- The presence of lactone groups can be observed leading to changes of pH in the medium. When coumarins are dissolved in ethanol, solutions change the color when acidified (yellow color disappears).
- The furan ring can be recognized by using the Erlich test. The extract is treated with a solution of dimethylamino-benzaldehyde (5% ethanol), and then acidified by bubbling gaseous hydrochloric acid. The orange color indicates a positive test.

The last test is commonly used for phytochemical screening that is initially performed in plant research. Carrying on this approach, Payo et al., (1996), from 39 Cuban species screened, detected that 51.2% were positive for coumarin test.

Other extraction methods used in coumarins are: microwave, sonication, and supercritical fluid extraction (SFE) [136], these tests also propose capillary electrophoresis for natural products isolation.

Therefore, on the isolation and analysis of coumarins diverse methods have been used: chromatography (paper chromatography, thin layer chromatography, gas chromatography, and high-performance liquid chromatography), titrimetric, and spectrophotometric (colorimetric and polarographic) methods [1].

Due to coumarin-characteristic chromophore groups and its strong UV absorption at around 300 nm, it is routinely possible to be detected by feasible methods such as ultraviolet–visible spectroscopy (UV–vis) [137]. UV–vis detector is used in high performance liquid chromatography (HPLC) and also other hyphenated techniques are employed to characterize and quantify natural products such as Liquid Chromatography (LC)–Photo Diode Array Detector (PDA), coupling of Mass Spectrometry to LC–[137], or Ultra Performance Liquid Chromatography coupled with Mass Spectrometry (UPLC-MS) [138].

A simple spectroscopic technique [35] and HPLC [85] were employed to determine coumarins in the Brazilian medicinal plant "guaco", *Mikania glomerata* (*Asteraceae*). Coumarin HPLC detection is also used in Cuba to standardize a sedative herbal medicine based on *Justicia pectoralis* (*Acathanceae*) [97, 139].

7. Conclusion

Coumarins have been increasingly attracting special interest as phytochemicals due to their underlying outstanding contributions in the prevention and treatment of diseases. Coumarins represent a diverse class of phytochemicals that are ubiquitous in the human diet. Some of the medicinal usages of extracts of plants containing coumarins have been proven in experimental models, which suggested that the extracts possess various pharmacological actions. Several related researches and developments make coumarins an extremely attractive scaffold. The role of coumarins as important phytochemicals and their interesting applications were presented and discussed in this book chapter. The origin, natural sources, biosynthesis, and applications were also described.

Acknowledgements

The authors thank the partial financial support of University of Santiago de Compostela, University of Camagüey Ignacio Agramonte Loynaz and Galician Plan of research, innovation and growth 2011-2015 (Plan I2C, ED481B 2014/086-0)

Author details

Maria João Matos[1], Lourdes Santana[1], Eugenio Uriarte[1], Orlando A. Abreu[2], Enrique Molina[1,2] and Estela Guardado Yordi[1,2*]

*Address all correspondence to: estela.guardado@reduc.edu.cu

1 Faculty of Pharmacy, University of Santiago de Compostela, Spain

2 Faculty of Chemistry, University of Camaguey Ignacio Agramonte Loynaz, Cuba

References

[1] Venugopala KN, Rashmi V, Odhav B. Review on Natural Coumarin Lead Compounds for Their Pharmacological Activity. BioMed Research International. 2013;2013:1-14. DOI:10.1155/2013/963248.

[2] Borges F, Roleira F, Milhazes N, Santana L, Uriarte E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. Curr Med Chem. 2005;12(8):887-916. DOI:10.2174/0929867053507315.

[3] Borges F, Roleira F, Milhazes N, Uriarte E, Santana L. Simple coumarins: Privileged scaffolds in medicinal chemistry. Front Med Chem Biol Inter. 2009;4:23-85. DOI: 10.2174/978160805207310904010023.

[4] Murray RDH. Naturally occurring plant coumarins. Progress in the Chemistry of Organic Natural Products. 1997;72:1-119. DOI:10.1007/978-3-7091-6527-0_1.

[5] Murray RDH, Mendez J, Brown SA. The natural coumarins occurrence. In Chemistry and Biochemistry. Chichester, UK: John Wiley and Sons; 1982. DOI: 10.1111/1365-3040.ep11611630.

[6] Matos MJ, Vazquez-Rodriguez S, Santana L, Uriarte E, Fuentes-Edfuf C, Santos Y, et al. Looking for new targets: simple coumarins as antibacterial agents. Medicinal chemistry. 2012;8(6):1140-5. DOI:10.2174/1573406411208061140.

[7] Qian L, Han X, Han H, Chen X, Yuan H. Research progress on coumarin and its derivatives. Guangzhou Huagong 2013;41(1):41-3.

[8] Zheng L, Zhao T, Sun L. Research progress of the pharmacological action and pharmacokinetics of coumarins. Shizhen Guoyi Guoyao. 2013;24(3):714-7.

[9] Fais A, Corda M, Era B, Fadda MB, Matos JM, Quezada E, et al. Tyrosinase Inhibitor Activity of Coumarin-Resveratrol Hybrids. Molecules 2009;14(7):2514-20 DOI: 10.3390/molecules14072514.

[10] Matos MJ, Vazquez-Rodriguez S, Santana L, Uriarte E, Fuentes-Edfuf C, Santos Y, et al. Synthesis and structure-activity relationships of novel amino/nitro substituted 3-arylcoumarins as antibacterial agents. Molecules 2013;18(2):1394-404. DOI:10.3390/molecules18021394.

[11] Chen Z. Coumarins In: Rensheng X, Yang Y, Weimin Z, editors. Introduction to Natural Products Chemistry2012. p. 205-24.

[12] Monga Paramjeet K, Sharma D, Dubey A. Comparative study of microwave and conventional synthesis and pharmacological activity of coumarins Journal of Chemical and Pharmaceutical Research. 2012;4(1):822-50.

[13] Bairagi SH, Salaskar PP, Loke SD, Surve NN, Tandel DV, Dusara MD. Medicinal significance of coumarins. International Journal of Pharmaceutical Research. 2012;4(2): 16-9.

[14] Batra N, Batra S, Pareek A, Nagori BP. Diverse pharmacological activities of 3-substituted coumarins: a review. International Research Journal of Pharmacy. 2012;3(7): 24-9.

[15] Wang H, Lu X, Yao H, Feng J, Liu R. Research progress on application of coumarin and its derivatives. Chemical Industry Times. 2009;23(8):40-3.

[16] Bubols GB, Vianna DR, Medina-Remon A, von Poser G, Lamuela-Raventos RM, Eifler-Lima VL, et al. The antioxidant activity of coumarins and flavonoids. Mini-Reviews in Medicinal Chemistry. 2013;13(3):318-34. DOI:10.2174/1389557511313030002.

[17] Matos MJ, Vina D, Vazquez-Rodriguez S, Uriarte E, Santana L. Focusing on new monoamine oxidase inhibitors: differently substituted coumarins as an interesting scaffold. Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) 2012;12(20):2210-39. DOI:10.2174/1568026611212200008.

[18] Kapoor S. The anti-neoplastic effects of coumarin: an emerging concept. Cytotechnology 2013;65(5):787-8. DOI:10.1007/s10616-013-9538-6.

[19] Vazquez-Rodriguez S, Matos MJ, Santana L, Uriarte E, Borges F, Kachler S, et al. Chalcone-based derivatives as new scaffolds for hA3 adenosine receptor antagonists. Journal of Pharmacy and Pharmacology. 2013 65(5):697-703. DOI:10.1111/jphp.12028.

[20] Xia L, Wang Y, Huang W, Qian H. Research advance of anticancer drugs with coumarin structures. Chinese Journal of New Drugs. 2013;22(20):2392-404.

[21] Bansal Y, Sethi P, Bansal G. Coumarin: a potential nucleus for anti-inflammatory molecules. From Medicinal Chemistry Research. 2013;22(7):3049-60. DOI:10.1007/s00044-012-0321-6.

[22] Kontogiorgis C, Detsi A, Hadjipavlou-Litina D. Coumarin-based drugs: a patent review (2008 - present). Expert Opinion on Therapeutic Patents 2012;22(4):437-54. DOI: 10.1517/13543776.2012.678835.

[23] OKennedy R, Thornes RD. Coumarins. Biology, Applications and Mode of Action. New York: John Wiley and Sons; 1997.

[24] Matos MJ, Santana L, Uriarte E, Delogu G, Corda M, Fadda MB, et al. New halogenated phenylcoumarins as tyrosinase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2011;21 (11):3342-5. DOI:10.1016/j.bmcl.2011.04.012.

[25] Song Y, Chen Z, Li H. Advances in coumarin-derived fluorescent chemosensors for metal ions. Current Organic Chemistry. 2012;16(22):2690-707. DOI: 10.2174/138527212804004544

[26] Chen G, Li H, Lan R, Li J. Research progress of coumarin-based fluorescent probes for ions of heavy and transition metals. Huaxue Tongbao. 2013;76(11):1002-10.

[27] Guha S, Dutta M, Das D. Multipurpose applications of coumarin derivatives with special emphasis on the fluorescent probes. Journal of the Indian Chemical Society. 2012;89(12):1603-32. DOI:10.1002/chin.201342230.

[28] Barcellona D, Vannini ML, Fenu L, Balestrieri C, Marongiu F. Warfarin or acenocoumarol: which is better in the management of oral anticoagulants? Thromb Haemost. 2008 100(6):1052-7.

[29] Gomez-Outes A, Suarez-Gea ML, Calvo-Rojas G, Lecumberri R, Rocha E, Pozo-Hernandez C, et al. Discovery of anticoagulant drugs: a historical perspective Current Drug Discovery Technologies. 2012;9(2):83-104. DOI:10.2174/157016381120902008 3.

[30] Schalekamp T, de Boer A. Pharmacogenetics of oral anticoagulant therapy. Curr Pharm Des. 2010;16(17):187-203. DOI:10.2174/138161210790112737.

[31] Daly AK. Optimal dosing of warfarin and other coumarin anticoagulants: the role of genetic polymorphisms. Archives of Toxicology. 2013;87(3):407-20. DOI:10.1007/s00204-013-1013-9.

[32] Milatova E, Milata V. Warfarin - its synthesis and properties in a twenty year retrospective. Ceska a Slovenska Farmacie 2013;62(3):111-9.

[33] Beinema M, Brouwers JR, Schalekamp T, Wilffert B. Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. Thromb Haemost. 1998 80(6): 899-902. DOI:DOI: 10.1160/TH08-04-0116.

[34] Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. Archives of Pharmacal Research. 2013;36(4):375-99. DOI:10.1007/s12272-013-0036-3.

[35] da Silva I, de Moraes M, Vieira L, Corrêa A, Cass Q, Cardoso C. Acetylcholinesterase capillary enzyme reactor for screening and characterization of selective inhibitors. J Pharm Biomed Anal 2013;73:44-52. DOI:doi:10.1016/j.jpba.2012.01.026.

[36] Huang L, Su T, Li X. Natural Products as Sources of New Lead Compounds for the Treatment of Alzheimer's Disease. Current topics in medicinal chemistry. 2013;13(15):1864-78. DOI:10.2174/15680266113139990142 .

[37] Patil PO, Bari SB, Firke SD, Deshmukh PK, Donda ST, Patil DAF, (),. A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters. 2013;21(9):2434-50. DOI:10.1016/j.bmc.2013.02.017.

[38] Zhou X, Wang X, Wang T, Kong L. Design, synthesis, and acetylcholinesterase inhibitory activity of novel coumarin analogues. Bioorganic & Medicinal Chemistry. 2008;16:8011-21. DOI:10.1016/j.bmc.2008.07.068.

[39] Anand P, Singh B, Singh N. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters. 2012;20(3): 1175-80. DOI:doi:10.1016/j.bmc.2011.12.042.

[40] Helguera AM, Perez-Machado G, Cordeiro MNDS, Borges F. Discovery of MAO-B inhibitors - present status and future directions part I: oxygen heterocycles and analogs. Mini-Reviews in Medicinal Chemistry. 2012;12(10):907-19. DOI: 10.2174/138955712802762301.

[41] Matos MJ, Santana L, Uriarte E, Serra S, Corda M, Fadda MB, et al. Tyrosine-like condensed derivatives as tyrosinase inhibitors. Journal of Pharmacy and Pharmacology. 2012 64(5):742-6. DOI:10.1111/j.2042-7158.2012.01467.x.

[42] Peng XM, Damu GLV, Zhou CH. Current developments of coumarin compounds in medicinal chemistry. Current Pharmaceutical Design. 2013;19(21):3884-930. DOI: 10.2174/1381612811319210013.

[43] Keating GJ, O'Kennedy R. The chemistry and occurrence of coumarins. O'Kennedy RTRD, editor. England: John Wiley & Sons West Sussex; 1997.

[44] Miranda M, Cuellar A. Farmacognosia y productos naturales. La Habana: Félix Varela; 2001.

[45] de Lira SP, Seleghim MHR, Williams DE, Marion F, Hamill P, Jean F, et al. A SARS-coronovirus 3CL protease inhibitor isolated from the marine sponge Axinella cf. corrugata: structure elucidation and synthesis. J Braz Chem Soc. 2007;18 (2). DOI: 10.1590/S0103-50532007000200030.

[46] Dewick PM. Medicinal Natural Products: A Biosynthetic Approach. 2a ed. England: John Wiley & Sons Ltd; 2002. DOI:10.1002/0470846275.

[47] Cai Y, Sun M, Xing J, Luo Q, Corke H. Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. Life Sci. 2006;78:2872-88. DOI:doi:10.1016/j.lfs.2005.11.004.

[48] Hoult J, Paya M. Pharmacological and biochemical actions of simple coumarins: natural products with therapeutic potential. General Pharmacology. 1996;27(4):713-22. DOI:10.1016/0306-3623(95)02112-4.

[49] Iranshahi M, Askari M, Sahebkar A, Hadjipavlou-Litina D. Evaluation of antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the prenylated coumarin umbelliprenin. DARU. 2009;17(2):99-103.

[50] Ribeiro CV, Kaplan MA. Tendências evolutivas de famílias produtoras de cumarinas em *angiospermae*. Quim Nova. 2002;25(4):533-8.

[51] Sakuma S, Yamashita S, Hiwatari K, Hoffman R, Pham W. Lectin-immobilized fluorescent nanospheres for targeting to colorectal cancer from a physicochemical perspective. Current Drug Discovery Technologies. 2011 8(4):367-78. DOI: 10.2174/157016311798109407.

[52] Zurita G, Briones M, Uraga E. Fotoquimioterapia en psoriasis: comparación de dos esquemas terapéuticos metotrexato más UVB vs. Puvaterapia. Revista Peruana de Dermatología. 2002;12(2).

[53] Bruneton J. Pharmacognosie -Phytochimie Plantes Médicinales. Tecnique et Documentation. 2e ed. Paris Lavoisier; 1993.

[54] Kontogiorgis C, Hadjipavlou-Litina DJ. Biological Evaluation of Several Coumarin Derivatives Designed as Possible Anti-inflammatory/Antioxidant Agents. Journal of

Enzyme Inhibition and Medicinal Chemistry. 2003;18(1):63-9. DOI: 10.1080/1475636031000069291.

[55] Correa PM. Diciona´rio de plantas u´ teis do Brasil e das exoticas cultivadas. Brazil: Ministério da Agricultura, Instituto Brasileiro de Desenvolvimento, Florestal; 1984.

[56] Lemmens RHMJ, Bunyapraphastara N. Plant resourses of South-East Asia. In: Lemmens RHMJ, Bunyapraphastara N, editors. Medicinal and poisonous plant. Leiden (Holanda): Backhuys; 2003.

[57] Newall C, Anderson L, Phillipson J. Herbal medicines. Aguide for health-care professionals. London: The pharmaceutical Press; 1996.

[58] Peris JB, Stübing G, Vanaclocha B. Fitoterapia aplicada. edicion r, editor. Valencia MICOF; 1995.

[59] Fuentes V, Exposito A. Las enecuestas botanicas sobre plantas medicinales en Cuba. Revista del Jardin Botanico Nacional. 1995;26:77-145.

[60] Robineau L. Famacopea vegetal caribeña. Martinique. F,W.I.: Ediciones Emile Désormeaux; 1997.

[61] Leal LKAM, Ferreira AAG, Bezerra GA, Matos FJA, Viana GSB. Anticonceptive, anti-inflammatory and bronchodilator activities of Brazilian medicinal plants containing coumarin: a comparative study. Journal of Ethnopharmacology. 2000;70 (2):151-9. DOI:10.1016/S0378-8741(99)00165-8.

[62] Kostova I. Synthetic and natural coumarins as cytotoxic agents. Current Medicinal Chemistry - Anti-Cancer Agents. 2005;5(1):29-46. DOI:10.2174/1568011053352550.

[63] Kostova I. Coumarins as Inhibitors of HIV Reverse Transcriptase. Current HIV Research. 2006;4(3):347-63. DOI:10.2174/157016206777709393.

[64] Kostova I. Studying plant derived coumarins for their pharmacological and therapeutic properties as potential anticancer drugs. Expert Opin Drug Discov. 2007;2(12): 1605-18. DOI:10.1517/17460441.2.12.1605.

[65] Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Nicolaides DN. Natural and synthetic coumarin derivatives with anti-inflammatory/antioxidant activities. Current Pharmaceutical Design. 2004;10(30):3813-33. DOI:10.2174/1381612043382710.

[66] Galvano F, Piva A, Ritieni A, Galvano G. Dietary strategies to counteract the effects of mycotoxins: A review. Journal of food protection. 2001;64(1):120-31.

[67] Hayes JD, Pulford DJ, Ellis EM, McLeod R, James RF, Seidegard J, et al. Regulation of rat glutathione S-transferase A5 by cancer chemopreventive agents: mechanisms of inducible resistance to aflatoxin B1. Chemico-Biological Interactions. 1998;111-112:51-67. DOI:10.1016/S0009-2797(97)00151-8.

[68] Kostova I, Mojzis J. Biologically active coumarins as inhibitors of HIV-1 (RT, IN and PR). Fut HIV Ther. 2007;1(3):315-29. DOI:10.2217/17469600.1.3.315.

[69] Rietjens IM, Martena MJ, Boersma MG, Spiegelenberg W, Alink GM. Molecular mechanisms of toxicity of important food-borne phytotoxins. Molecular Nutrition & Food Research. 2005;49(2):131-58. DOI:10.1002/mnfr.200400078.

[70] Riveiro ME, De Kimpe N, Moglioni A, Vazquez R, Monczor F, Shayo C, et al. Coumarins: Old Compounds with Novel Promising Therapeutic Perspectives. Curr Med Chem - Anti-Cancer Agents. 2010;17(13):1325-38. DOI:10.2174/092986710790936284.

[71] Gasparotto A, Brenzan M, Piloto I, García-Cortez D, Nakamura C, Dias-Filho V, et al. Estudo fitoquímico e avaliação da atividade moluscicida do Calophyllum brasiliense Camb (Clusiaceae). Quím Nova. 2005;28 (4):575-8. DOI:10.1590/S0100-40422005000400003.

[72] Rizk ET, Hassan SMM. Molluscicidal activity of furanocoumarins isolated from Ammi majus against Biomphalaria alexandrina snails. Egyptian Journal of Pharmaceutical Sciences. 2000;40(1):61-71.

[73] Sonnenberg H, Kaloga M, Eisenbach N, Fromming KK. Isolation and characterization of an angular-type dihydropyranocoumaringlycoside from the fruits of Ammi visnaga (L) Lam (Apiaceae). Zeitschrift für Naturforschung C. 1995;50(9-10):729-31. DOI:10.1515/znc-1995-9-1021.

[74] Shan B, Cai YZ, Sun M, Corke H. Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. J Agric Food Chem 2005;53(20):7749-59. DOI:10.1021/jf051513y.

[75] Ahmad MZ, Ali M, Mir SR. New sester- and triterpenic coumarin ethers from the roots of Aegle marmelos (L.) Corr. Journal of Natural Product and Plant Resources 2012;2(6):636-43.

[76] Ahmad MZ, Ali M, Mir SR. New sesqui- and diterpenic coumarin ethers from the roots of Aegle marmelos (L.) Corr. Natural Products Journal. 2012;2(4):252-8. DOI: 10.2174/2210315511202040252.

[77] Mustahil NA, Riyanto S, Sukari MA, Rahmani M, Mohd nor SM, Ali AM. Antileukemic activity of extracts and constituents of Aegle marmelos. Research Journal of Chemistry and Environment. 2013;17(1):62-7.

[78] Setzer WN, Setzer MC, Schmidt JM, Moriarity DM, Vogler B, Reeb S, et al. Cytotoxic components from the bark of Stauranthus perforatus from Monteverde, Costa Rica. Planta Medica. 2000;66(5):493-4. DOI:10.1055/s-2000-8595.

[79] Ramesh B, Pugalendi KV. Antihyperlipidemic and antidiabetic effects of Umbelliferone in streptozotocin diabetic rats. The Yale journal of biology and medicine. 2005;78(4):189-96.

[80] Yoo SW, Kim JS, Kang SS, Son KH, Chang HW, Kim HP, et al. Constituents of the fruits and leaves of Euodia daniellii. Arch Pharm Res (Korea). 2002;25(6):824-30. DOI: 10.1007/BF02976999.

[81] Karunai Raj M, Balachandran C, Duraipandiyan V, Agastian P, Ignacimuthu S. Antimicrobial activity of Ulopterol isolated from Toddalia asiatica (L.) Lam.: A traditional medicinal plant. Journal of Ethnopharmacology. 2012;140 (1):161- 5. DOI:10.1016/j.jep.2012.01.005.

[82] Ross SA, Sultana GN, Burandt CL, El Sohly MA, Marais JP, Ferreira DJ. Syncarpamide, a New Antiplasmodial (+)-Norepinephrine Derivative from Zanthoxylum syncarpum. Journal of Natural Products. 2004;67(1):88-90. DOI:10.1021/np030417t.

[83] Ming LC. Ageratum conyzoides: A tropical source of medicinal and agricultural products. In: Janick J, editor. Perspectives on new crops and new uses. Alexandria, VA.: ASHS Press; 1999. p. 469-73.

[84] Duke JA. Handbook of phytochemical constituents of GRAS herbs and other economic plants. Boca Raton, FL: CRC Press; 2000.

[85] Radünz LL, Melo EC, Barbosa LCA, Rocha RP, Berbert PA. Rendimento extrativo de cumarina de folhas de guaco (Mikania glomerata Sprengel) submetidas a diferentes temperaturas de secagem. Rev bras plantas med. 2012;14 (3):453-7.

[86] Ohkoshi E, Makino M, Fujimoto Y. Studies on the constituents of Mikania hirsutissima (Compositae). Chemical & Pharmaceutical Bulletin. 1999;47(10):1436-8. DOI: 10.1248/cpb.47.1436.

[87] Lo WL, Chang FR, Liaw CC, Wu YC. Cytotoxic coumaronochromones from the roots of Euchresta formosana. Planta Medica. 2002;68(2):146-51. DOI:10.1055/s-2002-20248.

[88] Uchiyama T, Hara S, Makino M, Fujimoto Y. seco-Adianane-type triterpenoids from Dorstenia brasiliensis (Moraceae). Phytochemistry. 2002;60(8):761-4. DOI:10.1016/S0031-9422(02)00180-2.

[89] Oh H, Ko EK, Jun JY, Oh MH, Park SU, Kang KH, et al. Hepatoprotective and free radical scavenging activities of prenylflavonoids, coumarin, and stilbene from Morus alba. Planta Medica. 2002;68(10):932. DOI:10.1055/s-2002-34930.

[90] Ross IA. Olea europaea L. In: A. RI, editor. Medicinal Plants of the World, Volume 3 Chemical Constituents, Traditional and Modern Medicinal Uses. TotowaNJ: Humana Press Inc; 2005. p. 273-400. DOI:10.1007/978-1-59259-887-8.

[91] Liang S, Shen Y-H, Tian J-M, Wu Z-J, Jin H-Z, Zhang W-D, et al. Three New Dicoumarins from Daphne feddei. HCA. 2009;92(1):133-8. DOI:10.1002/hlca.200800232.

[92] Cottiglia F, Loy G, Garau D, Floris C, Casu M, Pompei R, et al. Antimicrobial evaluation of coumarins and flavonoids from the stems of Daphne gnidium L. Phytomedicine. 2001;8(4):302-5.

[93] Yao L, Wang T, Wang H. Effect of soy skim from soybean aqueous processing on the performance of corn ethanol fermentation. Bioresource Technology. 2011;102(19): 9199-205. DOI:10.1016/j.biortech.2011.06.071.

[94] Riaz M, Malik A. Novel Coumarin Glycosides from Daphne oleoides. HCA 2001;84(3):656-61. DOI:10.1002/1522-2675(20010321)84:3<656::AID-HLCA656>3.0.CO; 2-D.

[95] Yesilada E, Taninaka H, Takaishi Y, Honda G, Sezik E, Momota H, et al. In vitro inhibitory effects of Daphne oleoides ssp. oleoides on inflammatory cytokines and activity-guided isolation of active constituents. Cytokine. 2001;13(6):359-64. DOI: 10.1006/cyto.2001.0838.

[96] Du J-L, Xu W-Z, Cheng X-R, Jin H-Z. A new coumarin from Daphne pedunculata. Journal Chemistry of Natural Compounds. 2013;49(3):426-7. DOI:10.1007/ s10600-013-0629-6.

[97] Rodríguez JE, López OD, Gil JM. Método para la cuantificación de cumarina en extracto seco a partir de extractos de Justicia pectoralis Jacq. Revista Cubana de Plantas Medicinales. 2008;13(3).

[98] Oliveira M, Lemos L, de Oliveira R, Dall 'Oglio E, de Sousa Júnior P, de Oliveira Martins D. Evaluation of toxicity of Calophyllum brasiliense stem bark extract by in vivo and in vitro assays. Journal of Ethnopharmacology. 2014 155(1):30-8. DOI: 10.1016/j.jep.2014.06.019.

[99] Hernández E, Batista A, Portuondo D, Tamayo V, Mora N, H. MJ, et al. Immunorestorative in immunosuppressed Balb/c mice and cytotoxic activity of water extract from Trichilia hirta root. BLACPMA 2010;9(6):457-64

[100] Puhan M, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendli O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. BMJ. 2006;332:266-70. DOI:10.1136/bmj.38705.470590.55.

[101] Liu RH. Health benefits of fruits and vegetables are from additive and synergistic combination of phytochemicals. Am J Clin Nutr. 2003;78(3):517S-20S.

[102] Spencer J, Abd el Mohsen M, Minihane A, Mathers J. Biomarkers of the intake of dietary polyphenols: strengths, limitations and application in nutrition research.. British Journal of Nutrition. 2008;99(01):12-22. DOI:10.1017/S0007114507798938.

[103] Bravo L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev. 1998;56:317-33. DOI:10.1111/j.1753-4887.1998.tb01670.x.

[104] Sun J, Chu Y-F, Wu X, Liu RH. Antioxidant and antiproliferative activities of fruits. J Agric Food Chem. 2002;50:7449-54.

[105] Chu Y-F, Sun J, Wu X, Liu RH. Antioxidant and antiproliferative activities of vegetables. J Agric Food Chem. 2002;50(23):6910-6. DOI:10.1021/jf020665f.

[106] Tapiero H, Tew K, Ba G, Mathe G. Polyphenols: do they play a role in the prevention of human pathologies? Biomed Pharmacother. 2002;56(4):200-7. DOI:10.1016/S0753-3322(02)00178-6.

[107] Temple NJ. Antioxidants and disease: more questions than answers. Nutrition Research. 2000;20(3):449-59. DOI:10.1016/S0271-5317(00)00138-X.

[108] Willett WC. Diet and health: what should we eat. Science 1994;264(5158):532-7. DOI: 10.1126/science.8160011.

[109] Willett WC. Balancing life-style and genomics research for disease prevention. Science 2002;296(5568):695-8. DOI:10.1126/science.1071055.

[110] Jaw-Ming Cherng Q, Wen Chiang A, Lien-Chai Chiang B. Immunomodulatory activities of common vegetables and spices of Umbelliferae and its related coumarins and flavonoids. Food Chemistry. 2008;106 (3):944-50. DOI:10.1016/j.foodchem.2007.07.005.

[111] Hudson JB, Graham EA, Harris L, Ashwood-Smith MJ. The unusual UVA-dependent antiviral properties of the furoisocoumarin, coriandrin. Photochemistry & Photobiology. 1993;57(3):491-6. DOI:10.1111/j.1751-1097.1993.tb02324.x.

[112] Kimura Y, Okuda H. Histamine-release effectors from Angelica dahurica var. dahurica root. Journal of Natural Products. 1997;60(3):249-51. DOI:10.1021/np960407a.

[113] Chen YF, Tsai HY, Wu TS. Anti-inflammatory and analgesic activities from roots of Angelica pubescens. Planta Medica. 1995;61(1):2-8. DOI:10.1055/s-2006-957987.

[114] Kuzel TM, Roenigk HH, Samuelson E, Rosen ST. Suppression of anti-interferon alpha-2a antibody formation in patients with mycosis fungoides by exposure to longwave UV radiation in the A range and methosalen ingestion. Journal of the National Cancer Institute. 1992;84(2):119-21. DOI:10.1093/jnci/84.2.119

[115] Evans WC. Trease and Evans Pharmacognosy. 16th edition ed: Elsevier Ltd.; 2009.

[116] Choi J, Lee KT, Ka H, Jung T, Jung HJ, Park HJ. Constituents of the essential oil of the Cinnamomum cassia stem bark and the biological properties. Archives of Pharmacal Research. 2001;24(5):418-23. DOI:DOI: 10.1007/BF02975187.

[117] Bourgaud F, Hehn A, Larbat R. Biosynthesis of coumarins in plants: a major pathway still to be unravelled for cytochrome P450 enzymes. Phytochemistry Reviews. 2006;5(2-3):293-308. DOI:10.1007/s11101-006-9040-2.

[118] Rosselli S, Maggio AM, Faraone N. The cytotoxic properties of natural coumarins isolated from roots of Ferulago campestris (Apiaceae) and of synthetic ester derivatives of aegelinol. Natural Product Communications. 2009;4(12):1701-6.

[119] Clark GS. Coumarin. An aroma chemical profile. Perfumer & Flavorist,. 1995;20:23-34.

[120] Nykanen I, editor. The volatile compounds of Hierochloe odorata. Proceedings of the alko symposium on flavour research of alcoholic beverages; 1984 Helsinki, Finland: Foundation for Biotechnical and Industrial Fermentation Research.

[121] Lake BG. Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment. Food and Chemical Toxicology. 1999;37(4):423-53. DOI:10.1016/S0278-6915(99)00010-1.

[122] European Council. Council Directive of 22 June 1988 on the approximation of the laws of the member states relating toflavourings for use in foodstuffs and to source materials for their production. In: Communities OJotE, editor.1988.

[123] AFC. Opinion of the scientific panel on food additives, flavour-ings, processing aids and materials in contact with food (AFC) on a request from the Commission related to Coumarin. EFSA Journal. 2004;104:1-36. DOI:10.2903/j.efsa.2004.104.

[124] Beamand JA, Barton PT, Price RJ, G. LB. Lack of effect of coumarin on unscheduled DNA synthesis in precision-cut human liver slices. Food Chem Toxicol. 1998 36(8): 647-53. DOI:doi:10.1016/S0278-6915(98)00025-8.

[125] IARC. Coumarin. IARC monographs on the evaluation of carcinogenic risks to humans Some Industrial Chemicals. Lyon, France: International Agency for Research on Cancer; 2000. p. 193-226.

[126] Liu RH. Potential Synergy of Phytochemicals in Cancer Prevention: Mechanism of Action. J Nutr. 2004;134(12 Suppl):3479S-85S.

[127] Godfrey KM, Lillycrop KA, Hanson MA, Burdge GC. Epigenetic Mechanisms in the Developmental Origins of Adult Disease. In: H.I. R, R.O.C. O, F. B, editors. Epigenetic Aspects of Chronic Diseases. London Springer London; 2011. p. 187-204 DOI: 10.1007/978-1-84882-644-1_13.

[128] Mazzio EA, Soliman KFA. Epigenetics and Nutritional Environmental Signals. Integrative and Comparative Biology. 2014;54(1):21-30. DOI:10.1093/icb/icu049.

[129] Gerhäuser C. Cancer cell metabolism, epigenetics and the potential influence of dietary components - A perspective. Biomedical Research. 2012;23(1):1-21.

[130] Kontogiorgis CA, Bompou E-M, Ntella M, Berghe W. Natural Products from Mediterranean Diet: From Anti-Inflammatory Agents to Dietary Epigenetic Modulators. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry. 2010;9(2):101-24. DOI:10.2174/187152310791110652.

[131] Milenkovic D, Vanden Berghe UGent W, Boby C, Leroux C, Declerck K, Szarc vel Szic K, et al. Dietary flavanols modulate the transcription of genes associated with cardiovascular pathology without changes in their DNA methylation state. PLOS ONE. 2014;9(4):e95527. DOI:10.1371/journal.pone.0095527.

[132] Schnekenburgera M, Dicatoa M, Diederich M. Plant-derived epigenetic modulators for cancer treatment and prevention. Biotechnology Advances. 2014;32(6):1123-32. DOI:10.1016/j.biotechadv.2014.03.009.

[133] Vanden Berghe W. Epigenetic impact of dietary polyphenols in cancer chemoprevention: Lifelong remodeling of our epigenomes. Pharmacological Research 2012;65(6): 565-76. DOI:10.1016/j.phrs.2012.03.007.

[134] Maulik N, Gautam M. Nutrition, epigenetic mechanisms, and human disease. Boca Raton, FL: CRC Press Taylor & Francis Group; 2011.

[135] Olaharski A, Rine J, Marshall BL, Babiarz J, Zhang L, Verdin E, et al. The Flavoring Agent Dihydrocoumarin Reverses Epigenetic Silencing and Inhibits Sirtuin Deacetylases. PLoS Genet. 2005;1(6):e77. DOI:10.1371/journal.pgen.0010077.

[136] Delazar A, Nahar L, Hamedeyazdan S, Sarker SD. Microwave-Assisted Extraction in Natural Products Isolation. In: Sarker S, Nahar L, editors. Natural Products Isolation, Methods in Molecular Biology. LLC: Springer Science+Business Media; 2012. p. 103-4. DOI:10.1007/978-1-61779-624-1.

[137] Sarker DS, Nahar L. An Introduction to Natural Products Isolation. In: Sarker DS, Nahar L, editors. Natural Products Isolation, Methods in Molecular Biology: Humana Press; 2012. p. 1-25. DOI:10.1007/978-1-61779-624-1.

[138] Dugrand A, Alexandre O, Thibault D, Alain H, Yann F, Bourgaud F. Coumarin and Furanocoumarin Quantitation in Citrus Peel via Ultraperformance Liquid Chromatography Coupled with Mass Spectrometry (UPLC-MS). Journal of Agricultural and Food Chemistry. 2013;61(45):10677–84. DOI:10.1021/jf402763t.

[139] Rodríguez JE, López OD, Núñez Y, Rodríguez C, Nogueira A. Obtención de extractos secos a partir de extractos acuosos de Justicia pectoralis (tilo). Revista Cubana de Plantas Medicinales. 2013;18(4).