Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS

J. Serb. Chem. Soc. 85 (5) 575–600 (2020)
JSCS–5323

Review

REVIEW

Furofuran lignans of *Artemisia* genus: Isolation, biosynthesis and biological activity

JOVANA D. ICKOVSKI, JOVANA LJ. PAVLOVIĆ, MILAN N. MITIĆ, IVAN R. PALIĆ, DANIJELA A. KOSTIĆ, GORAN M. PETROVIĆ and GORDANA S. STOJANOVIĆ*#

Department of Chemistry, Faculty of Science and Mathematics, Višegradska 33, 18000 Niš, Serbia

(Received 10 December 2019, revised 20 January, accepted 31 January 2020)

Abstract: Since ancient times, medicinal plants and pharmacologically active products obtained from different natural sources play an important role in human health. Plants belonging to the genus *Artemisia* possess a great biological potential and it is a well-studied genus in the fields such as systematics (including molecular phylogenetics) and genome organization. Many species of the genus (*e.g.*, *A. absinthium*, *A. annua*, *A. vulgaris*, *A. abrotanum*, *A. arborescens*) are widely exploited, because of their high economic value as medicines, food and ornamentals. Withal, in such a large genus, some hiatus must inevitably exist, concerning attainments and potentials that individual species possess. Most of the studies are focused on bioactivity and pharmacology of sesquiterpene lactones. Lignans are unjustly neglected, even though they as well exhibit a wide range of bioactivities. Motivated by that fact, we tried to consolidate findings on bioactive lignans accumulated through the years, with the logical perspectives on further work on isolation and identification of new bioactive lignans and the exploitation of lignans as substances of potential pharmacological interest.

Keywords: *artemisia*; lignan; sesamin; sesartemin; diayangambin; epiyangambin.

CONTENTS

* Corresponding author. E-mail: gocast@pmf.ni.ac.rs
https://doi.org/10.2298/JSC191210009I

1. INTRODUCTION

1.1. Genus Artemisia *L.: An overview*

The genus *Artemisia* L. is the largest of subtribe Artemisiinae Less. and tribe Anthemideae Cass., and one of the largest and most widely distributed genera of the family Asteraceae, which has been divided into four subgenera (*Artemisia*, *Absinthium*, *Dracunculus* and *Seriphidium*),[1–4] whose number is increased with the proposal of another subgenus endemic to North America (*Tridentatae*).[5] It is a heterogenous genus that comprises around 600 species at specific and subspecific levels, present in all continents but Antarctica, mostly distributed in the Northern Hemisphere (temperate zones of Europe, Asia and North America), with no more than 25 species in the Southern Hemisphere.[1] In addition to the widespread distribution and a large representation of species within the genus *Artemisia*, the occurrence of the endemic species in certain areas is quite high. Some examples are the whole subgenus *Tridentatae* (Rydb.) McArthur in the western United States of America, where some of its species dominate landscapes, *A. afra* Jacq. in South Africa, *A. argentea* L'Hér. in Madeira, *A. canariensis* Less. (*A. thuscula* Cav.) in the Canary Islands, *A. gorgonum* Webb. in Hook in Cape Verde, *A. granatensis* Boiss. in the Spanish Sierra Nevada, *A. magellanica* Sch. Bip. in Argentina, *A. mauiensis* Skottsb. in Hawaii (USA), *A. melanolepis* in the Iranian mount Damavand, *A. molinieri* Quézel, Barbero & R. Loisel in only two locations in south-east France and *A. negrei* Ouyahya in Morocco.[1] Withal the genus has been the object of numerous systematic, including molecular phylogenetics[4–11] and taxonomic studies.[12,13] The genus has also been thoroughly studied from the phytochemical,[14–18] pharmacological[19–22] and biotechnological point of view.[23–29] Many of *Artemisia* species have been frequently utilized for many various purposes such as medicines (*A. cina*, *A. santonica* L., *A. maritime*, *A. herba-alba*, *A. pallens* Wallich ex Besser, *A. afra*, *A. ludoviciana* Nutt. for their antihelminic activity and *A. annua*, *A. apiacea.* Hance, *A. lancea* Vaniot, *A. afra*, *A. abrotanum* for their antimalarial activities),[30–36] food (edible plants, condiments and ingredients of beverages: *A. absinthium*, *A. dracunculus*, *A. genipi* and related species and *A. vulgaris*)[1,37,38] and ornaments (*A. arborescens* and *A. vulgaris*).[39–41]

An intensive investigation of the phytochemicals of the genus *Artemisia* reveals that the *Artemisia* species comprise mainly terpenoids, flavonoids, coumarins, caffeoylquinic acids, sterols and acetylenes.[42–50] The literature review revealed that most of the attention was paid to bioactive constituents of the essential oils, with a major focus on sesquiterpene lactones with potential pharmacological and medicinal activity.[51–55] Despite the vast number of phytochemical compo-

sition related studies of species belonging to genus *Artemisia*, majority of them are still based on the investigation of sesquiterpene lactones, as a consequence of their pharmacological activity.[14,56–60] Artemisinin, a cadinane-type sesquiterpene lactone with a 4,6-endoperoxide function, is an antimalarial drug derived from *A. annua* L.[61] Santonin, a sesquiterpene lactone, isolated from various Asian species of *Artemisia* genus, especially *A. china* and *A. maritima*, is responsible for antihelmintic activity.[62] Arglabin, a guaianolide type of sesquiterpene lactone, isolated from *A. glabella* Kar. et Kir. and *A. myriantha*, shows promising antitumor activity against different tumor cell lines.[63]

On the other side, lignans are still insufficiently explored. These compounds are found in diverse species of the plant kingdom, including members of pteridophytes, gymnosperms and angiosperms.[64] Although lignans exhibit a wide variety of bioactivities on plants, insects and mammals,[65–69] they are of especial interest due to the unique antitumor-associated activities[70–74] and reduction of lifestyle-related diseases (anti-inflammatory, immunosuppression, cardiovascular and antioxidant).[75–79]

The plant lignans most commonly distributed in foods are lariciresinol, mataairesinol, pinoresinol and secoisolariciresinol. Several other lignans are present in some foods, including medioresinol (in sesame seeds, rye and lemons), syringaresinol (in grains), sesamin and the lignan precursor sesamolin (in sesame seeds).[80–82] The amount of lignans in food is generally low, with the exceptions of flaxseed and sesame seeds, which have a lignan content a hundred times higher than other dietary sources.[82,83] The specific distribution and the low amount of production in plants, some of which are endangered species, restrain the efficient and stable production of beneficial lignans.[84] Therewithal, plant sources of lignans are frequently limited because of the high cost of plant collection, poor cultivation systems and long growth phase.[85–89] An exhaustive literature survey on phytochemical reports of the genus *Artemisia* reveals that the *Artemisia* species comprises mainly furofuran lignans (2,6-diarylfurofurans).[90–98]

1.2. Lignans

Lignans represent a large group of naturally occurring phenolic compounds, widely distributed within the plant kingdom. The term lignan originated from Haworth,[99] to describe a group of secondary plant metabolites, which molecular backbone consists of two phenylpropanoid (C6-C3) units. Lignans are phenylpropane dimers linked *via* β-β′ (8-8′) carbon atoms, with a different degree of oxidation in the side-chain and a different substitution pattern in the aromatic moieties.[100] The lignans are bioactive, non-nutrient, non-caloric phenolic plant compounds, and they should not be confused with lignins.[82] Lignans are stereospecific dimers of monolignols, coniferyl or cinnamyl alcohol, while lignins are racemic polymers built from the hydroxycinnamic alcohols, coniferyl alcohol and

sinapyl alcohol, with minor amounts of *p*-coumaryl alcohol.[82,101–103] Based on the type of carbon skeleton, cyclization pattern and the way in which oxygen is incorporated in the molecule, lignans are classified into six subgroups: dibenzylbutanes, dibenzylbutyrolactones, arylnaphthalenes, dibenzocyclooctadienes, substituted tetrahydrofurans and 2,6-diarylfurofurans.[100] In addition, these lignans can be further classified into three categories depending on the oxidation state of the C9(C9′) positions, which are located at the terminal of the propyl side chain: lignans with 9(9′)-oxygen, lignans without 9(9′)-oxygen and dicarboxylic acid lignans (Fig. 1).

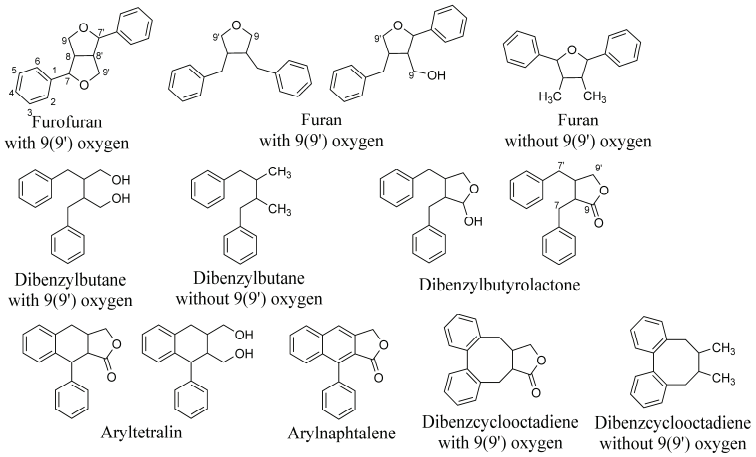


Fig. 1. Lignans classification based on the type of carbon skeleton, cyclization pattern and oxidation state of the C9(C9′) positions.

Apart from the fact that lignans are structurally diverse, they show substantial diversity in the terms of enantiomeric composition.[104] Naturally occurring lignans have been found to exist exclusively as one enantiomer, or as enantiomeric mixtures with various enantiomeric compositions. The enantiomeric composition of the plant lignans in trees and medicinal herbs and shrubs is commonly known, and usually only one of the enantiomers occurs in a certain species.[105–107]

1.3. Lignans of Artemisia *genus*

Lignans are a large and diverse class of natural products composing of phenylpropanoid dimers in which C6-C3 units are linked by the central carbon of their propyl side chains. The furofuran lignans represent one of the major subclasses of the lignan family. Due to their structural diversity and broad bioactivities, natural furofuran lignans have attracted increasing research attention. As previously mentioned, a literature survey on the type of lignans in members of the genus *Artemisia* revealed that furofuran lignans are characteristic for *Artemisia* species (lignan's profile mainly consists of furofuran lignans). Furofuran lignans have been

found throughout the plants from roots, stems, leaves, bulbs, barks to seeds. Research progress on the naturally occurring furofuran lignans within the plant species of *Artemisia* genus reported in the literature (chemical structures, names, corresponding sources and references) is summarized in Fig. 2. and Table I.

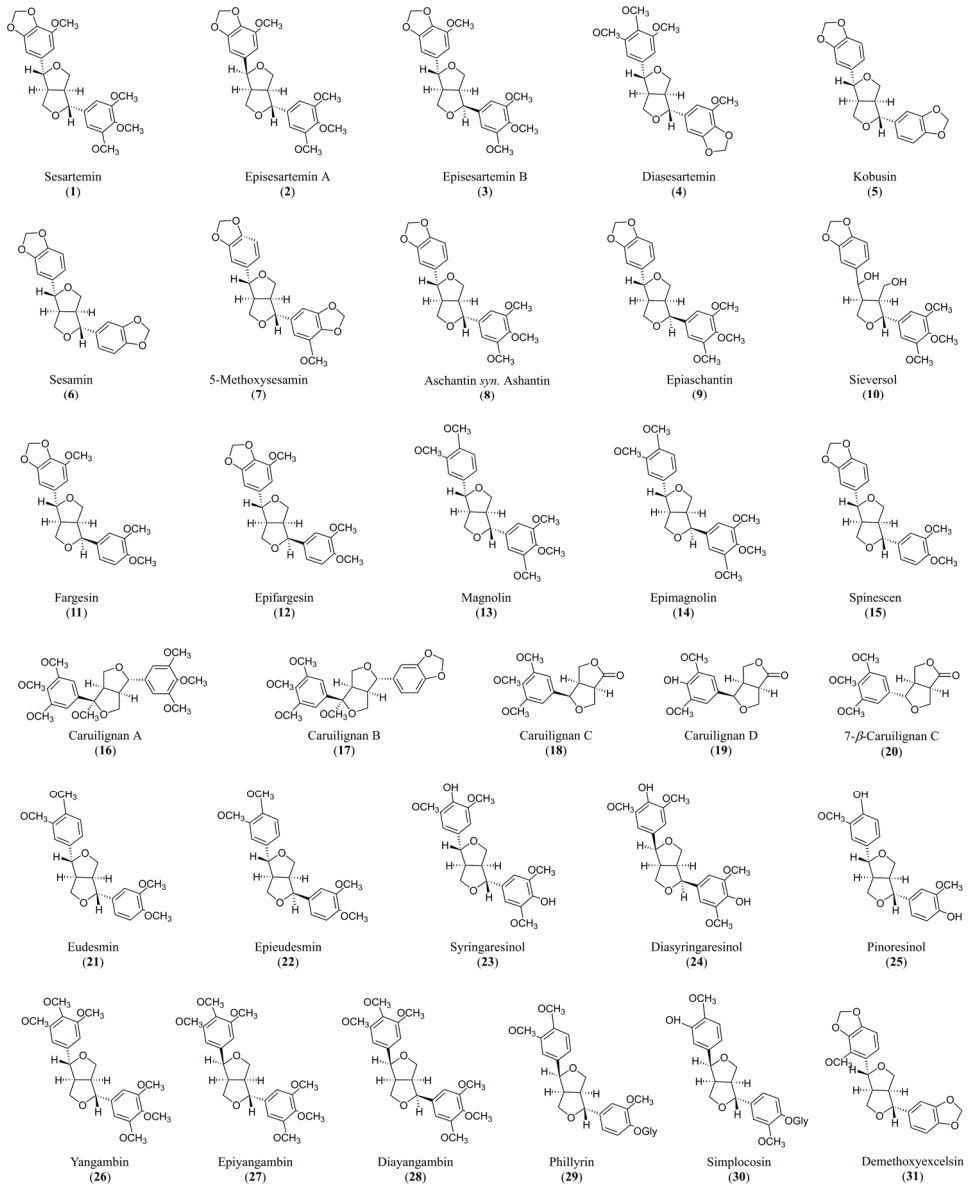


Fig. 2. Structures of lignans isolated form *Artemisia* species.

TABLE I. The lignans isolated from *Artemisia* species

Plant	Plant part	Lignans	Ref.
A. absinthium L.	Aerial parts	9, 1, 28, 27, 18	94
A. absinthium L.	Fresh roots	1, 2, 3, 4, 26, 27, 28, 9, 11, 12, 22, 14	92
A. absinthium L.	Aerial parts	28, 1, 27, 23, 18, 20, 26	108
A. absinthium L.	Fresh roots	6, 9, 1	91
A. arborescens L.	Aerial parts	6, 26, 27, 8, 11, 1, 15, 31, 25	92,95
A. canariensis Less.	Fresh roots	6, 8, 1, 26, 27, 11	91
A. caruifolia Buch.-Ham. ex Roxb.	Aerial parts	16, 17, 18, 19	97
A. gorgonum Webb.	Aerial parts	21, 13, 14, 8, 5, 6	93
A. gorgonum Webb.	Fresh roots	6, 8, 1, 26, 14, 11	92
A. jacutica Drob.	Fresh roots	6, 8, 1, 26	92
A. macrocephala Jacq. ex Bess.	Fresh roots	1, 26	92
A. minor Jacq. ex Bess.	Aerial parts	23, 24	98
A. sieversiana Willd.	Fresh roots	1, 26, 27, 28, 9, 8, 12, 11, 22, 14, 6	92
A. sieversiana Willd.	Aerial parts	27, 28, 7, 29, 30, 10	96,90
A. austro-yunnanensis	Whole plant	25, 23	109

2. LIGNANS BIOSYNTHESIS

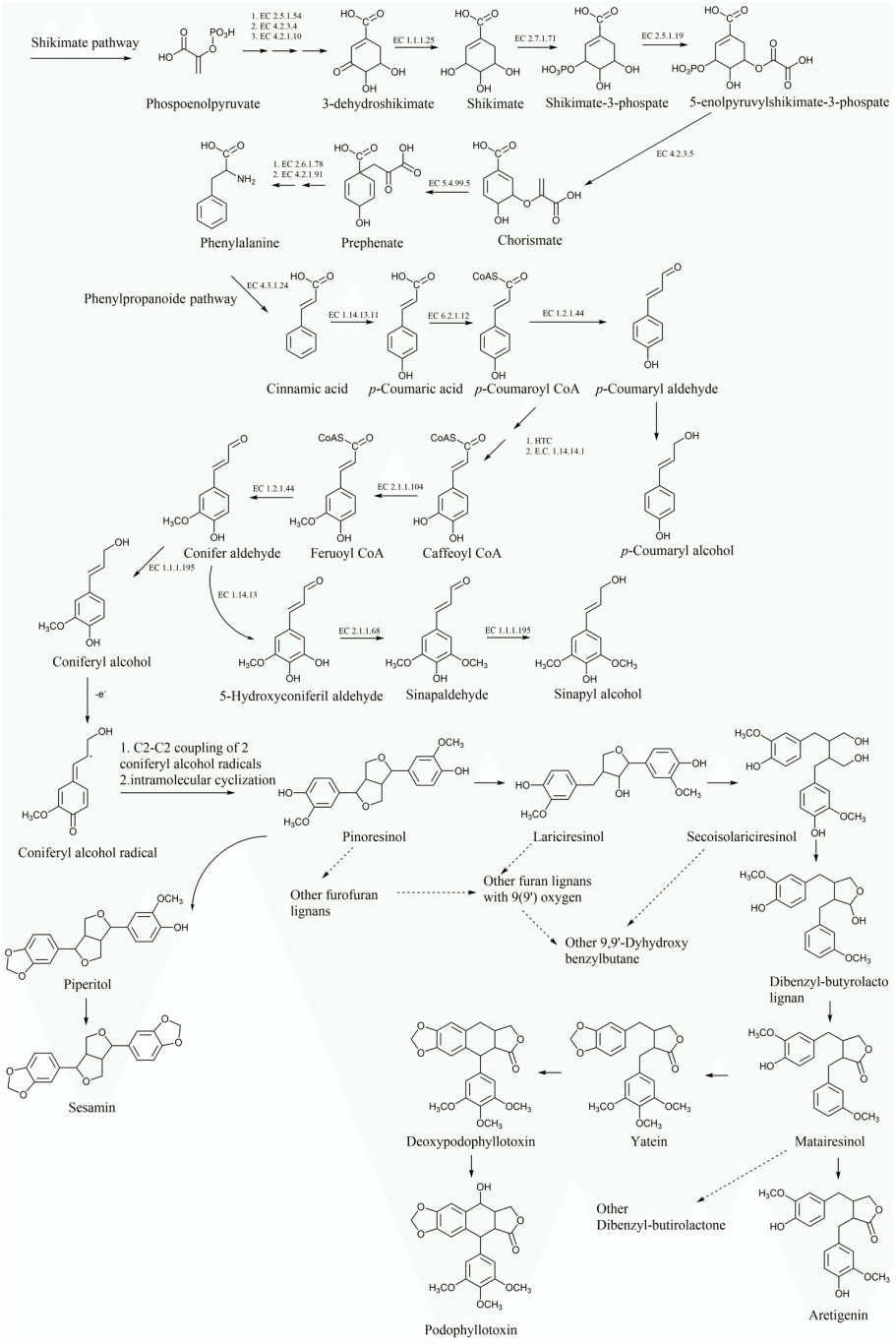
Phenylpropanoid metabolism is a convoluted network of biosynthetic pathways, which lead to the synthesis of a vast number of secondary metabolites. The plant shikimate pathway is the entry to the biosynthesis of phenylpropanoids, where just a few intermediates represent the core unit for the further biosynthesis of secondary metabolites, including flavonoids, isoflavonoids, lignins and lignans. The shikimate pathway results in the biosynthesis of chorismate, which is the branch point for the synthesis of aromatic amino acids tryptophan on the one hand and phenylalanine and tyrosine on the other hand.[110,111] Chorismic acid is transformed into prephenic acid *via* a Claisen rearrangement, which transfers the phosphoenolpyruvate derived side-chain so that it becomes directly bonded to the carbocycle and thus builds up the basic carbon skeleton of phenylalanine. Decarboxylative aromatization of prephenic acid yields phenylpyruvic acid and pyridoxal phosphate-dependent transamination leads to L-phenylalanine.[112,113] The conversation of phenylalanine to the hydroxycinnamic acids (*p*-coumaric, ferulic and sinapic acids) and the monolignols (*p*-coumaryl, coniferyl and sinapyl alcohols) is the start point of phenylpropanoid pathway. Phenylalanine ammonia-lyase and tyrosine ammonia-lyase catalyze the non-oxidative deamination of phenylalanine to trans-cinnamate and direct the carbon flow from the shikimate pathway to the various branches of the general phenylpropanoid metabolism.[112] Subsequent steps, *i.e.*, hydroxylation of cinnamic acid by cinnamate 4-hydroxylase which leads to the biosynthesis of *p*-coumaric acid and activation of coumaric acid by 4-coumaroyl CoA-ligase which leads to the biosynthesis of *p*-coumaroyl-CoA, are mandatory and provide the basis for all subsequent branches and resulting metabolites.[113,114] *p*-Coumaroyl-CoA is a precursor for the biosyn-

thesis of *p*-coumaryl alcohol and coniferyl alcohol. As part of monolignol biosynthesis (building blocks of lignans and lignins), *p*-coumaroyl-CoA can undergo two types of modifications: reduction of the carboxyl group on the propane side chain to alcohol and substitution of the phenyl ring. The two predominant monolignols are coniferyl alcohol and sinapyl alcohol.[114]

Although lignans and neolignans are abundant class of phytochemicals, little is known about the specific biosynthetic steps leading to the biosynthesis of complex lignans. During the years, the majority of the studies were devoted to understanding the biosynthesis of podophyllotoxin, thanks to which the biosynthesis of lignans with 9(9′)-oxygen is very well studied. These type of lignans are formed by enantioselective dimerization of two coniferyl alcohol units with the aid of a dirigent protein to give rise to pinoresinol (**25**, furofuran). Pinoresinol (**25**) is then reduced to secoisolariciresinol (dibenzylbutane) by pinoresinol/lariciresinol reductase, *via* lariciresinol (furan), which is in turn oxidized to afford matairesinol (dibenzylbutyrolactone) by secoisolariciresinol dehydrogenase. The conversion from coniferyl alcohol to secoisolariciresinol has been demonstrated in various plant species (*Forsythia*, *Linum* and *Podophyllum*), which strongly suggests that this is the general biosynthetic pathway of lignans.[84,105,115] Lignans and neolignans are normally found in optically active forms. They are composed of only one enantiomer or both, but with one of them being in excess. This implies that lignan biosynthesis is under strict enantioselective control.[86]

For example, (+)-pinoresinol (**25**) is found in *F. suspense*[116,117] and (–)-secoisolariciresinol and (–)-matairesinol occur in *F. intermedia*.[118] Lignans are generally believed to be formed by a phenolic oxidative coupling process[119] more precisely, by a large number of distinct radical coupling modes of phenoxyl radical. Those coupling modes can be either stereoselective and/or regiospecific in coupling origin.[120] The first demonstration of phenoxyl radical coupling control was reported during the investigation of (+)-pinoresinol (**25**) formation from coniferyl alcohol in *Forsythia* species.[121,122] It was suggested that the dirigent protein bind and orient coniferyl alcohol-derived radicals in such a way as to enable 8,8′ coupling at the si-si face with subsequent intramolecular cyclization to afford (+)-pinoresinol (**25**).[122] Since the initial discovery of this protein from *F. intermedia*, homology searches in sequence databases have revealed the existence of additional genes encoding putative dirigent proteins, from a variety of species.

One of the proposed biosynthetic routes[123] starts with coniferyl alcohol and subsequent formation of (+)-pinoresinol (**25**). The enzyme pinoresinol/lariciresinol reductase converts this compound to (+)-lariciresinol and then to (–)-secoisolariciresinol. The enzyme secoisolariciresinol dehydrogenase converts into (–)--matairesinol. The conversion from (–)-matairesinol to podophyllotoxin is likely to be similar to the route shown in Scheme 1. Matairesinol is metabolized to arc-



Scheme 1. (Adapted from literature[86,101,114]) Part of the shikimate and phenylpropanoid biosynthetic pathways and possible biosynthetic pathways for various types of lignans. The

enzymes involved in the shikimate pathway are: DAHP synthase (EC 2.5.1.54), 3-dehydroquinate synthase (EC 4.2.3.4), 3-dehydroquinate dehydratase (EC 4.2.1.10), shikimate dehydrogenase (EC 1.1.1.25), shikimate kinase (EC 2.7.1.71), 5-enolpyruvylshikimate 3-phosphate synthase (EC 2.5.1.19), chorismate synthase (EC 4.2.3.5), chorismate mutase (EC 5.4.99.5), prephenate aminotransferase (EC 2.6.1.78) and arogenate dehydratase (EC 4.2.1.91). The enzymes involved in phenylpropanoid pathway are: phenylalanine ammonia lyase (EC 4.3.1.24), cinnamic acid 4-hydroxylase (EC 1.14.13.11), 4-coumaric acid:CoA ligase (EC 6.2.1.12), cinnamoyl-CoA:NADP oxidoreductase (EC. 1.2.1.44), hydroxycinnamoyl-CoA shikimate/quinatehydroxy-cinnamoyl transferase (HTC), *p*-coumaroyl-CoA 3′-hydroxylase (EC 1.14.14.1), caffeoyl-CoA *O*-methyltransferase (EC 2.1.1.104), cinnamyl alcohol dehydrogenase (EC 1.1.1.195), aldehyde/coniferyl alcohol 5-hydroxylase (EC 1.14.13), 5-hydroxyconiferaldehyde/5-hydroxyconiferyl alcohol *O*-methyltransferase (EC 2.1.1.68).

tigenin by matairesinol *O*-methyltransferase *via* methylation of a phenolic hydroxyl group in various plants including *F. koreana*, *Carthamus tinctorius* and *Anthriscus sylvestris*.[124,125] In *Linum*, *Anthriscus* and *Podophyllum* plants, matairesinol is also converted into hinokinin, yatein, or PTOX *via* multiple biosynthetic pathways, although all of the relevant enzymes have not yet been identified.[86,107] In *Sesamum* plants pinoresinol (**25**) is metabolized into piperitol, followed by further conversion into (+)-sesamin (**6**) by a cytochrome P450 family enzymes.[86,107,126]

3. ISOLATION OF LIGNANS

Lignans are natural products with highly diverse structures, which affects their separation. Lignan aglycones are the most prevalent natural form of this compounds, so the high hydrophobicity of this compounds, as well as the separation itself can be influenced by skeletal substitution, the position of the substituent, partition coefficient, isomerism and size of the molecule. For example, in aryltetraline lignans podophyllotoxine and α-peltatine the position of OH group is decisive factor: if it is in 7α position the substance is less hydrophobic, than in the case of substitution in position 6 on the aromatic ring. In the case of hydroxyl group glycosylation, hydrophilicity rises significantly.[127] The introduction of an additional hydroxyl group on position 7′ (matairesinol transformation to hydroxymatairesinol) leads to a significant increase of polarity. A similar effect occurs during glucosylation (mono and diglucoside of secoisolariciresinol). Size of the molecule has a significant influence on the separation of the lignan molecules. The higher molecular mass of an aglycone the lower mobility, though in this case the chromatographic behavior can hardly be predicted.

Solvent extraction is a traditional method for extracting lignans from plant sources. However, other less polar components present in most plant tissues may interfere with the subsequent separation of lignans if a polar solvent is used. Therefore, the sequential solvent extraction is recommended for efficient separation of lignan compounds. Extraction in Soxhlet extractor is a widely used method. It

can be used for sequential extraction, with solvents with increasing polarity, which is usually started with non-polar organic solvents such as petroleum ether, hexane or dichloromethane.[127,128] During this ”pre-extraction”, the extraction of a part of lignans can occur as well. Preparation of lignan extracts with a low content of ballast substances by a common extraction is practically impossible; lipophilic solvents extract not only undesirable substances but also lignans which are without OH groups or possibly with maximum one hydroxyl group.[129–131]

After removing lipidic substances, polar solvents (ethanol, methanol and acetone) are used for the preparation of the total extract. In some cases, the addition of polar solvents such as water to the sample may increase the recovery of more polar compounds such as lignan glycosides. Lignans of low or medium polarity can be efficiently extracted with a less polar solvent. Direct extraction with a hot polar solvent, appropriate for lignans of low polarity, has also been used for extraction of some plant lignans.[119,130,132,133]

A recently introduced method for extraction of plant lignans. the accelerated solvent extraction, is carried out at higher temperature and pressure and under inert nitrogen atmosphere. This method may enable fast and convenient extraction using relatively small amounts of solvents[128,134,135]. It has been successfully used for extraction of lignans from the wood of certain trees (*Picea abies*, Pineceae).[128,136–138] Lignans in some plant materials require special pretreatments before extraction. Polar lignans, present in the plant as ester-linked oligomers or polymers,[139,140] seem to be readily soluble in aqueous methanol or ethanol. Nonetheless, the subsequent hydrolysis is required to release free aglycone. Furthermore, additional hydrolysis steps, enzymatic or non-enzymatic, can be used for the release of free aglycone.[137,138] Percolation at room temperature is also used for lignan extraction (*e.g.*, lignans from the twigs of *Magnolia thailandica* were defatted with hexane and continuously extracted with mixture of dichloromethane and methanol).[141]

Purification of total extracts with lignan content is quite time-consuming and laborious. Methanol extracts are usually concentrated, diluted with water, this suspension fractioned with *n*-hexane and consequently with chloroform,[142] dichloromethane[143,144] or ethyl acetate,[145] to obtain a lignan fraction. For example, syringaresinol (**23**) from the crude extract of *M. thailandica* was obtained as follows: crude extract was subjected to silica gel column chromatography with ethyl acetate–hexane and methanol–ethyl acetate mixtures to give seven fractions. Fraction which contained syringaresinol (**23**) was fractionated on a silica gel column with ethyl acetate-hexane mixture to yield six subfractions. Syringaresinol (**23**) was gathered from one of the subfractions *via* crystallization by ethanol.[141] The details of the previously employed extraction and chromatographical methods for isolation of *Artemisia* genus plant lignans are summarized in Table II.

TABLE II. Details of previously employed analytical techniques for isolation of lignans from different plant sources

Plant	Part	Isolated lignans	Extraction	Isolation technique	Ref.
A. absinthium	Aerial parts	**28**, **1**, **27**, **23**, **18**, **20**, **26**	Ethanol, 95 %	Successive extraction with ether, $CHCl_3$, ethyl acetate. Chromatography: silica gel column (petroleum ether:ethyl acetate) gives 6 fractions. Fractionation (fraction 4): silica gel column chromatography (petroleum ether:ethyl acetate, 10:1 → 1:2) gives 14 sub-fractions. Separation (sub-fractions 8, 10, 13): open column chromatography (CH_3OH:H_2O, 40:60 → 90:10), semi-preparative HPLC (acetonitrile:H_2O, 50:50), sephadex LH-20 column chromatography (methanol).	108
A. arborescens	Aerial parts	**6**, **26**, **27**, **8**, **1**, **15**, **25**	Maceration (methanol)	Chromatography; silica gel column chromatography (hexane:ether, 2:1, ether, ether:CH_3OH, 6:1) gives 3 fractions. Medium pressure column chromatography: hexane:ether, 1:2.	95
A. absinthium	Fresh roots	**1**, **2**, **3**, **4**	Petrol (60–80 °C):ether, 2:1	Chromatography: resin was dissolved in ether, TLC on silica gel with ether:petrol, 4:1. Fractionation: silica gel column (petrol:ether, ether 100:0 → 0:100 and CH_3OH:ether, 3:97 → 10:90 %). The lignan containing fractions (petrol:ether–CH_3OH:ether, 50–10 %) were also subjected to preparative TLC.	92
A. caruifolia	Aerial parts	**6**, **1**, **16**, **17**, **18**, **19**	Refluxing (methanol). Methanol extract was partitioned with $CHCl_3$ and H_2O	Chromatography ($CHCl_3$ extract): silica gel column (hexane:ethyl acetate, 7:3→3:1 and ethylacetate:ethanol:H_2O, 6:2:1), gives 4 fractions. Open column chromatography (fraction 1) with 60–100 % methanol gives 3 sub-fractions. Preparative TLC (sub-fractions): SiO_2, benzene:acetone, 9:1 gives sesamin (**6**) and sesartemin (**1**). Open column chromatography (fraction 2 and 3) with 40–60 % methanol. HPLC preparative chromatography of sub-fractions gives caruilignans.	97

TABLE II. Continued

Plant	Part	Isolated lignans	Extraction	Isolation technique	Ref.
A. absinthium	Aerial parts	**27**, **1**	Maceration (CH_2Cl_2, 2 days)	Chromatography: silica gel, CH_2Cl_2:CH_3OH, 98:2 → 40:60, gives 4 fractions. Semipreparative HPLC: isocratic, H_2O:acetonitrile, 40:60.	46
		9, **1**, **28**, **27**, **18**	Ethanol, 70 %	Fractionation: petroleum ether, CH_2Cl_2, ethyl acetate and butanol, successively. Chromatography (CH_2Cl_2 fraction): silica gel column chromatography with petroleum ether:ethyl acetate, 10:0 → 5:1 and CH_2Cl_2:CH_3OH, 100:0 → 5:1. Sephadex LH-20 column chromatography with $CHCl_3$:CH_3OH, 1:1.	94

4. BIOLOGICAL ACTIVITY OF FUROFURAN LIGNANS

Yamauchi *et al.*[146] synthesized nine oxygenated furofuran lignans and found that the tertiary hydroxy group on the furofuran ring affected the degree of antioxidant activity. Pinoresinol (**25**), sesamin (**6**) and their glycosides are metabolized by intestinal microflora to yield enterodiol and enterolactone which are supposed to protect against estrogen-dependent cancers,[147,148] and which are known as enterolignans or mammalian lignans.[149–151] These metabolized lignans elicited their estrogen-like activity in mammals. For example, enterolignans bind to the mammalian estrogen receptors, which are key regulatory factors in the sexual maturation of genital organs.[152,153] Enterolignans, combined with other intestinal flora-generating metabolites of isoflavones and coumestans, are also called phytoestrogens.[84]

In human intestinal Caco 2 cells, pinoresinol (**25**) decreased the production of inflammatory factors, such as interleukin-6 and prostaglandin E2, following the down-regulation of Cox-2, an inducible prostaglandin synthase that is responsible for the synthesis of prostaglandin H.[154] Sesamin (**6**) reduced signaling downstream of mitogen-activated protein kinase, and potently reduce breast tumor growth.[155] Lee *et al.*[156] demonstrate the role of magnolin (**13**) as a metastatic inhibitor in lung cancer cells. Epieudesmin (**22**) has been shown to have antineoplastic activity against the murine P388 lymphocytic leukemia cell line and several human cancer cell lines (BXPC-3, MCF-7, SF268, NCI-H460, KM20L2 and DU-145).[157]

Yangambin (**26**) prevents the cardiovascular collapse observed during anaphylactic and endotoxic/septic shocks, as well as the vascular and cardiac hypo-

responsiveness to catecholamines in endotoxic shock.[77] Diayangambin (**28**)[158] and fargesin (**11**)[159] have been reported to exert anti-inflammatory activity.

The findings of Serra *et al.*[160] indicate that yangambin (**26**) shows an antagonistic action on LTB4 receptors and suggest that it may be useful in the treatment of some allergic inflammatory responses. Phillyrin (**29**) has an anti-obesity effect in nutritive obesity mice.[161]

Cyclic adenosine monophosphate (AMP) is found to be the second messenger inside cells, so compounds that act to alter cyclic AMP metabolism have been the subject of many studies. Nikaido *et al.* presented in their paper that pinoresinol (**25**) and pinoresinol-*β*-D-glucoside showed cyclic AMP phosphordiesterase inhibitory activity.[162] Kobusin (**5**), fargesin (**11**) and epieudesmin (**22**) were assayed for inhibitory activity against nitric oxide production in LPS stimulated RAW 264.7 cell, but all lignans were inactive.[163] Rimando *et al.*[164] studied furofuran lignans epiyangambin (**27**), diayangambin (**28**), diasesartemin (**4**) and epiaschantin (**9**) for their phytotoxicity. Diayangambin (**28**) was the most phytotoxic to *Lactuca sativa*, showing strong inhibitory activity. Diayangambin (**28**) was more active than epiyangambin (**27**) and diasesartemin (**4**) in inhibiting the growth of *Agrostis stolonifera*. All of these compounds inhibited all phases of onion root cell division. Fargesin (**11**) and sesamin (**6**), which have very similar structures to epiyangambin (**27**), diayangambin (**28**), diasesartemin (**4**) and epiaschantin (**9**), were shown to inhibit germination of peanut and cucumber.[165]

Sesamin (**6**) is used as an antioxidant.[166] The antioxidative propensity of sesamin (**6**) is likely to be involved in protecting the liver from oxidation by alcohols, lipids and oxygen radicals.[84,167–169]

Sesamin (**6**) and its metabolites exhibited antihypertensive activities.[76,170–172] Sesamin (**6**) is also an insecticide.[173] Sesamin (**6**), pinoresinol (**25**) and kobusin (**5**) have various biological activities, which include synergistic effects with pyrethrum insecticides[174–177] and inhibitors of Δ5 desaturases in mammals.[178] Sesamin (**6**) has an anti-inflammatory effect by specifically inhibiting Δ5 desaturase in polyunsaturated fatty acid biosynthesis.[179] Sesamin (**6**), pinoresinol (**25**) and kobusin (**5**) also have significant plant protective properties as antioxidants, as well as having important roles in health protection.[180]

This lignans, when provided in the diet, can reduce serum cholesterol level,[181] as well as increase vitamin E activities[182,183] and the availability of *γ*-tocopherol *in vivo*.[184] The lignans epiyangambin (**27**) and sesartemin (**1**) reduce spontaneous locomotor activity and isolation-induced aggression in mice.[185] Epiyangambin (**27**) and epimagnolin (**14**) possessed strong selective inhibition of PAF-induced platelet aggregation.[186] Epiyangambin (**27**) and yangambin (**26**) competitively inhibited platelet activating factor (PAF)-induced rabbit platelet aggregation in a dose-dependent manner, but they had no effect on the platelet aggregation induced by collagen, thrombin or ADP.[187] These results indicated

that both lignans were potent and selective antagonists of PAF.[188,189] Sesamin (**6**) feeding is associated with reduced serum levels of triacylglycerol,[190–192] cholesterol[193,194] and phospholipid[190] in rodents.

Dietary sesamin (**6**) also reduces hepatic concentrations of triacylglycerol[191,193] and cholesterol[190,194] but increases phospholipid levels accompanying liver hypertrophy,[190,191,195] although temporarily.[194] Kiso[196] found that sesamin (**6**) was absorbed by the route of the portal vein and metabolized to mono- or di- catechol metabolite by drug metabolizing enzymes in the liver cells. It is suggested that sesamin (**6**) ingestion regulated the transcription levels of hepatic metabolizing enzymes for lipids and alcohol.

Ashakumary *et al.*[197] demonstrated that dietary sesamin (**6**) greatly increased the hepatic activity of fatty acid oxidation enzymes, including carnitine palmitoyltransferase, acyl-CoA dehydrogenase, acyl-CoA oxidase, 3-hydroxyacyl-CoA dehydrogenase, enoyl-CoA hydratase and 3-ketoacyl-CoA thiolase. Sesamin (**6**) also increased the activity of 2,4-dienoyl-CoA reductase and Δ^3,Δ^2--enoyl-CoA isomerase, enzymes involved in the auxiliary pathway for *β*-oxidation of unsaturated fatty acids. Furofuran lignans: sesamin (**6**), aschantin (**8**), sesartemin (**1**) and yangambin (**26**) showed weak activity against *Staphylococcus aureus*. Sesartemin (**1**) and yangambin (**26**) also showed weak activity against *Escherichia coli*, while sesamin (**6**) and aschantin (**8**) were inactive.[198] Epiaschantin (**9**) exhibited moderate antimicrobial activity against strains of Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and the yeast *Candida albicans*.[199]

Kawamura *et al.*[200] investigated the antifungal activity of epieudesmin (**22**) against *Trametes versicolor* and *Fomitopsis palustris*. Lignan showed antifungal activity. MacRae *et al.*[201] tested a number of lignans and found that antiviral activity is specific to a certain classes of lignans. Episesartemin B (**3**), sesartemin (**1**), epiyangambin (**27**) and yangambin (**26**) were all without antiviral effect, although these lignans are known to have a number of biological activities.[202] Three diepoxy-pinoresinol glycosides, one diepoxy-syringaresinol glycoside, pinoresinol (**25**) and syringaresinol (**23**) were tested for inhibitory activity against tobacco mosaic virus. Pinoresinol-4′*O*-[4″,6″*O*-(*E*)-diferuloyl]-*β*-D-glucopyranoside, pinoresinol-4′*O*-[3″,6″*O*-(*E*)-diferuloyl]-*β*-D-glucopyranoside and syringaresinol-4′*O*-[4″,6″*O*-(*E*)-diferuloyl]-*β*-D-glucopyranoside exhibited moderate activities in inhibiting the multiplication of the tobacco mosaic virus[203]. Ortet *et al.*[57] evaluated *in vitro* cytotoxicity of eudesmin (**21**), magnolin (**13**), epimagnolin (**14**), aschantin (**8**), kobusin (**5**) and sesamin (**6**) against various human and murine tumor and normal cells and antimalarial activity against chloroquine-resistant *Plasmodium falciparum*. Tested compounds showed no cytotoxic activity against human tumor cells. With the exception of the sesamin (**6**), all other lignans showed weak cytotoxic activity against murine normal cells. Furthermore,

the cytotoxicity of sesamin (**6**) on mammalian normal cells was unnoticeable. Epimagnolin (**14**), aschantin (**8**), kobusin (**5**) and sesamin (**6**) showed mild antiplasmodial activities. The cytotoxic activity of caruilignan A (**16**), caruilignan B (**17**), caruilignan C (**18**), caruilignan D (**19**), sesamin (**6**), and sesartemin (**1**) were tested using Meth-A (sarcoma) and LLC (Lowis lung carcinoma) cell lines. Caruilignan A (**16**), caruilignan B (**17**), caruilignan C (**18**), sesamin (**6**) and sesartemin (**1**) were found to be cytotoxic only against the Meth-A cell line.[97] Fargesin (**11**), epieudesmin (**22**) and sesamin (**6**) were effective against trypomastigotes, but these compounds were highly toxic to mammalian cells and no parasite selectivity could be identified.[204]

5. CONCLUSION

This review represents furofuran lignans, their isolation from the plants of the genus *Artemisia*, along with their biological activity. Extensive literature survey, revealed that lignans have been obtained just from ten species of the *Artemisia* genus: *A. absinthium*, *A. arborescens*, *A. canariensis*, *A. caruifolia*, *A. gorgonum*, *A. jacutica*, *A. macrocephala*, *A. minor, A. sieversiana*, *A. austroyunnanensis*, although the genus includes a large number of species. Despite the isolation and characterization of numerous lignans from different plant species, there is a lot of an unfinished work left on this class of secondary metabolites, especially within the plant species of *Artemisia* genus, primarily because lignans represent a huge source of potentially bioactive compounds.

Further work on the isolation of lignans and determination of differences in the lignan patterns among *Artemisia* species belonging to a different section of the genus could have chemotaxonomic significance. Lignans are characterized by the stereoselective oxidative coupling of two phenylpropane units; the presence of chiral centres is an interesting challenge that needs to be overcome for the synthesis of these compounds. Although during the last decade, the total synthesis of several biologically active lignans has been achieved, there is still much left to learn about the lignan biosynthetic pathways.

ABBREVIATIONS

ADP – adenosine diphosphate
AMP – adenosine monophosphate
BXPC-3 – human pancreatic cancer cell line
CoA – coenzyme A
Cox-2 – cyclooxygenase-2
DU-145 – human prostate cancer cell line
EC 1.1.1.195 – cinnamyl alcohol dehydrogenase
EC 1.1.1.25 – shikimate dehydrogenase
EC 1.14.13 – aldehyde/coniferyl alcohol 5-hydroxylase
EC 1.14.13.11 –cinnamic acid 4-hydroxylase
EC 1.14.14.1 – *p*-coumaroyl-CoA 3′-hydroxylase

EC. 1.2.1.44 – cinnamoyl-CoA:NADP oxidoreductase
EC 2.1.1.104 – caffeoyl-CoA *O*-methyltransferase
EC 2.1.1.68 – 5-hydroxyconiferaldehyde/5-hydroxyconiferyl alcohol *O*-methyltransferase
EC 2.5.1.19 – 5-enolpyruvylshikimate 3-phosphate synthase
EC 2.5.1.54 – DAHP synthase
EC 2.6.1.78 – prephenate aminotransferase
EC 2.7.1.71 – shikimate kinase
EC 4.2.1.10 – 3-dehydroquinate dehydratase
EC 4.2.1.91 – arogenate dehydratase
EC 4.2.3.4 – 3-dehydroquinate synthase
EC 4.2.3.5 – chorismate synthase
EC 4.3.1.24 – phenylalanine ammonia lyase
EC 5.4.99.5 – chorismate mutase
EC 6.2.1.12 – 4-coumaric acid:CoA ligase
HTC – hydroxycinnamoyl-CoA shikimate/quinatehydroxy-cinnamoyl transferase
KM20L2 – human colon tumor cell line
LLC – Lowis lung carcinoma cell line
LPS – lipopolysaccharide
LTB4 – leukotriene B4 receptors
MCF-7 – human breast cancer cell line
Meth-A – sarcoma cell line
NCI-H460 – human lung cancer cell line
P388 – murine lymphocytic leukemia cell line
PAF – platelet activating factor
PTOX – podophyllotoxin
RAW 264.7 – murine macrophage cell line
SF268 – human brain tumor cell line

Acknowledgment. Support of the Ministry of Education, Science and Technological Development of Serbia (Project No. 172047) is gratefully acknowledged.

И З В О Д

ФУРАНОФУРАНСКИ ЛИГНАНИ РОДА *Artemisia*: ИЗОЛОВАЊЕ, БИОСИНТЕЗА И БИОЛОШКА АКТИВНОСТ

ЈОВАНА Д. ИЦКОВСКИ, ЈОВАНА Љ. ПАВЛОВИЋ, МИЛАН Н. МИТИЋ, ИВАН Р. ПАЛИЋ, ДАНИЈЕЛА А. КОСТИЋ, ГОРАН М. ПЕТРОВИЋ и ГОРДАНА С. СТОЈАНОВИЋ

Департман за хемију, Природно–математички факултет, Универзитет у Нишу, Вишеградска 33, 18000 Ниш

Од давнина лековите биљке и фармаколошки активни производи добијени из различитих природних извора играју важну улогу у здрављу људи. Биљке које припадају роду *Artemisia* поседују велики биолошки потенцијал и прилично су добро проучаван род у областима као што су систематика (укључујући молекуларну филогенетику) и организација генома. Многе врсте овог рода (*A. absinthium, A. annua, A. vulgaris, A. abrotanum, A. arborescens*) су широко искоришћаване, због своје велике економске вредности, као лекови, храна и украси. Ипак, у тако великом роду неизбежно постоје многобројне разлике, које се тичу употребљивости и потенцијала појединих врста. Већина студија усмерена је на биоактивност и фармакологију сесквитерпенских лактона. Лигнани су неправедно занемарени, иако и они имају веома значајна својства. Мотивисани том чињени-

цом покушали смо да објединимо резултате о биоактивним лигнанима, који су објављивани током година, а са логичним циљем даљег рада на изоловању и идентификовању нових биолошки активних лигнана и њиховој, потенцијалној, фармаколошкој експлоатацији.

(Примљено 10. децембра 2019, ревидирано 20. јануара, прихваћено 31. јануара 2020)

REFERENCES

1. J. Vallès, S. Garcia, O. Hidago, J. Martín, J. Pellicer, M. Sanz, T. Garnatje, in *Advances in Botanical Research*, Vol. 60, J. C. Kader, M. Delseny, Eds., Academic press, London, 2011, p. 349 (https://doi.org/10.1016/B978-0-12-385851-1.00015-9)
2. J. Martin, M. Torrel, J. Valles, *Plant Biol.* **4** (2001) 372 (https://dx.doi.org/10.1055/s-2001-16462)
3. J. Martin, M. Torrel, J. Valles, *Plant Biol.* **5** (2003) 85 (https://dx.doi.org/10.1055/s-2003-37979)
4. L. E. Watson, P. L. Bates, T. M. Evans, M. M. Unwin, J. R. Estes, *BMC Evol. Biol.* **2** (2002) 17 (https://dx.doi.org/10.1186/1471-2148-2-17)
5. E. D. McArthur, in *Proceedings of Sagebrush steppe ecosystem symposium*, Boise, ID, USA, 1999, 2000, p. 9 (https://www.fs.usda.gov/treesearch/pubs/30023)
6. K. Bremer, C. Humphries, *Bull. Nat. Hist. Mus.* **23** (1993) 71 (https://ia800506.us.archive.org/25/items/bulletinofnatura90natulond/bulletinofnatura90natulond.pdf)
7. D. J. Mabberley, *Mabberley's Plant-Book: A Portable Dictionary of Plants, Their Classifications and Uses*, Cambridge University Press, Cambridge, 2008, ISBN: 9781107115026
8. J. Pellicer, J. Vallès, A. A. Korobkov, T. Garnatje, *Taxon* **60** (2011) 691 (https://dx.doi.org/10.1002/tax.603006)
9. J. Vallès, M. Torrell, T. Garnatje, N. Garcia-Jacas, R. Vilatersana, A. Susanna, *Plant Biol.* **5** (2003) 274 (https://dx.doi.org/10.1055/s-2003-40790)
10. M. Sanz, R. Vilatersana, O. Hidalgo, N. Garcia-Jacas, A. Susanna, G. M. Schneeweiss, J. Vallès, *Taxon* **57** (2008) 66 (https://dx.doi.org/10.2307/25065949)
11. S. D'Andrea, R. Caramiello, S. Ghignone, C. Siniscalco, *Plant Biosyst.* **137** (2003) 121 (https://dx.doi.org/10.1080/11263500312331351381)
12. M. Q. Hayat, M. Ashraf, M. A. Khan, G. Yasmin, N. Shaheen, S. Jabeen, *Int. J. Agric. Biol.* **11** (2009) 542 (http://www.fspublishers.org/published_papers/91324_..pdf)
13. C. Oberprieler, R. Vogt, L. E. Watson, in *Flowering Plants. Eudicots: Asterales. The families and genera of vascular plants*, Vol. 8, J. W. Kadereit, C. Jeffrey, Eds., Springer-Verlag, Berlin, 2007, p. 342 ISBN: 978-3-540-31051-8
14. G. D. Brown, *Molecules* **15** (2010) 7603 (https://dx.doi.org/10.3390/molecules15117603)
15. A. Rustaiyan, S. Masoudi, *Phytochem. Lett.* **4** (2011) 440 (https://dx.doi.org/10.1016/j.phytol.2011.07.003)
16. M. Soliman, *Arch. Phytopathol. Plant Protect.* **40** (2007) 128 (https://dx.doi.org/10.1080/03235400500355808)
17. P. Blagojević, N. Radulović, R. Palić, G. Stojanović, *J. Agric. Food Chem.* **54** (2006) 4780 (https://dx.doi.org/10.1021/jf060123o)
18. H. Q. Tang, J. Hu, L. Yang, R. X. Tan, *Planta Med.* **66** (2000) 391 (https://dx.doi.org/10.1055/s-2000-8538)
19. H. M. Kim, J. Y. Seo, K. H. Liu, J. S. Kim *PloS One* **9** (2014) e101486 (https://dx.doi.org/10.1371/journal.pone.0101486)

20. M. A. Foglio, P. C. Dias, M. A. Antonio, A. Possenti, R. A. F. Rodrigues, É. F. da Silva, V. L. G. Rehder, J. E. de Carvalho, *Planta Med.* **68** (2002) 515 (https://dx.doi.org/10.1055/s-2002-32570)
21. M. Sayyah, L. Nadjafnia, M. Kamalinejad, *J. Ethnopharmacol.* **94** (2004) 283 (https://dx.doi.org/10.1016/j.jep.2004.05.021)
22. G. A. R. A. Jaleel, H. M. I. Abdallah, N. E. L. S. Gomaa, *Asian Pac. J. Trop. Biomed.* **6** (2016) 44 (https://dx.doi.org/10.1016/j.apjtb.2015.10.005)
23. I. A. Graham, K. Besser, S. Blumer, C. A. Branigan, T. Czechowshi, L. Elias, I. Guterman, L. Harvey, P. G. Isaac, A. M. Khan, T. R. Larson, Y. Li, T. Pawson, T. Penfield, A. M. Rae, D. A. Rathbone, S. Reid, J. Ross, M. F. Smalwood, V. Sequra, T. Townsend, D. Vyas, T. Winzer, D. Bowles, *Science* **327** (2010) 328 (https://dx.doi.org/10.1126/science.1182612)
24. W. J. M. Lommen, E. Schenk, H. J. Bouwmeester, F. W. A. Verstappen, *Planta Med.* **72** (2006) 336 (https://dx.doi.org/10.1055/s-2005-916202)
25. J. H. Wiersema, B. León, *World economic Plants: A Standard Reference*, CRC Press, Boca Raton, FL, 1999 ISBN: 0-8493-2119-0
26. E. A. Brisibe, E. A. Uyoh, F. Brisibe, P. M. Magalhães, J. F. S. Ferreira, *Afr. J. Biotechnol.* **7** (2008) 4884 (https://www.ajol.info/index.php/ajb/article/view/59696)
27. J. C. Laughlin, G. N. Heazlewood, B. M. Beattie, in *Artemisia*, 1st ed., C. W. Wright, Ed., Taylor & Francis, London, 2002 p. 127 ISBN: 0-203-34643-2
28. D. D. Zhai, H. Z. Jin, J. J. Zhong, *Chin. Chem. Let.* **21** (2010) 590 (https://dx.doi.org/10.1016/j.cclet.2010.01.034)
29. M. N. Binet, D. van Tuinen, N. Deprêtre, N. Koszela, C. Chambon, S. Gianinazzi, *Mycorrhiza* **21** (2011) 523 (https://dx.doi.org/10.1007/s00572-010-0354-y)
30. L. Bézanger-Beauquesne, M. Pinkas, M. Torck, F. Trotin, *Plantes médicinales des régions tempérées* 2nd ed., Maloine Publishers, Paris, 1990 ISBN: 2-224-02009-0
31. R. N. Kulkarni, in *Artemisia*, 1st ed., C. W. Wright, Ed., Taylor & Francis, London, 2002 p. 97 ISBN: 0-203-34643-2
32. M. Heinrich, in *Artemisia*, 1st ed., C. W. Wright, Ed., Taylor & Francis, London, 2002, p. 87 ISBN: 0-203-34643-2
33. P. Proksch, in *Artemisia*, 1st ed., C. W. Wright, Ed., Taylor & Francis, London, 2002, p. 81 ISBN: 0-203-34643-2
34. P. A. Linley, in *Artemisia*, 1st ed., C. W. Wright, Ed., Taylor & Francis, London, 2002, p. 112 ISBN: 0-203-34643-2
35. E. Hsu, *Trans. R. Soc. Trop. Med. Hyg.* **100** (2006) 505 (https://dx.doi.org/10.1016/j.trstmh.2005.09.020)
36. M. Willkox, *J. Altern. Complement. Med.* **15** (2009) 101 (https://dx.doi.org/10.1089/acm.2008.0327)
37. M. A. Bonet Galobart, X. J. Vallès, *Plantes, remeis i cultura popular del Montseny: Etnobotànica d'una reserva de la biosfera*, Brau Edicions, Figueres, Museu de Granollers-Ciencies Naturals, Granollers, 2006 ISBN: 9788487790546
38. S. Sanmi, *Chado: The Way of Tea. A Japanese Tea Master's Almanac,* Tuttle Pubishing, Boston, MA, 2005 ISBN: 13:978-4629-0036-7
39. J. Cullen, in *The European Garden Flora. A Manual for the Identification of Plants Cultivated in Europe, Both Out-of-Doors and Under Glass*, Vol. 6, J. Cullen, J. C. M. Alexander, C. D. Brickell, J. R. Edmondson, P. S. Green, V. H. Heywood, P. M. Jorgenson, S. L. Jury, S. G. Knees, H. S. Maxwell, D. M. Miller, N. K. B. Robson, S. M.

Walters, P. F. Yeo, Eds., Cambridge University Press, Cambridge, 2000, p. 601 ISBN: 0-521-42097-0
40. S. Garcia, T. Garnatje, J. D. Twibell, J. Vallès, *Genome* **49** (2006) 244 (https://dx.doi.org/10.1139/g05-105)
41. G. E. Schuman, G. S. Howard, *J. Range. Manage.* **31** (1978) 392 (https://dx.doi.org/10.2307/3897367)
42. J. F. Ferreira, D. L. Luthria, T. Sasaki, A. Heyerick, *Molecules* **15** (2010) 3135 (https://dx.doi.org/10.3390/molecules15053135)
43. S. J. Lee, H. Y. Chung, C. G. A. Maier, A. R. Wood, R. A. Dixon, T. J. Mabry, *J. Agric. Food Chem.* **46** (1998) 3325 (https://dx.doi.org/10.1021/jf9801264)
44. K. M. Valant-Vetschera, R. Fisher, E. Wollenweber, *Biochem. Syst. Ecol.* **31** (2003) 487 (https://dx.doi.org/10.1016/S0305-1978(02)00178-3)
45. A. R. Bilia, P. Melillo de Malghaes, M. C. Bergonzi, F. F. Vincieri, *Phytomedicine* **13** (2006) 487 (https://dx.doi.org/10.1016/j.phymed.2006.01.008)
46. A. Aberham, S. S. Cicek, P. Schneider, H. Stuppner, *J. Agric. Food Chem.* **58** (2010) 10817 (https://dx.doi.org/10.1021/jf1022059)
47. R. X. Tan, H. Lu, J. L. Wolfender, T. T. Yu, W. F. Zheng, L. Yang, S. Gafner, K. Hostettmann, *Planta Med.* **65** (1999) 64 (https://dx.doi.org/10.1055/s-1999-13965)
48. R. G. Kelsey, F. Shafizadek, *Phytochemistry* **18** (1979) 1591 (https://dx.doi.org/10.1016/0031-9422(79)80167-3)
49. N. S. Radulović, P. D. Blagojević, B. K. Zlatković, R. M. Palić, *S. Afr. J. Chem.* **62** (2009) 30 (http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0379-43502009000100034)
50. N. S. Radulović, P. J. Randjelović, N. M. Stojanović, P. D. Blagojević, Z. Z. Stojanović--Radić, I. R. Ilić, V. B. Djordjević, *Food Chem. Toxicol.* **58** (2013) 37 (https://dx.doi.org/10.1016/j.fct.2013.04.016)
51. T. Efferth, A. Sauerbrey, A. Olbrich, E. Gebhart, P. Rauch, H. O. Weber, J. G. Henqstler, M. E. Halatsch, M. Volm, K. D. Tew, D. D. Ross, J. O. Funk, *Mol. Pharmacol.* **64** (2003) 382 (https://dx.doi.org/10.1124/mol.64.2.382)
52. Q. Li, P. J. Weina, W. K. Milhous, *Curr. Drug Ther.* **2** (2007) 210 (https://dx.doi.org/10.2174/157488507781695649)
53. E. Nibret, M. Wink, *Phytomedicine* **17** (2010) 369 (https://dx.doi.org/10.1016/j.phymed.2009.07.016)
54. Y. Tariku, A. Hymete, A. Hailu, J. Rohloff, *Chem. Biodivers.* **7** (2010) 1009 (https://dx.doi.org/10.1002/cbdv.200900375)
55. Y. Tariku, A. Hymete, A. Hailu, J. Rohloff, *Chem. Biodivers.* **8** (2011) 614 (https://dx.doi.org/10.1002/cbdv.201000331)
56. M. Chadwick, H. Trewin, F. Gawthrop, C. Wagstaff, *Int. J. Mol. Sci.* **14** (2013) 12780 (https://dx.doi.org/10.3390/ijms140612780)
57. R. Ortet, S. Prado, E. L. Regaldo, A. V. Frederick, J. Media, J. Mendiola, O. P. Thomas, *J. Ethnopharmacol.* **138** (2011) 637 (https://dx.doi.org/10.1016/j.jep.2011.09.039)
58. A. E. Vega, G. H. Wendel, A. O. Maria, L. Pelzer, *J. Ethnopharmacol.* **124** (2009) 653 (https://dx.doi.org/10.1016/j.jep.2009.04.051)
59. T. Guardia, A. O. Juarez, E. Guerreiro, J. Guzmán, L. Pelzer, *J. Ethnopharmacol.* **88** (2003) 195 (https://dx.doi.org/10.1016/S0378-8741(03)00211-3)
60. B. Ivanescu, A. Miron, A. Corciova, *J. Anal. Methods Chem.* **2015** (2015) 1 (http://dx.doi.org/10.1155/2015/247685)

61. C. Liu, *Chin. Herb. Med.* **9** (2017) 101 (https://dx.doi.org/10.1016/S1674-6384(17)60084-4)
62. H. Wagner, in *The Biology and Chemistry of the Compositae*, Vol. 2, V. H. Heywood, J. B. Harborne, B. L. Turner Eds., Academic Press, London, 1977, p. 412 ISBN: 0123468019
63. T. E. Shaikenov, S. M. Adekenov, N. N. Belyaev, G. K. Zakiryanova, in *Arglabin. Its Structure, Properties and Usage*, Economy Printing, Portsmouth, VA, 1997, p. 21 (https://www.researchgate.net/profile/Nikolai_Belyaev/publication/260283583_Mechanism_of_action_of_the_sesquiterpene_from_Artemisia_glabella_Arglabin_in_transformed_tumor_cells/links/00463530780bfcea34000000/Mechanism-of-action-of-the-sesquiterpene-from-Artemisia-glabella-Arglabin-in-transformed-tumor-cells.pdf.)
64. J. L. Rios, R. M. Giner, J. M. Prieto, *New findings on the bioactivity of lignans*, in *Bioactive Natural Products. Studies in Natural Products Chemistry*, Vol. 26G, A. ur-Rahman, Ed., Elsevier Science, Amsterdam, 2002, p. 183 (https://dx.doi.org/10.1016/S1572-5995(02)80008-4)
65. H. Satake, E. Ono, J. Murata, *J. Agric. Food Chem.* **61** (2013) 11721 (https://dx.doi.org/10.1021/jf4007104)
66. A. Oliva, R. A. Moraes, S. B. Watson, S. O. Duke, F. E. Dayan, *Pestic. Biochem. Phys*. **72** (2002) 45 (https://dx.doi.org/10.1006/pest.2002.2582)
67. J. Harmatha, L. Dinan, *Phytochem. Rev.* **2** (2003) 321 (https://dx.doi.org/10.1023/B:PHYT.0000045494.98645.a3)
68. H. Nishiwaki, M. Kumamoto, Y. Shuto, S. Yamauchi, *J. Agric. Food Chem.* **59** (2011) 13089 (https://dx.doi.org/10.1021/jf203222w)
69. P. Carillo, C. Cozzolino, B. D'Abrosca, F. Nacca, M. DellaGreca, A. Fiorentio, A. Fuggi, *The Open Bioact. Compd. J.* **3** (2010) 18 (https://dx.doi.org/10.2174/1874847301003010018)
70. N. M. Saarinen, A. Wärri, M. Airio, A. Smeds, S. Mäkelä, *Mol. Nutr. Food Res*. **51** (2007) 857 (https://dx.doi.org/10.1002/mnfr.200600240)
71. K. Buck, A. K. Zaineddin, A. Vrieling, J Linseisen, J. Chang-Claude, *Am. J. Clin. Nutr.* **92** (2010) 141 (https://dx.doi.org/10.3945/ajcn.2009.28573)
72. M. Gordaliza, M. A. Castro, J. M. del Corral, A. S. Feliciano, *Curr. Pharm. Des.* **6** (2000) 1811 (https://dx.doi.org/10.2174/1381612003398582)
73. P. A. S. Alphonse, R. E. Aluko, *Discovery Phytomedicine* **2** (2015) 12 (https://doi.org/10.15562/PHYTOMEDICINE.2015.24)
74. A. Bylund, N. Saarinen, J. X. Zhang, A. Bergh, A. Widmark, A. Johansson, E. Lundin, H. Adlercreutz, G. Hallmans, P Stattin, S. Makela, *Exp. Biol. Med.* **230** (2005) 217 (https://dx.doi.org/10.1177/153537020523000308)
75. G. L. Zhang, N. Li, Y. H. Wang, Y. T. Zheng, Z. Zhang, M. W. Wang, *J. Nat. Prod.* **70** (2007) 662 (https://dx.doi.org/10.1021/np0605236)
76. D. Nakano, C. Itoh, M. Takaoka, Y. Kiso, T. Tanaka, Y. Matsumura, *Biol. Pharm. Bull.* **25** (2002) 1247 (https://dx.doi.org/10.1248/bpb.25.1247)
77. E. Tibiriçá, *Cardiovasc. Drug Rev.* **19** (2001) 313 (https://dx.doi.org/10.1111/j.1527-3466.2001.tb00073.x)
78. M. Saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep.* **22** (2005) 696 (https://dx.doi.org/10.1039/b514045p)
79. M. Azam, M. Ajitha, Phyllanthin, *Int. J. Pharmacogn. Phytochem. Res.* **9** (2017) 1081 (https://dx.doi.org/10.25258/phyto.v9i08.9615)

80. A. I. Smeds, P. C. Eklund, R. E. Sjöholm, S. M. Willför, S. Nishibe, T. Deyama, B. R. Holmbom, *J. Agric. Food Chem.* **55** (2007) 1337 (https://dx.doi.org/10.1021/jf0629134)
81. J. L. Peñalvo, S. M. Heinonen, A. M. Aura, H. Adlercreutz, *J. Nutr.* **135** (2005) 56 (https://dx.doi.org/10.1093/jn/135.5.1056)
82. J. Peterson, J. Dwayer, H. Adlercreutz, A. Scalbert, P. Jacques, M. L. McCullough, *Nutr. Rev*. **68** (2010) 571 (https://dx.doi.org/10.1111/j.1753-4887.2010.00319.x)
83. J. L. Peñalvo, K. M. Haajanen, N. Botting, H. Adlercreutz, *J. Agric. Food Chem.* **53** (2005) 9342 (https://dx.doi.org/10.1021/jf051488w)
84. H. Satake, T. Koyama, S. E. Bahabadi, E. Matsumoto, E. Ono, J. Murata, *Metabolites* **5** (2015) 270 (https://dx.doi.org/10.3390/metabo5020270)
85. T. Umezawa, *Wood Res.* **90** (2003) 27 (http://hdl.handle.net/2433/53098)
86. S. Suzuki, T. Umezawa, *J. Wood Sci.* **53** (2007) 273 (https://dx.doi.org/10.1007/s10086-007-0892-x)
87. J. L. Peñalvo, H. Adlercreutz, M. Uehara, A. Ristimaki, S. Watanabe, *J. Agric. Food Chem.* **56** (2008) 401 (https://dx.doi.org/10.1021/jf072695u)
88. N. Hata, Y. Hayashi, E. Ono, H. Satake, A. Kobayashi, T. Muranaka, A. Okazawa, *Plant Biotechnol.* **30** (2013) 1 (https://dx.doi.org/10.5511/plantbiotechnology.12.1021a)
89. F. A. Macías, A. López, R. M. Varela, A. Torres, J. M. G. Molinillo, *J. Agric. Food Chem*. **52** (2004) 6443 (https://dx.doi.org/10.1021/jf048945d)
90. S. J. Liu, Z. X. Liao, C. Liu, L. J. Ji, H. F. Sun, *Fitoterapia* **97** (2014) 43 (https://dx.doi.org/10.1016/j.fitote.2014.05.007)
91. H. Greger, *Planta Med.* **35** (1979) 84 ISSN: 0032-0943
92. H. Greger, *Biochem. Syst. Ecol.* **9** (1981) 165 (https://dx.doi.org/10.1016/0305-1978(81)90035-1)
93. R. Ortet, S. Prado, E. Mouray, O. P. Thomas, *Phytochemistry* **69** (2008) 2961 (https://dx.doi.org/10.1016/j.phytochem.2008.09.022)
94. N. J. Chi, Y. Liu, H. A. Aisa, *Chem. Nat. Compd.* **48** (2012) 666 (https://dx.doi.org/10.1007/s10600-012-0342-x)
95. J. A. Marco, J. F. Sanz-Cervera, V. Garcia-Lliso, J. Valles-Xirau, *Phytochemistry* **44** (1997) 1133 (https://dx.doi.org/10.1016/s0031-9422(96)00720-0)
96. R. X. Tan, H. Q. Tang, J. Hu, B. Shuai, *Phytochemistry* **49** (1998) 157 (https://dx.doi.org/10.1016/S0031-9422(97)00889-3)
97. C. M. Ma, N. Nakamura, B. S. Min, M. Hattori, *Chem. Pharm. Bull.* **49** (2001) 183 (https://dx.doi.org/10.1248/cpb.49.183)
98. Z. Z. He, J. F. Yan, Z. J. Song, F. Ye, X. Liao, S. L. Peng, L. S. Ding, *J. Nat. Prod.* **72** (2009) 1198 (https://dx.doi.org/10.1021/np800643n)
99. R. D. Haworth, *Ann. Rep. Prog. Chem.* **33** (1936) 266 (https://dx.doi.org/10.1039/AR9363300228)
100. J. Y. Pan, S. L. Chen, M. H. Yang, J. Wu, J. Sinkkonen, K. Zou, *Nat. Prod. Rep.* **26** (2009) 1251 (https://dx.doi.org/10.1039/b910940d)
101. R. Hatfield, W. Vermerris, *Plant Physiol.* **126** (2001) 1351 (https://dx.doi.org/10.1104/pp.126.4.1351)
102. R. Vanholme, B. Demedts, K. Morreel, J. Ralph, W. Boerjan, *Plant Physiol.* **153** (2010) 895 (https://dx.doi.org/10.1104/pp.110.155119)
103. W. Boerjan, J. Ralph, M. Baucher, *Ann. Rev. Plant Biol.* **54** (2003) 519 (https://dx.doi.org/10.1146/annurev.arplant.54.031902.134938)
104. T. Umezawa, T. Okunishi, M. Shimada, *Wood Res.* **84** (1997) 62 (http://hdl.handle.net/2433/53199)

105. T. Umezawa, T. Okunishi, M. Shimada, in *Lignin and lignan biosynthesis. ACS symposium series,* Vol. 697, N. G. Lewis, S. Sarkanen, Eds., The American Chemical Society, Washington, DC, 1998, p. 377 (https://dx.doi.org/10.1021/bk-1998-0697.ch024)
106. A. I. Smeds, P. C. Eklund, S. M. Willför, *Food Chem.* 134 (2012) 1991 (https://dx.doi.org/10.1016/j.foodchem.2012.03.133)
107. T. Umezawa, *Phytochem. Rev.* **2** (2003) 371 (https://dx.doi.org/10.1023/B:PHYT.0000045487.02836.32)
108. A. Tulake, Y. Jiang, P. F. Tu, *J. Chin. Pharmaceut. Sci.* **21** (2012) 360 (doi:10.5246/jcps.2012.04.050)
109. J. Chi, B. C. Li, B. T. Yang, M. Zhang, *J. Chem. Soc. Pak.* **38** (2016) 533 (https://inis.iaea.org/search/search.aspx?orig_q=RN:48009478)
110. L. M. Weaver, K. Herrmann, *Trends Plant Sci.* **2** (1997) 346 (https://dx.doi.org/10.1016/S1360-1385(97)84622-5)
111. K. M. Herrmann, L. M. Weaver, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **50** (1999) 473 (https://dx.doi.org/10.1146/annurev.arplant.50.1.473)
112. T. Vogt, *Mol. Plant* **3** (2010) 2 (https://dx.doi.org/10.1093/mp/ssp106)
113. A. A. Dar, N. Arumugam, *Bioorg. Chem.* **50** (2013) 1 (https://dx.doi.org/10.1016/j.bioorg.2013.06.009)
114. W. Vermeris, R. Nicholson, *Phenolic compound biochemistry,* Springer, Amsterdam, 2006 ISBN: 1402051638
115. R. B. Teponno, S. Kusari, M. Spiteller, *Nat. Prod. Rep.* **33** (2016) 1044 (https://dx.doi.org/10.1039/c6np00021e)
116. S. Kitagawa, S. Nishibe, R. Benecke, H. Thieme, *Chem. Pharm. Bull.* **36** (1988) 3667 (https://dx.doi.org/10.1248/cpb.36.3667)
117. T. Umezawa, L. B. Davin, E. Yamamoto, D. G. I. Kingston, N. G. Lewis, *J. Chem. Soc. Chem. Commun.* **20** (1990) 1405 (https://dx.doi.org/10.1039/c39900001405)
118. T. Umezawa, L. B. Davin, N. G. Lewis, *J. Biol. Chem.* **266** (1991) 10210 (http://www.jbc.org/content/266/16/10210.short)
119. D. M. Pereira, P. Valentao, J. A. Pereira, P. B. Andrade, *Molecules* **14** (2009) 2202 (https://dx.doi.org/10.3390/molecules14062202)
120. L. B. Davin, N. G. Lewis, *Curr. Opin. Biotechnol.* **16** (2005) 407 (https://dx.doi.org/10.1016/j.copbio.2005.06.011)
121. P. W. Paré, H. B. Wang, L. B. Davin, N. G. Lewis, *Tetrahedron Lett.* **35** (1994) 4731 (https://dx.doi.org/10.1016/S0040-4039(00)76953-X)
122. L. B. Davin, H. B. Wang, A. L. Crowell, D. L. Bedgar, D. M. Martin, S. Sarkanen, N. G. Lewis, *Science* **275** (1997) 362 (https://dx.doi.org/10.1126/science.275.5298.362)
123. Z. Q. Xia, M. A. Costa, J. Proctor, L. B. Davin, N. G. Lewis, *Phytochemistry* **55** (2000) 537 (https://dx.doi.org/10.1016/S0031-9422(00)00242-9)
124. T. Umezawa, S. K. Ragamustari, T. Nakatsubo, S. Wada, L. Li, M. Yamamura, N. Sakakibara, T. Hattori, S. Suzuki, V. L. Chiang, *Plant Biotechnol.* **30** (2013) 97 (https://dx.doi.org/10.5511/plantbiotechnology.12.1230a)
125. S. K. Ragamustari, M. Yamamura, E. Ono, T. Hattori, S. Suzuki, H. Suzuki, D. Shibata, T. Umezawa, *Plant Biotechnol.* **31** (2014) 257 (https://dx.doi.org/10.5511/plantbiotechnology.14.0722a)
126. L. Wang, S. Yu, C. Tong, Y. Zhao, Y. Liu, C. Song, Y. Zhang, X. Zhang, Y. Wang, W. Hua, D. Li, D. Li, F. Li, J. Yu, C. Xu, X. Han, S. Huang, S. Tai, J. Wang, X. Xu, Y. Li, Y. Liu, R. K. Varshey, J. Wang, X. Zhang, *Genome Biol.* **15** (2014) R39 (https://dx.doi.org/10.1186/gb-2014-15-2-r39)

127. G. Stojanović, T. Hashimoto, Y. Asakawa, R. Palić, *Biochem. Syst. Ecol.* **33** (2005) 207 (https://dx.doi.org/10.1016/j.bse.2004.07.004)
128. S. Willför, J. Hemming, M. Reunanen, B. Holmbom, *Holzforschung* **57** (2003) 359 (https://dx.doi.org/10.1515/HF.2003.054)
129. A. Koulman, R. Bos, M. Medarde, N. Pras, W. J. Quax, *Planta Med.* **67** (2001) 858 (https://dx.doi.org/10.1055/s-2001-18849)
130. N. Takaku, D. H. Choi, K. Mikame, T. Okunishi, S. Suzuki, H. Ohashi, T. Umezawa, M. Shimada, *J. Wood Sci.* **47** (2001) 476 (http://hdl.handle.net/2433/53139)
131. L. Opletal, H. Sovová, M. Bártlová, *J. Chromatogr., B* **812** (2004) 357 (https://dx.doi.org/10.1016/j.jchromb.2004.07.040)
132. F. Kawamura, S. Kawai, H. Ohashi, *Phytochemistry* **44** (1997) 1351 (https://dx.doi.org/10.1016/S0031-9422(96)00705-4)
133. F. Abe, T. Yamauchi, A. S. C. Wan, *Chem. Pharm. Bull.* **36** (1988) 795 (https://dx.doi.org/10.1248/cpb.36.795)
134. S. Willför, J. Hemming, M. Reunanen, C. Eckerman, B. Holmbom, *Holzforschung* **57** (2003) 27 (https://dx.doi.org/10.1515/HF.2003.005)
135. S. Willför, P. Eklund, R. Sjöholm, M. Reunanen, R. Sillanpää, S. von Schoultz, J. Hemming, L. Nisula, B. Holmbom, *Holzforschung* **59** (2005) 413 (https://dx.doi.org/10.1515/HF.2005.067)
136. S. M. Willför, M. O. Ahotupa, J. E. Hemming, M. H. T. Reunanen, P. C. Eklund, R. E. Sjöholm, C. S. E. Eckerman, S. P. Pohjamo, B. R. Holmbom, *J. Agric. Food Chem.* **51** (2003) 7600 (https://dx.doi.org/10.1021/jf030445h)
137. S. Willför, L. Nisula, J. Hemming, M. Reunanen, B. Holmbom, *Holzforschung* **58** (2004) 335 (https://dx.doi.org/10.1515/hf.2004.052)
138. S. Willför, L. Nisula, J. Hemming, M. Reunanen, B. Holmbom, *Holzforschung* **58** (2004) 650 (https://dx.doi.org/10.1515/HF.2004.119)
139. J. D. Ford, K. S. Huang, H. B. Wang, L. B. Davin, N. G. Lewis, *J. Nat. Prod.* **64** (2001) 1388 (https://doi.org/10.1021/np010367x)
140. A. Kamal-Eldin, N. Peerlkamp, P. Johnsson, R. Andersson, R. E. Andersson, L. N. Lundgren, P. Aman, *Phytochemistry* **58** (2001) 587 (https://dx.doi.org/10.1016/S0031-9422(01)00279-5)
141. W. Monthog, S. Pitchuanchom, N. Nuntasen, W. Pompimon, *Am. J. Appl. Sci.* **8** (2011) 1268 (https://dx.doi.org/10.3844/ajassp.2011.1268.1271)
142. Y. Y. Chen, F. R. Chang, Y. C. Wu, *J. Nat. Prod.* **89** (1996) 904 (https://dx.doi.org/10.1021/np960414z)
143. A. M. A. P. Fernandes, A. L. Prado, L. E. S. Barata, M. Q. Paulo, N. R. Azevedo, P. H. Ferri, *Phytochem. Anal.* **8** (1997) 8 (https://dx.doi.org/10.1002/(SICI)1099-1565(199701)8:1<18::AID-PCA330>3.0.CO;2-B)
144. T. R. Sharma, B. M. Singh, N. R. Sharma, R. S. Chauhan, *J. Plant Biochem. Biotechnol.* **9** (2000) 49 (https://dx.doi.org/10.1007/BF03263084)
145. J. K. Bastos, W. J. Kopycki, C. L. Burandt, N. P. D. Nanayakkara, J. D. McChesney, *Phytochem. Anal.* **6** (1995) 101 (https://dx.doi.org/10.1002/pca.2800060207)
146. S. Yamauchi, T. Ina, T. Kirikihira, T. Masuda, *Biosci. Biotechnol. Biochem.* **68** (2004) 183 (https://dx.doi.org/10.1271/bbb.68.183)
147. H. Adlercreutz, *Environ. Health Perspect.* **103** (1995) 103 (https://dx.doi.org/10.1289/ehp.95103s7103)
148. E. Fuss, *Phytochem. Rev.* **2** (2003) 307 (https://dx.doi.org/10.1023/B:PHYT.0000045500.56476.f5)

149. S. Heinonen, T. Nurmi, K. Liukkonen, K. Poutanen, K. Wähälä, T. Deyama, S. Nishibe, H. Adlercreutz, *J. Agric. Food Chem.* **49** (2001) 3178 (https://dx.doi.org/10.1021/jf010038a)
150. J. W. Lampe, C. Atkinson, M. A. Hullar, *J. AOAC Int.* **89** (2006) 1174 (https://www.ncbi.nlm.nih.gov/pubmed/16915861)
151. Z. Liu, N. M. Saarinen, L. U. Thompson, *J. Nutr.* **136** (2006) 906 (https://dx.doi.org/10.1093/jn/136.4.906)
152. S. O. Mueller, S. Simon, K. Chae, M. Metzler, K. S. Korach, *Toxicol. Sci.* **80** (2004) 4 (https://dx.doi.org/10.1093/toxsci/kfh147)
153. P. Penttinen, J. Jaehrling, A. Damdimopoulos, J. Inzunza, J. G. Lemmen, P. van der Saag, K. Pettersson, G. Gauglitz, S. Mäkelä, I. Pongratz, *Endocrinology* **148** (2007) 4875 (https://dx.doi.org/10.1210/en.2007-0289)
154. A. During, C. Debouche, T. Raas, Y. Larondelle, *J. Nutr.* **142** (2012) 1798 (https://dx.doi.org/10.3945/jn.112.162453)
155. J. S. Truan, J. M. Chen, L. U. Thompson, *Nutr. Cancer* **64** (2012) 65 (https://dx.doi.org/10.1080/01635581.2012.630165)
156. C. J. Lee, M. H. Lee, S. M. Yoo, K. I. Choi, J. H. Song, J. H. Jang, S. R. Oh, H. W. Ryu, H. S. Lee, Y. J. Surh, Y. Y. Cho, *BMC Cancer* **15** (2015) 576 (https://dx.doi.org/10.1186/s12885-015-1580-7)
157. G. R. Pettit, Y. Meng, R. P. Gearing, D. L. Herald, R. K. Pettit, D. L. Doubek, J. C. Chapuis, L. P. Tackett, *J. Nat. Prod.* **67** (2004) 214 (https://dx.doi.org/10.1021/np030125s)
158. E. J. D. Leon, D. A. Olmedo, P. N. Solıs, M. P. Gupta, M. C. Terencio, *Planta Med.* **68** (2002) 1128 (https://dx.doi.org/10.1055/s-2002-36355)
159. Y. S. Lee, B. Y. Cha, S. S. Choi, Y. Harada, B. K. Choi, T. Yonezawa, T. Teruya, K. Nagai, J. T. Woo, *BioFactors* **38** (2012) 300 (https://doi.org/10.1002/biof.1022)
160. M. F. Serra, B. L. Diaz, E. O. Barreto, A. P. B. Pereira, M. C. R. Lima, J. M. B. Barbosa-Filho, R. S. B. Cordeiro, M. A. Martins, P. M. R. D. Silva, *Planta Med.* **63** (1997) 207 (https://dx.doi.org/10.1055/s-2006-957654)
161. Y. Zhao, F. Li, J. Yang, X. An, M. Zhou, *J. Chin. Med. Mater.* **28** (2005) 123 (https://www.ncbi.nlm.nih.gov/pubmed/15981888)
162. T. Nikaido, T. Ohmoto, T. Kinoshita, U. Sankawa, S. Nishibe, S. Hisada, *Chem. Pharm. Bull.* **29** (1981) 3586 (https://dx.doi.org/10.1248/cpb.29.3586)
163. D. X. Li, M. Liu, X. J. Zhou, *China J. Chin. Mater. Med.* **40** (2015) 2843 (https://www.ncbi.nlm.nih.gov/pubmed/26666037)
164. A. M. Rimando, F. E. Dayan, J. R. Mikell, R. M. Moraes, *Nat. Toxins* **7** (1999) 39 (https://dx.doi.org/10.1002/(SICI)1522-7189(199902)7:1<39::AID-NT38>3.0.CO;2-2)
165. P. V. Bhiravamurty, R. D. Kanakala, E. V. Rao, K. V. Sastry, *Curr. Sci.* **48** (1979) 949 (http://agris.fao.org/agris-search/search.do?recordID=US201302112425)
166. T. J. Mabry, A. Ulubelen, *J. Agric. Food Chem.* **28** (1980) 188 (https://dx.doi.org/10.1021/jf60228a024)
167. K. Akimoto, Y. Kitagawa, T. Akamatsu, N. Hirose, M. Sugano, S. Shimizu, H. Yamada, *Ann. Nutr. Metab.* **37** (1993) 218 (https://dx.doi.org/10.1159/000177771)
168. M. Tada, Y. Ono, M. Nakai, M. Harada, H. Shibata, Y. Kiso, T. Ogata, *Anal. Sci.* **29** (2013) 89 (https://dx.doi.org/10.2116/analsci.29.89)
169. C. M. Liu, G. H. Zheng, Q. L. Ming, C. Chao, J. M. Sun, *J. Agric. Food Chem.* **61** (2013) 1146 (https://dx.doi.org/10.1021/jf304562b)

170. S. Sirato-Yasumoto, M. Katsuta, Y. Okuyama, Y. Takahashi, T. Ide, *J. Agric. Food Chem.* **49** (2001) 2647 (https://dx.doi.org/10.1021/jf001362t)
171. T. Miyawaki, H. Aono, Y. Toyoda-Ono, H. Maeda, Y. Kiso, K. Moriyama, *J. Nutr. Sci Vitaminol.* **55** (2009) 87 (https://dx.doi.org/10.3177/jnsv.55.87)
172. M. Nakai, M. Harada, K. Nakahara, K. Akimoto, H. Shibata, W. Miki, Y. Kiso, *J. Agric. Food Chem.* **51** (2003) 1666 (https://dx.doi.org/10.1021/jf0258961)
173. R. C. Roark, *Econ. Bot.* **1** (1947) 437 (https://dx.doi.org/10.1007/BF02858908)
174. H. L. Haller, F. B. LaForge, W. N. Sullivan, *J. Org. Chem.* **7** (1942) 185 (https://dx.doi.org/10.1021/jo01196a012)
175. H. L. Haller, F. B. LaForge, W. N. Sullivan, *J. Econ. Entomol.* **35** (1942) 247 (https://dx.doi.org/10.1093/jee/35.2.247)
176. H. L. Haller, E. R. McGovran, L. D. Goodhue, W. N. Sullivan, *J. Org. Chem.* **7** (1942) 183 (https://dx.doi.org/10.1021/jo01196a011)
177. J. E. Casida, *J. Agric. Food Chem.* **18** (1970) 753 (https://dx.doi.org/10.1021/jf60171a013)
178. S. Shimizu, K. Akimoto, Y. Shinmen, H. Kawashima, M. Sugano, H. Yamada, *Lipids* **26** (1991) 512 (https://dx.doi.org/10.1007/BF02536595)
179. T. Phitak, P. Pothacharoen, J. Settakorn, W. Poompimol, B. Caterson, P. Kongtawelert, *Phytochemistry* **80** (2012) 77 (https://dx.doi.org/10.1016/j.phytochem.2012.05.016)
180. M. J. Kato, A. Chu, L. B. Davin, N. G. Lewis, *Phytochemistry* **47** (1998) 583 (https://dx.doi.org/10.1016/S0031-9422(97)00727-9)
181. F. Hirata, K. Fujita, Y. Ishikura, K. Hosoda, T. Ishikawa, H. Nakamura, *Atherosclerosis* **122** (1996) 135 (https://dx.doi.org/10.1016/0021-9150(95)05769-2)
182. K. Yamashita, Y. Iizuka, T. Imai, M. Namiki, *Lipids* **30** (1995) 1019 (https://dx.doi.org/10.1007/BF02536287)
183. K. Yamashita, Y. Nohara, K. Katayama, M. Namiki, *J. Nutr.* **122** (1992) 2440 (https://dx.doi.org/10.1093/jn/122.12.2440)
184. A. Kamal-Eldin, D. Pettersson, L. A. Appelqvist, *Lipids* **30** (1995) 499 (https://dx.doi.org/10.1007/BF02537023)
185. W. D. MacRae, G. H. N. Towers, *J. Ethnopharmacol.* **12** (1984) 75 (https://dx.doi.org/10.1016/0378-8741(84)90087-4)
186. J. J. Chen, Y. L. Chang, C. M. Teng, I. S. Chen, *Planta Med.* **66** (2000) 251 (https://dx.doi.org/10.1055/s-2000-8562)
187. K. H. Lee, Z. Xiao, *Phytochem. Rev.* **2** (2003) 341 (https://dx.doi.org/10.1023/b:phyt.0000045495.59732.58)
188. H. C. Castro-Faria-Neto, P. T. Bozza, H. N. Cruz, C. L. M. Silva, F. A. Violante, J. M. Barbosa-Filho, G. Thomas, M. A. Martins, E. V. Tibiriçá, *Planta Med.* **61** (1995) 101 (https://dx.doi.org/10.1055/s-2006-958025)
189. H. C. Castro-Faria-Neto, M. A. Martins, P. M. R. Silva, P. T. Bozza, H. N. Cruz, M. de Queiroz-Paulo, M. A. C. Kaplan, R. S. B. Cordeiro, *J. Lipid Mediat.* **7** (1993) 1 (https://www.ncbi.nlm.nih.gov/pubmed/8358020)
190. M. Sugano, T. Inoue, K. Koba, K. Yoshida, N. Hirose, Y. Shinmen, K. Akimoto, T. Amachi, *Anticancer Res.* **54** (1990) 2669 (https://dx.doi.org/10.1080/00021369.1990.10870374)
191. N. Hirose, F. Doi, T. Ueki, K. Akazawa, K. Chijiiwa, M. Sugano, K. Akimoto, S. Shimizu, H. Yamada, *Anticancer Res.* **12** (1992) 1259 (https://www.ncbi.nlm.nih.gov/pubmed/1386971)

192. H. Ogawa, S. Sasagawa, T. Murakami, H. Yoshizumi, *Clin. Exp. Pharmacol. Physiol.* **22** (1995) 310 (https://dx.doi.org/10.1111/j.1440-1681.1995.tb02932.x)
193. N. Hirose, T. Inoue, K. Nishihara, M. Sugano, K. Akimoto, S. Shimizu, H. Yamada, *J. Lipid Res.* **32** (1991) 629 (https://www.ncbi.nlm.nih.gov/pubmed/1856608)
194. T. Ogawa, T. Makino, N. Hirose, M. Sugano, *Carcinogenesis* **15** (1994) 1663 (https://dx.doi.org/10.1093/carcin/15.8.1663)
195. J. Y. Gu, Y. Wakizono, A. Tsujita, B. O. Lim, M. Nonaka, K. Yamada, M. Sugano, *Biosci. Biotechnol. Biochem.* **59** (1995) 2198 (https://dx.doi.org/10.1271/bbb.59.2198)
196. Y. Kiso, *BioFactors* **21** (2004) 191 (https://dx.doi.org/10.1002/biof.552210139)
197. L. Ashakumary, I. Rouyer, Y. Takahashi, T. Ide, N. Fukuda, T. Aoyama, T. Hashimoto, M. Mizugaki, M. Sugano, *Metabolism* **48** (1999) 1303 (https://dx.doi.org/10.1016/S0026-0495(99)90272-X)
198. R. Christov, V. Bankova, I. Tsvetkova, A. Kujumgiev, A. D. Tejera, *Fitoterapia* **70** (1999) 89 (https://dx.doi.org/10.1016/s0367-326x(98)00044-6)
199. E. M. Suleimenov, F. M. Smagulova, R. B. Seidakhmetova, R. M. Aksartov, V. A. Raldugin, S. M. Adekenov, *Chem. Nat. Compd.* **43** (2007) 232 (https://dx.doi.org/10.1007/s10600-007-0090-5)
200. F. Kawamura, S. Ohara, A. Nishida, *Holzforschung* **58** (2004) 189 (https://dx.doi.org/10.1515/HF.2004.028)
201. W. D. MacRae, J. B. Hudson, G. H. N. Towers, *Planta Med.* **55** (1989) 531 (https://dx.doi.org/10.1055/s-2006-962087)
202. W. D. MacRae, G. H. N. Towers, *Phytochemistry* **23** (1984) 1207 (https://dx.doi.org/10.1016/S0031-9422(00)80428-8)
203. M. A. Ouyang, Y. S. Wein, Z. K. Zhang, Y. H. Kuo, *J. Agric. Food Chem.* **55** (2007) 6460 (https://dx.doi.org/10.1021/jf0709808)
204. P. Sartorelli, C. S. Carvalho, J. Q. Reimão, H. Lorenzi, A. G. Tempone, *Planta Med.* **76** (2010) 1454 (https://dx.doi.org/10.1055/s-0029-1240952).