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PHENOLIC COMPOUNDS OF LAURUS NOBILIS (REVIEW)

Dmitry A. Konovalov[1], Naida M. Alieva[2]

[1] Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University
11, Kalinin ave., Pyatigorsk, Stavropol region, Russia 357532
[2] Dagestan State Medical University. 1, Lenin sq., Makhachkala, Dagestan republic, Russia 367000

E-mail: d.a.konovalov@pmedpharm.ru

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One of the most famous plants of the laurel family (Lauraceae) is Laurus nobilis L.
The aim of the study was to review scientific information on the study of phenolic compounds of wild-growing and cultivated Laurus nobilis L.
Materials and methods. The study was performed using information retrieval (PubMed, ScholarGoogle) and library databases (eLibrary, Cyberleninca), as well as ResearchGate application for semantic search. The research methods are analysis and synthesis of the scientific literature data for the period from 2000 up to the present.
Results. The data presented in the review show that leaves, fruits, and shoots of Laurus nobilis L. are valuable sources of phenolic compounds, such as phenolic acids, flavonoids, and proanthocyanidins. The quantitative content of these groups of substances varies depending on the collecting ground, the source of raw materials (cultivated or wild plants), the time (phase) of their harvesting, the method of drying, extraction from raw materials, etc. Phenolic compounds exhibit a pronounced antioxidant and antiradical activity, have an inhibitory effect on NO production, sodium-potassium adenosine triphosphatase, on tumour cell lines (HeLa, MCF7, NCI-H460 and HCT15), and are characterised by an antibacterial action against gram-positive and gram-negative bacteria.
Conclusion. The analysis of the available scientific information showed that the phenolic compounds of Laurus nobilis L. are one of the main groups of the active compounds of this plant. The use of this information is essential for the development of **new effective medicines based on the raw materials of Laurus nobilis L..**
Keywords: Laurus nobilis L., phenolic compounds, quantification , antioxidant, anticancer activity

ФЕНОЛЬНЫЕ СОЕДИНЕНИЯ ЛАВРА БЛАГОРОДНОГО (ОБЗОР)

Д.А. Коновалов[1], Н.М. Алиева[2]

[1] Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации
357532, Россия, Ставропольский край, г. Пятигорск, пр. Калинина, 11
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Дагестанский государственный медицинский университет» Министерства здравоохранения Российской Федерации. 367000, Россия, Республика Дагестан, г. Махачкала, пл. Ленина, 1.

E-mail: d.a.konovalov@pmedpharm.ru

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Одним из самых известных растений семейства лавровые (Lauraceae) является лавр благородный (Laurus nobilis L.).
Целью исследования являлся обзор научной информации по изучению фенольных соединений дикорастущего и культивируемого лавра благородного.

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ОРИГИНАЛЬНАЯ СТАТЬЯ
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Материалы и методы. Исследование проводилось с использованием информационно-поисковых (PubMed, ScholarGoogle) и библиотечных баз данных (eLibrary, Cyberleninca), а также приложения ResearchGate для семантического поиска. Методы исследования – анализ и обобщение научной литературы за период с 2000 года по настоящее время.

Результаты. Представленные в обзоре данные показывают, что листья, плоды и побеги лавра благородного являются ценными источниками фенольных соединений, таких как фенольные кислоты, флавоноиды, проантоцианидины. Количественное содержание этих групп веществ варьирует в зависимости от места сбора, источника сырья (культивируемые или дикорастущие растения), времени (фазы) его заготовки, способа сушки, извлечения из сырья и т.д. Фенольные соединения проявляют выраженную антиоксидантную и антирадикальную активность, оказывают ингибирующее влияние на продукцию оксида азота, натрий-калиевую аденозинтрифосфатазу, на линии опухолевых клеток (HeLa, MCF7, NCI-H460 и HCT15), характеризуются антибактериальным действием в отношении грамположительных и грамотрицательных бактерий.

Заключение. Анализ доступной научной информации показал, что фенольные соединения лавра благородного являются одной из основных групп действующих соединений этого растения. Использование этих данных важно для разработки новых эффективных лекарственных средств на основе сырья лавра благородного.

Ключевые слова: лавр благородный, Laurus nobilis, фенольные соединения, количественное определение, антиоксидантная, противораковая активность

INTRODUCTION

The Laurel family (*Lauraceae*) includes more than 2500 plant species that grow in the subtropics and tropics of East Asia, South and North America. One of the most famous and most commonly used plants from this family is *Laurus nobilis* L. The name of the plant is dedicated to Apollo, the ancient Greek sun god, and is a symbol of peace and victory. Laurel wreaths covered the heads of emperors, generals and poets.

The natural habitats of this evergreen plant are the territories of the Mediterranean countries with high annual rainfall [1]. It is grown as a decorative species in Europe, Russia, the USA and other countries, cultivated in Turkey, Algeria, Morocco, Portugal, Spain, Italy, France, Russia and Mexico [2].

Laurus nobilis L. leaves are widely used in traditional dishes of peoples of not only the Mediterranean but also many other countries [5]. The leaves and fruits of the plant are used in traditional medicine of peoples of different countries to reduce high blood glucose levels, in the treatment of diseases caused by fungal and bacterial infections. Extracts from laurel leaves exhibit anti-inflammatory, soothing, antiepileptic properties [6–10]. Infusion of dry leaves is used for various gastrointestinal diseases, as well as for flatulence as a carminative [11]. *Laurus nobilis* L. fruits were included in the sixth edition of the Russian Pharmacopoeia and the State Pharmacopoeia of the USSR of the first edition. Laurel leaves are official raw materials (*Lauri Folium*) in Iran [12].

It has been experimentally established that the biologically active compounds in the essential oil and leaf extracts, promote healing of small wounds [13], have anti-inflammatory, analgetic [14], immunostimulating [15], neuroprotective [13, 16], anticholinergic, antioxidant, antiulcer, anticonvulsant, antimutagenic, insecticidal, antibacterial, antiviral, antifungal [13] and larvicidal [17] effects. Some publications are devoted to characterizing the anticancer potential of the essential oil [18], methanol [19], ethanol and water extracts [20] from laurel leaves and its fruits. The scientific literature describes antibacterial properties of the essential oil [21–22] and a few kinds of extracts: water [23], ethanol [24] and methanol [25]. According to some researchers, the antibacterial activity of the extracts is associated with the presence of terpene and phenolic substances [26–27]. *Laurus nobilis* L. leaves are also included in the herbal tea [28] and drugs for the treatment of diabetes [29–30], and their extracts - in the composition of biologically active food additives [31]. *Laurus nobilis* L. essential oil is used in cosmetology and in the production of perfumes and soaps.

The chemical composition of the leaves was studied quite widely in different countries where this plant grows in natural habitats or is cultivated. In previous studies, different groups of chemical compounds in *Laurus nobilis* L. leaves and fruits were found. According to the results of a lot of studies [32–33], 1,8-Cineol is the main component of *Laurus nobilis* L. leaf essential oil (up to 70%). *Laurus nobilis* L. fruits contain fatty and essential oils. It is this mixture that was previously known as “laurel oil” and included laurostearin, a lauric acid ester as one of its components. The composition of fruits fatty acids was studied by B. Ozcan et al. [7]. The roots and leaves of *Laurus nobilis L.* are a source of sesquiterpene lactones [34]. Two distinct chemical types containing laurenobiolide and costunolide, as the main substances, were identified in them [35–37]. Sesquiterpene lactones found in *Laurus nobilis L.* leaves, have different pharmacological properties: inhibition of NO production [36] and ethanol absorption [38], an increased activity of hepatic glutathione S-transferase [3]. In the last decade, the cytotoxic activity of these compounds against various tumour cell lines, has been actively studied [39–40]. Quite often, the antioxidative activity of various extracts from the leaves of wild-growing [10, 41–42] and cultivated *Laurus nobilis L.* [6, 11] was investigated. In recent years, several review papers devoted to the biologically active compounds of *Laurus nobilis L.,* have appeared [13, 43]. However, in these articles, the information on the accumulation of phenolic compounds in the plant is extremely limited. Phenolic compounds of leaves and fruits of wild-growing and cultivated *Laurus nobilis L.* have been studied in different habitats. The

growing interest in this group of natural compounds of *Laurus nobilis L.* is associated not only with the variety of identified structures but also with the relevant types of pharmacological activity (antioxidant and anticancer) that are associated with it.

THE AIM of the study was to review scientific information on the study of phenolic compounds of wild-growing and cultivated *Laurus nobilis L.*

MATERIALS AND METHODS

The study was performed using information retrieval (PubMed, ScholarGoogle,) and library databases (eLibrary, Cyberleninca), as well as ResearchGate application for the semantic search. The research methods are: analysis and synthesis of the scientific literature data for the period from 2000 up to the present.

RESULTS

In the study by H.W. Kang et al. [44], ethanol extract from laurel leaves was cytotoxic to *Staphylococcus aureus 209p* and had the highest alkylperoxy radical-trapping (ROO·) activity among 120 species of the plants studied. After processing this extract with chloroform, ethyl acetate, n-butanol and water, the ethyl acetate fraction showed the highest activity. The authors isolated the main flavonol from the leaves of the plant, which was identified as isoquercitrin by spectral characteristics **(1)** (see Table 1). The further study of the antioxidant activity of this compound established its comparability to the effect of the known antioxidants such as epigallocatechin, resveratrol and higher than that of butyl hydroxyanisole, butylhydroxytoluene and ascorbic acid.

Several compounds including phenolic glucoside (**2**) and flavonoids (**3** и **4**), were isolated by S. de Marino et al [45] from methanol extract of fresh *Laurus nobilis L.* leaves. The study of these substances' effect on nitric oxide production in the rats' macrophages activated by lipopolysaccharide (J774), showed that kaempferol-3-O-α-L-(3", 4"-di-E-p-coumaroyl) rhamnoside is the most active of them (**3**).

Methanol extracts of five types of the plant materials purchased at Droga (Portoroz, Slovenia), including *Laurus nobilis L.* leaves, were investigated by a group of authors [46]. The total amount of phenolic compounds was determined by the colourimetric method using the Folin – Ciocalteu reagent. In the extract of *Laurus nobilis L.* leaves, their content was 99.7 g/kg (in gallic acid equivalents). In acid hydrolysed extracts, proanthocyanidins were studied spectrophotometrically at the wavelength of 540 nm (29.9 g/kg in total). Free flavones (apigenin and luteolin) and flavonols (kaempferol, myricetin and quercetin) in hydrolysed extracts were determined by HPLC. The detection was carried out at 367 nm using standard samples of apigenin, luteolin, quercetin, myricetin and kaempferol as external standards. The authors identified quercetin and kaempferol. The flavonoid content was 80.1 mg/kg (in total).

The composition of the anthocyanins isolated from peeled *Laurus nobilis L.* seeds was first determined by L. Longo and G. Vasapollo [47]. The compounds were isolated with a 0.1% aqueous methanol solution acidified with hydrochloric acid, followed by purification of the extract in a C-18 solid-phase cartridge; then they were identified by HPLC-MS analysis. The content of anthocyanins in the fruits was 217 mg/g. The main anthocyanins are cyanidin 3-O-glucoside (5.90 mg/g, i.e. 41% of the total amount) and cyanidin 3-O-rutinoside (6.116 mg/g – 53%). Besides, two minor anthocyanins were identified as 3-O-glucoside (7) and 3-O-rutinoside peonidin (8) (10.6 mg/g, i.e. 5% of the total amount) (see Table 1).

Laurus nobilis L. leaves collected by V. Papageorgiou et al. in the Patra region (Greece) in the first half of February, May, August and November 2007, were divided into two parts. The first part of the samples was subjected to the air-shadow drying at ambient temperature, and the other one was freeze-dried for 6 hours at –60°C [48]. The total amount of phenolic compounds was determined by the colourimetric method using the Folin – Ciocalteu reagent [49] and gallic acid as a standard. The absorption spectrum of relatively distilled water was measured at 765 nm, and the calibration curve was plotted using the data of gallic acid. Colourimetry was also used to determine the total amount of flavonoids, with epicatechin as the reference substance. The spectrum of the mixture was measured at 510 nm. The results showed a significant difference in the content of the total amount of phenolic compounds depending on the phase of the plant development. The amount of flavonoids in the extract from *Laurus nobilis L.* leaves collected in May (at the beginning of fruiting) amounted to 2.90 mg/g in terms of epicatechin and dry raw materials. The total amount of phenolic compounds reached a maximum level during the fruiting initiation stage (80.30 mg, calculated in gallic acid equivalents / g of dry raw materials), while the lowest content was noted at the end of the fruiting period (22.90 mg/g, calculated in gallic acid equivalents and dry raw materials). These results were significantly different from those established during the period of full bloom (51.30 mg/g in gallic acid equivalents and dry raw materials) and in the budding stage (42.60 mg gallic acid equivalents/g and dry raw materials). The *Laurus nobilis L.* extracts obtained from freeze-dried raw materials, showed a similar seasonal variation. The main phenolic components in all the extracts studied, were flavonoids. The concentration of luteolin **(9)** was relatively high (ranging from 0.20 to 4.50 mg/g of dry weight). Phenolic acids – 3,4-dihydroxybenzoic **(10)**, gallic **(11)**, vanillic **(12)** and rosmarinic **(13)** ones - were found in low concentrations (see Table 1). Freeze-drying caused a significant decrease (by almost 50%) in the total amount of phenolic compounds and flavonoids in almost all the studied samples of laurel leaves. To a great extent, this was due to a decrease in the content of luteolin and most phenolic acids (mainly hydroxycinnamic acids). This study result is consistent with the data obtained by other authors, according to which freeze-drying caused a loss of 87% of the total amount of flavonols in the extracts of *Posidonia oceanica* L. [50].

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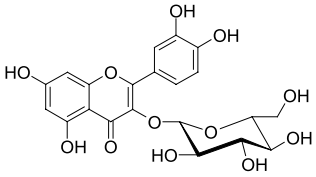

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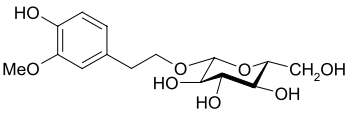

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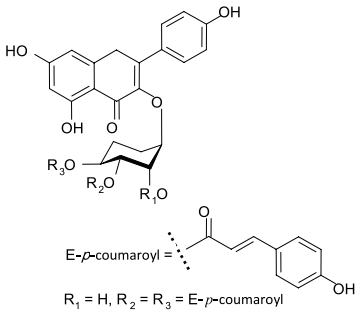

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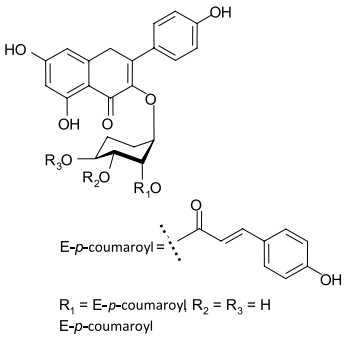

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Table 1 – Phenolic compounds of Laurus nobilis L.

Order numbers	Groups of substances / names of compounds	Morphological parts of the plant	Content, %	Pharmacological activity	Reference
		Flavonoids			
1.	Isoquercitrin (**1**)*	Leaves	+**	Antioxidant activity	[44]
2.	Kaempferol-3-O-α-L- (3", 4"-di-E-p-coumaroyl) rhamnoside (**3**)	Leaves	0.00027	Inhibitor of nitric oxide production in LPS-activated murine macrophages (J774)	[45]
3.	Kaempferol-3-O-α-L-(2"-E-p-coumaroyl) rhamnoside (**4**)	Leaves	0.00022	–***	[45]
4.	Luteolin (**9**)	Leaves	up to 0.45 ± 0.05 (dry weight)	–	[48]
5.	Kaempferol-3-O-glucopyranoside (**16**)	Leaves	0.0092	Antioxidant activity	[11]
6.	Kaempferol-3-O-rhamnopyranoside (**17**)	Leaves	0.00112	Antioxidant activity	[11]
7.	Kaempferol-3-O-(2",4"-di-E-p-coumaroyl)-rhamnoside (**18**)	Leaves	0.00916	Antioxidant activity	[11]
8.	Kaempferol-3-O-arabinopyranoside (**19**)	Leaves	0.0064	Antioxidant activity	[11]
9.	Kaempferol-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] (**20**)	Leaves	0.00112	Antioxidant activity	[11]
10.	Quercetin-3-O-glucopyranoside (**21**)	Leaves	0.0152	Antioxidant activity	[11]
11.	Quercetin-3-O-rhamnopyranoside (**22**)	Leaves	0.0084	Antioxidant activity	[11]
12.	Quercetin-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] (**23**)	Leaves	0.0062	Antioxidant activity	[11]
13.	3'-Methoxyquercetin-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] (**24**)	Leaves	0.00488	Antioxidant activity	[11]
14.	3'-Methoxyquercetin-3-O-glucopyranoside (**25**)	Leaves	0.008	Antioxidant activity	[11]
15.	Izovitexin-2"-rhamnoside (**27**)	Leaves	0.00536	Antioxidant activity	[11]
16.	Rutin (**29**)	Leaves	0.0929 ± 0.19 (dry weight)	Antioxidant activity	[54]

Continuation of table 1

Order numbers	Groups of substances / names of compounds	Morphological parts of the plant	Content, %	Pharmacological activity	Reference
17.	Kaempferol-3-O-α-L-(3″-Z, 4″-di-E-p-coumaroyl)-rhamnopyranoside (**30**)	Leaves	0.000627	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
18.	Kaempferol-3-*O*-α-L-(3″, 4″-di-Z-p-coumaroyl)-rhamnopyranoside (**31**)	Leaves	0.000307	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
19.	Kaempferol-3-*O*-α-L-(3″, 4″-di-E-p-coumaroyl)-rhamnopyranoside (**32**)	Leaves	0.00243	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
20.	Kaempferol-3-*O*-α-L-(2″-*E*, 4″-*Z*-di-p-coumaroyl)-rhamnopyranoside (**33**)	Leaves	0.00275	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
21.	Kaempferol-3-*O*-α-L-(2″, 4″-di-E-p-coumaroyl)-rhamnopyranoside (**34**)	Leaves	0.0105	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
22.	Kaempferol-3-*O*-α-L-(2″-*Z*, 4″-E-di-p-coumaroyl)-rhamnopyranoside (**35**)	Leaves	0.00349	Sodium-potassium adenosine triphosphatase inhibitor. Antibacterial activity against St. aureus, B. subtilis, M. luteus, S. typhimurium, Pr. vulgaris	[55]
23.	2′,β-Dihydroxy-α,β-dihydrochalcon-α-O-hexoside (**37**)	Leaves	+	–	[56]
24.	2′-Dihydroxy-α,β-dihydrochalcon-α-O-hexoside (**40**)	Leaves	+	–	[56]
25.	Apigenin-6,8-di-C-hexoside (**41**)	Leaves	+	–	[56]
26.	Apigenin-6-C-(2″-O-deoxyhexosyl)-hexoside (**42**)	Leaves	+	–	[56]
27.	Apigenin-8-C-hexoside (**43**)	Leaves	+	–	[56]
28.	Quercetin-3-O-(6″-O-deoxyhexosyl)-hexoside (**44**)	Leaves	+	–	[56]
29.	Tetramethoxydihydroquercetin-3-O-pentoside (**45**)	Leaves	+	–	[56]
30.	Kaempferol-3-O-(6″-O-deoxyhexosyl)-hexoside (**46**)	Leaves	+	–	[56]
31.	Quercetin-3-O-hexoside (isomer 1 and 2) (**47**)	Leaves	+	–	[56]
32.	Isorhamnetin-3-O-(6″-O-deoxyhexosyl)- hexoside (**48**)	Leaves	+	–	[56]
33.	Quercetin-3-O-pentoside (**49**)	Leaves	+	–	[56]
34.	Kaempferol-3-O-hexoside (**50**)	Leaves	+	–	[56]
35.	Quercetin-3-O-deoxyhexoside (**51**)	Leaves	+	–	[56]
36.	Isorhamnetin-3-O-hexoside (**52**)	Leaves	+	–	[56]
37.	Kaempferol-3-O-pentoside (**53**)	Leaves	+	–	[56]
38.	Kaempferol-3-O-deoxyhexoside (**54**)	Leaves	+	–	[56]
39.	Luteolin-6-C-glucoside (**59**)	Leaves	+	–	[57]
40.	Apigenin-8-C-glucoside (**60**)	Leaves	+	–	[57]
41.	Apigenin-6-C-glucoside (**61**)	Leaves	+	–	[57]

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End of table 1

Order numbers	Groups of substances / names of compounds	Morphological parts of the plant	Content, %	Pharmacological activity	Reference
42.	Quercetin-3-O-glucoside (**62**)	Leaves	+	–	[57]
43.	Kaempferol-3-O-rutinoside (**63**)	Leaves	+	–	[57]
44.	Kaempferol-3-O-glucoside (**64**)	Leaves	+	–	[57]
	Phenolic acids				
45.	3,4-Dihydroxybenzoic acid (**10**)	Leaves	до 5.0 ± 0.4 (dry weight)	–	[48]
46.	Gallic acid (**11**)	Leaves	до 1.40 ± 0.15 (dry weight)	Antioxidant activity	[48]
		Fruits	0.02	–	[61]
47.	Vanillic acid (**12**)	Leaves	до 1.40 ± 0.15 (dry weight)	Antioxidant activity	[48, 52]
48.	Rosmarinic acid (**13**)	Leaves	до 0.02 (dry weight)	Antioxidant activity	[48]
49.	Caffeic acid (**14**)	Leaves	+	Antioxidant activity	[52]
50.	Ferulic acid (**15**)	Leaves	+	Antioxidant activity	[52]
51.	3,4-Dihydroxybenzoic acid hexoside (**36**)	Leaves	+	–	[56]
52.	Coumaric acid hexoside (**39**)	Leaves	+	–	[56]
53.	Coumaric acid (**65**)	Leaves	+	–	[59]
54.	2-Hydroxycinnamic acid (**66**)	Leaves	+	–	[59]
	Anthocyanins				
55.	Cyanidin-3-O-glucoside (**5**)	Fruits	0.56	–	[47]
56.	Cyanidin-3-O-rutinoside (**6**)	Fruits	0.73	–	[47]
57.	Peonidine-3-O-glucoside (**7**)	Fruits	0.0063 в сумме	–	[47]
58.	Peonidine-3-O-rutinoside (**8**)	Fruits	+	-	[47]
	Phenolic glycosides				
59.	2-(4-Hydroxy-3-methoxy-phenyl)-ethyl-O-β-D-glucopyrano-side (**2**)	Leaves	0.00032	–	[45]
60.	1-(2′-Hydroxyphenyl)-1-hydroxy-phenylpropane-α-O-hexoside (**38**)	Leaves	+	–	[56]
	Flavan-3-ols				
61.	Catechin (**26**)	Leaves	0.00916	Antioxidant activity	[11]
			1.06	–	[61]
62.	Epicatechin hexoside (**55**)	Leaves	+	–	[57]
63.	(+)-Gallocatechin (**56**)	Leaves	+	–	[57]
64.	(+)-Catechin (**57**)	Leaves	+	–	[57]
65.	(-)-Epicatechin (**58**)	Leaves	+	–	[57]
66.	Epicatechin (**67**)	Leaves	1.29	–	[61]
		Fruits	0.65		
67.	Epigallocatechin (**68**)	Leaves	0.40	–	[61]
		Fruits	0.51		
68.	Epicatechin gallate (**69**)	Fruits	0.16	–	[61]
69.	Cinnamtannin B1 (**28**)	Leaves	0.00092	Antioxidant activity	[11]

** – the number of the compound in the text of the article;*
*** – the compound was found out but its quantitative content was not established;*
**** – the activity of this compound was not determined in this study*

Similar changes, i.e., the destruction of hydroxycinnamic acids and flavonoids and an increase in the content of gallic acid, were known before, but no reasons had been established [51]. According to the authors, it is quite possible, that the stage of thawing of plant material after freeze-drying could lead to a loss in the content of hydroxycinnamic acids and flavonoids.

Using high-performance liquid chromatography (HPLC), M. Muchuweti et al. [52] established the presence of caffeic **(14)**, ferulic **(15)** and vanillic **(12)** acids in the laurel leaf extracts (see Table 1).

The antioxidant activity and the total amount of the phenolic compounds of some spices (*Mentha piperita* L., *Rhus coriaria* L., *Thymbra spicata*, *Salvia officinalis*, *Rosmarinus officinalis* L., *Capparis ovata* L., *Origanum vulgare* L., *Laurus nobilis* L. and *Capsicum annum* L.) were determined by A. Ünver et al. [53]. The highest values of the antioxidant activity in TEAC units (Trolox Equivalent Antioxidant Capacity) were obtained for sage (1.783) and rosemary (1.241). For the extraction from *Laurus nobilis* L. leaves, it amounted to 1.001 ± 0.020 mmol TE/g of the extract. The values of the antiradical activity were IC_{50}, mg/ml) – 1.901 ± 0.034 mg/ml. The total amount of phenolic compounds (colourimetry with the Folin – Ciocalteu reagent) was 288.15 ± 1.34 mg/g of the extract, in terms of the equivalent amount of gallic acid.

Phytochemical studies of the infusion of the *Laurus nobilis* L. leaves collected in November 2003 in S. Basilio (Cagliari, Sardinia, Italy) were carried out by a group of authors [11] using semi-preparative HPLC with a diode matrix as a detector and tandem mass spectrometry. The following substances were found in the aqueous leaf infusion: kaempferol-3-O-glucopyranoside (16); kaempferol-3-O-rhamnopyranoside **(17)**; kaempferol-3-O-(2”, 4”-di-E-p-coumaroyl)-rhamnoside **(18)**; kaempferol-3-O-arabinopyranoside **(19)**; kaempferol-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] **(20)**; quercetin-3-O-glucopyranoside **(21)**; quercetin-3-O-rhamnopyranoside**(22)**;quercetin-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] **(23)**; 3’-methoxyquercetin-3-O-[6-O-(rhamnopyranosyl) glucopyranoside] **(24)**; 3’-methoxyquercetin-3-O-glucopyranoside **(25)**; catechin **(26)**; 2”-rhamnosylisovitexin **(27)**; cinnamtannin B1 **(28)** (see Table. 1).

The content of kaempferol and quercetin derivatives in the infusion was 0.31 ± 0.01 mg/100 ml and 2.11 ± 0.01 mg/100 ml, respectively. Thus, by the researchers’ data, per 200 ml of infusion, the quantitative content of flavonoids was approximately 5.0 mg.

M. Lu et al. [54] found out the presence of flavonoids and phenolic acids in ethanol extracts of *Laurus nobilis L.* leaves. The content of phenolic acids established by the method of ultra-performance liquid chromatography, was 474.1 ± 12.7 (mg/g dry weight), rutin **(29)** –929.4 ± 19.3 (μg/g dry weight) and unidentified flavonoids – 2138.2 ± 42.7 (mg/g dry weight). The total amount of phenolic compounds (colorimetry according to Folin – Ciocalteu) in gallic acid equivalents and dry raw materials was 46.79 ± 3.22 mg/g.

B. Kaurinovic et al. studied the leaves of cultivated laurel collected in June 2008 in the vicinity of Ulcinj (Montenegro) [42]. The amount of flavonoids in the dried leaves was determined by the colourimetric method based on the property of flavonoids and flavone glycosides to form complexes with aluminium ions. The absorption of the investigated solutions was measured at λ = 430 nm.

The determination results are shown in Table 2.

The maximum amount of flavonoids was found in the ethyl acetate fraction and the smallest in water. The results of the study of the antiradical activity of these extracts against free radicals (DPPH, NO, $O_2^{\bullet-}$) are presented in Table 3. Ethyl acetate extract showed the strongest inhibitory effect since the IC_{50} value was reached at the lowest concentration.

The results obtained, characterise the pronounced inhibitory effect of flavonoids from ***Laurus nobilis L.*** leaves against DPPH radicals.

Solid amorphous substances have been isolated from the ***Laurus nobilis L.*** leaves purchased in Turkey (Orege Forest Agricultural and Food Products Foreign Trade Ltd.) in August 2007, as a result of extraction (CH_2Cl_2, MeOH), subsequent fractionation and separation, using normal phase vacuum flash chromatography on silica gel and semi-preparative HPLC [55]. Metabolites have been identified as kaempferol-3-O-α-L-(3”-Z, 4”-E-di-p-coumaroyl) -rhamnopyranoside **(30)**, kaemperol-3-O-α-L-(3”, 4”-di-Z-p-coumaroyl)-rhamnopyranoside **(31)**, kaempferol-3-O-α-L-(3”, 4”di-E-p-coumaroyl)-rhamnopyranoside **(32)**, kaempferol-3-O-α-L-(2”-E, 4”-Z-di-p-coumaroyl)-rhamnopyranoside **(33)**, kaempferol-3-O-α-L-(2”,4”-di-E-p-cumaroyl)-rhamnopyranoside **(34)** and kaempferol-3-O-α-L-(2”-Z, 4”-E-di-p-coumaroyl)-rhamnopyranoside **(35)** (see Table 1).

All the compounds have been tested in vitro for their ability to inhibit sodium-potassium adenosine triphosphatase isolated from pig cerebral cortex.

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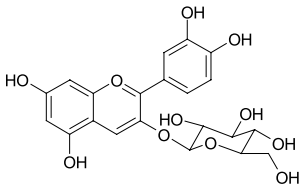

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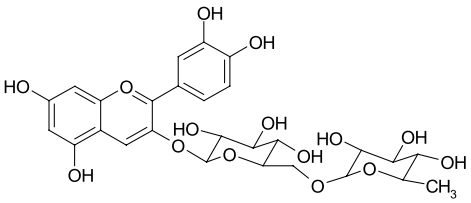

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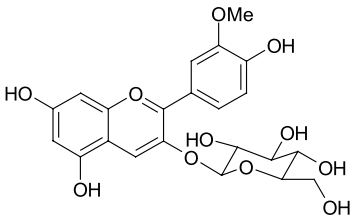

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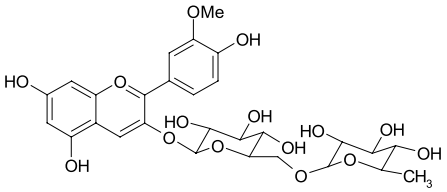

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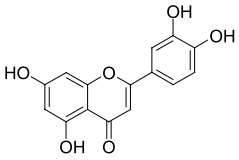

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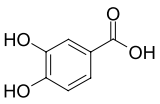

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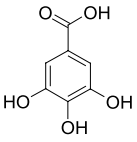

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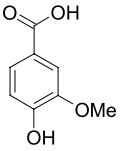

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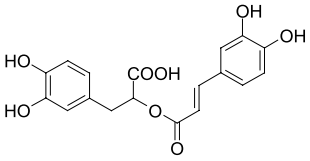

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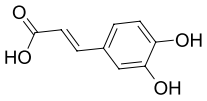

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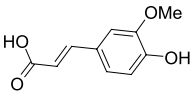

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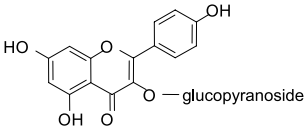

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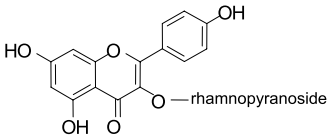

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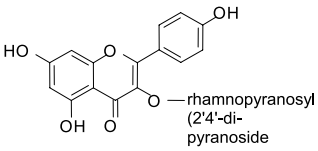

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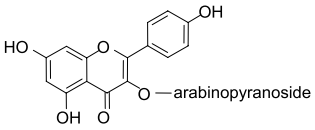

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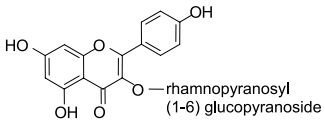

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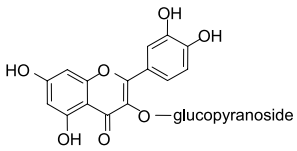

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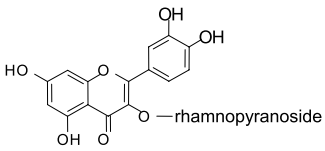

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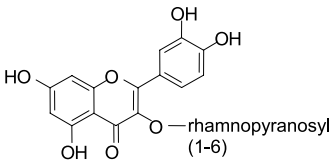

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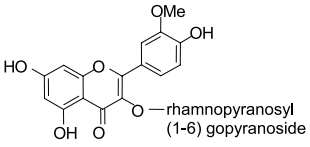

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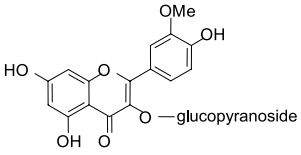

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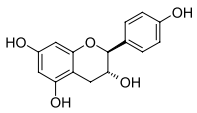

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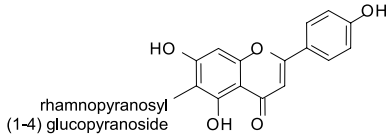

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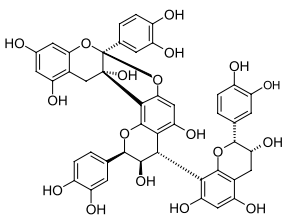

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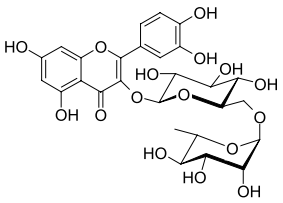

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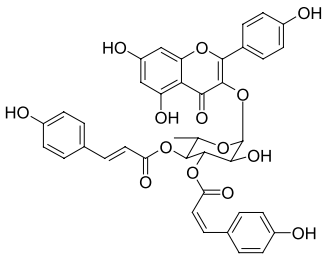

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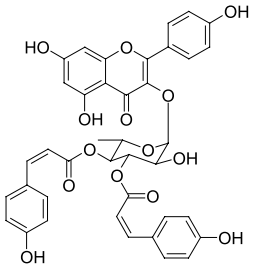

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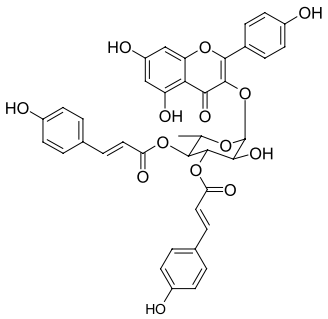

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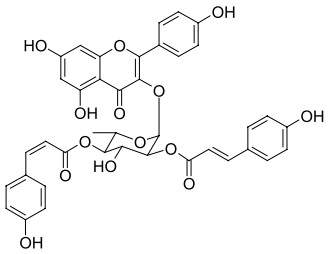

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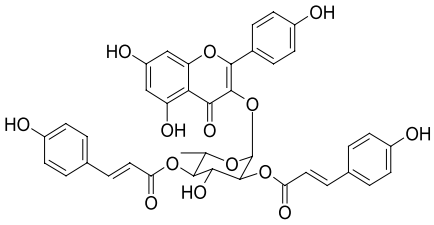

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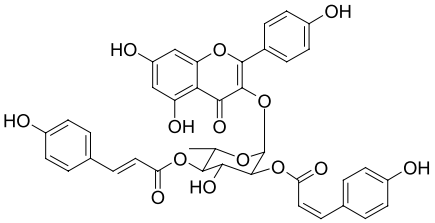

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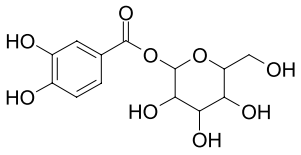

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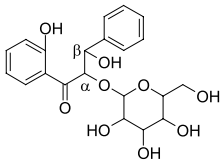

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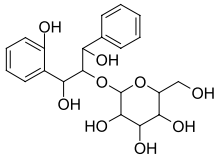

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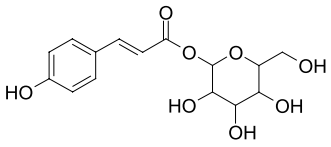

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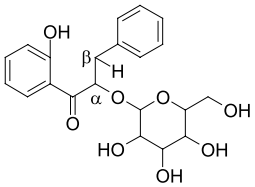

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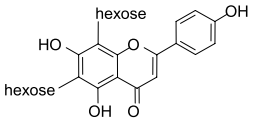

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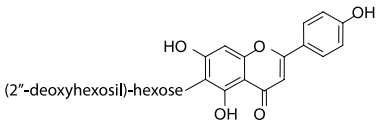

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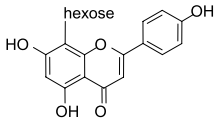

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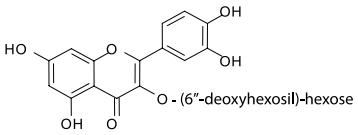

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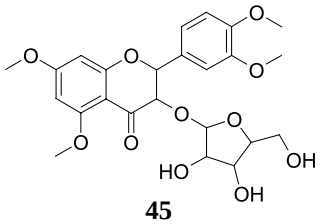

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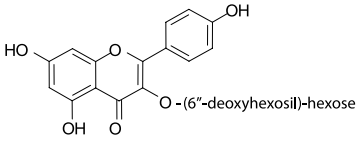

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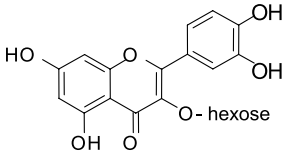

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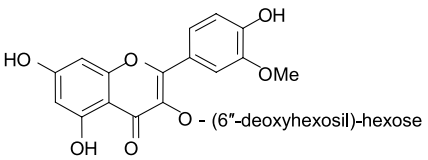

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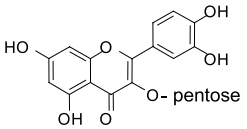

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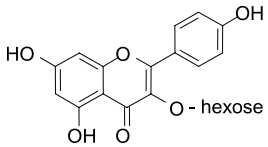

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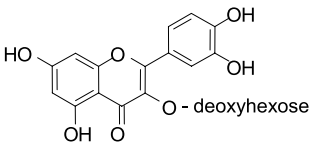

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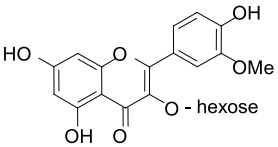

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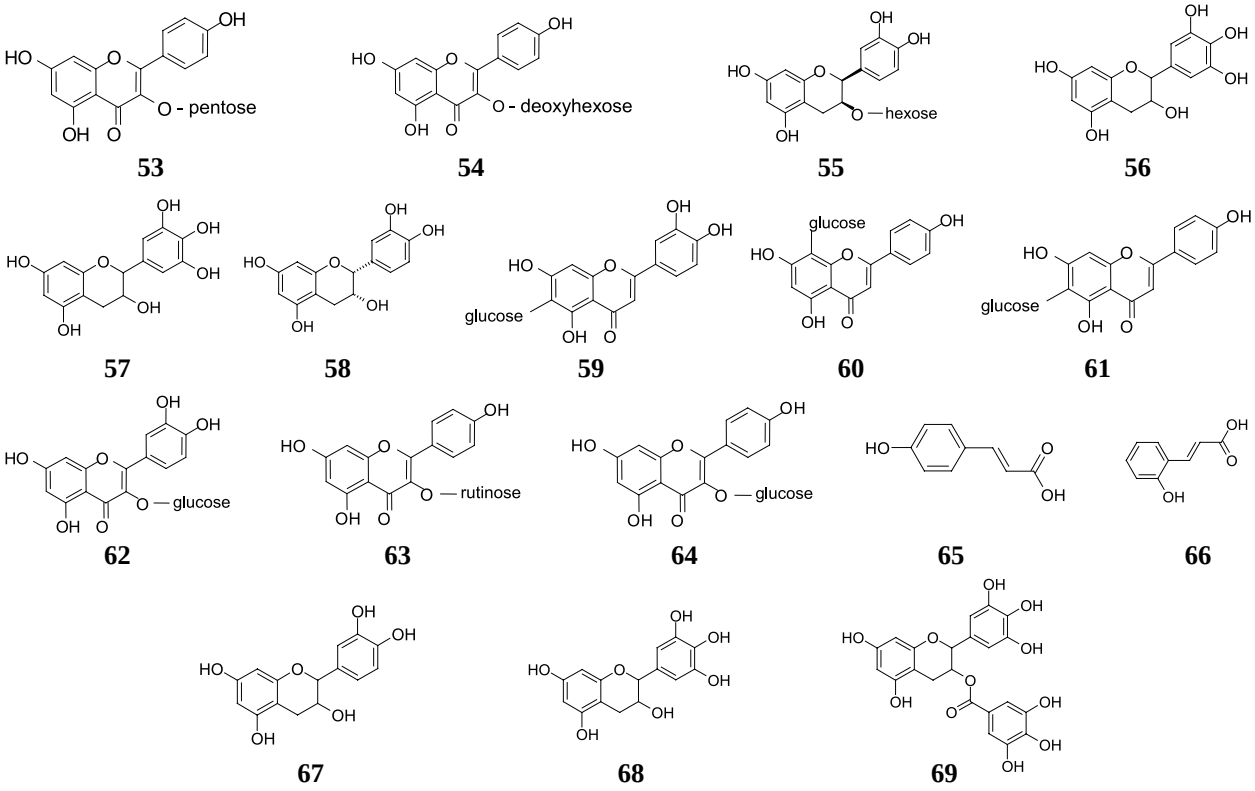

Table 2 – The content of the total amount of flavonoids in the extracts from *Laurus nobilis L.* leaves according to Kaurinovic et al. [42]

The total amount of flavonoids (mg/g) in the extracts				
Ethanolic	Chloroformic	Ethyl acetate	Butanol	Aqueous
0.76	1.02	1.56	1.07	0.68

Table 3 – Antiradical activity of extracts from *Laurus nobilis L.* leaves according to Kaurinovic et al [42]

Radicals	IC_{50} (μg/cm³)				
	Extracts				
	Ethanol	Chloroformic	Ethyl acetate	Butanol	Aqueous
DPPH*	127.38	139.42	83.24	181.35	161.83
$O_2^{\bullet-}$	327.60	429.43	163.57	288.64	486.32
NO	168.77	322.84	158.63	386.80	618.42

*Note: * – DPPH – 1,1-diphenyl-2-picrylhydrazyl*

Table 4 – The inhibitory activity of kaempferol glycosides from the *Laurus nobilis L.* leaves in regards to sodium-potassium adenosine triphosphatase according to Lee et al. [55]

Order numbers	Compounds	IC_{50} (μM)
1 (**30**)*.	Kaempferol-3-O-α-L-(3"-Z, 4"-E-di-p-coumaroyl)-rhamnopyranoside	6.4±0.3
2 (**31**).	Kaempferol-3-O-α-L-(3", 4"-di-Z-p-coumaroyl)-rhamnopyranoside	10.4±0.6
3 (**32**).	Kaempferol-3-O-α-L-(3",4"-di-E-p-coumaroyl)-rhamnopyranoside	5.0±0.1
4 (**33**).	Kaempferol-3-O-α-L-(2"-E,4"-Z-di-p-coumaroyl)-rhamnopyranoside	4.0±0.1
5 (**34**).	Kaempferol-3-O-α-L-(2",4"-di-E-p-coumaroyl)-rhamnopyranoside	5.2±0.2
6 (**35**).	Kaempferol-3-O-α-L-(2"-Z,4"-E-di-p-coumaroyl)-rhamnopyranoside	5.1±0.1
7.	Kaempferol**	>669.3
8.	Afzelin**	>463.0
9.	*p*-Coumaric acid**	>1218.0
10	Ouabain**	4.6±0.1

*Note: * – The number indicated in brackets, corresponds to the connection number in the text.*
*** – The compounds used as reference samples.*

Table 5 – Groups of phenolic compounds identified in *Laurus nobilis* L. leaves and extracts from them (mg/g, n = 18) [58]

Sample of raw materials/extract	The quantitative content of phenolic compounds			
	Flavan-3-ols	Flavones	Flavonoids	Phenolic compounds
Cultivated	*56 ± 8	4.4 ± 0.2	26 ± 2	86 ± 11
Wild	60 ± 4	2.6 ± 0.4	7 ± 2	71 ± 6
Methanolic extract	63.6 ± 0.4	4 ± 1	19 ± 10	86 ± 11
Aqueous extract	52 ± 5	3 ± 1	15 ± 9	70 ± 5

*Note: * – average value.*

Table 6 – Results of the quantitative determination of phenolic compounds in the leaves and shoots of *Laurus nobilis* L., according to Musienko and Kyslychenko [60]

Order numbers	Quantitative content (x ± Δx),% in terms of dry raw materials (n = 5)		
	Oxidizable phenols	Hydroxycinnamic acids	Flavonoids
Shoots			
1	4.80 ± 0.12	1.35 ± 0.08	0.85 ± 0.03
2	4.54 ± 0.17	1.29 ± 0.07	0.81 ± 0.07
Leaves			
1	5.25 ± 0.16	1.73 ± 0.05	0.95 ± 0.06
2	5.04 ± 0.11	1.71 ± 0.05	0.91 ± 0.05

Note. 1 – a sample from the vicinity of Alushta, 2 – a sample from the vicinity of Rybachye

Table 7 – The quantitative content of phenolic compounds and flavonoids in Laurus nobilis L. leaves, according to Vinha et al. [62]

Extracts	Phenolic compounds, mg/g, in terms of gallic acid	Flavonoids, mg/g, in terms of epicatechin
Aqueous	14.37±0.79	14.12±0.93
Hydroalcoholic (water-ethanol 1: 1)	43.03±0.35	30.15±0.25
Alcoholic	31.09±0.31	20.88±0.88

Table 8. Composition of monomeric (catechin and epicatechin) and oligomeric flavan-3-ols (A-type proanthocyanidins) in Laurus nobilis L. leaves, according to Vinha et al. [62]

Flavan-3-ols	Extracts		
	Aqueous	Hydroalcoholic (water-ethanol 1: 1)	Alcoholic
(+)-Catechin	0.41*	0.58	0.04
(-)-Epicatechin	0.99	3.44	0.67
Amount of the monomers	1.40	4.02	0.71
Dimeric proanthocyanidins	1.49	16.97	5.25
Trimeric proanthocyanidins 1	0.48	1.24	0.32
Trimeric proanthocyanidins 2	1.73	5.05	2.46
Tetrameric proanthocyanidins	1.02	1.16	0.32
Amount of flavan-3-ols	6.12	28.44	9.06

** – the results are given in mg/g in terms of epicatechin and dry weight.*

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The comparison of the relationship between the structure and activity of acylated kaempferol glycosides shows that substance 3**(32)**, which has an E-p-coumaroyl group in position C-3" in the rhamnopyranoside ring, was more active than substances 1(**30**) and 2**(31)** with Z-p-coumaroyl groups in position C-3". Substances 5**(34)** and 6**(35)** had almost the same IC_{50} values in regards to Na / K adenosine triphosphatase. Of all the tested substances, substance 4**(33)** showed the most powerful inhibitory potential. According to the authors' data, the presence of E-p-coumaroyl in position C-2"and Z-p-coumaroyl in position C-4" in the rhamnopyranoside ring, determined a high inhibitory activity of the studied compounds. Sodium-potassium adenosine triphosphatase inhibitors are known to have a significant therapeutic potential for some heart diseases, such as heart failure and cardiac arrhythmias. Therefore, the obtained results allow us to further continue the research in this direction. The antibacterial activity of acylated kaempferol glycosides has also been studied in regards to several gram-positive and gram-negative bacteria: *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Salmonella typhimurium*, *Proteus vulgaris*, *Escherichia coli*. Substances 1–6 (Table 4) showed an inhibitory activity in regards to all the studied bacteria, with the exception of E. coli. Substances 4**(33)** and 6**(35)** showed a minimum inhibitory concentration in the range of 0.65–2.08 μg/ml. The activity of the studied compounds was slightly inferior to the effect of the ampicillin comparison drug.

S. Pacifico et al., isolated and identified more than 20 phenolic compounds [56] from the polar fractions of the methanol extract of the *Laurus nobilis* L**.** leaves collected in Caserta (Italy) in May 2011. They are: hexoside 3,4-dihydroxybenzoic acid **(36)**; 2',β-dihydroxy-α, β-dihydrochalcon-α-O-hexoside **(37)**; 1-(2'-hydroxyphenyl)-1-hydroxyphenylpropan-α-O-hexoside **(38)**; coumaric acid hexoside **(39)**; 2'-hydroxy-α, β-dihydrochalcon-α-O-hexoside **(40)**; apigenin-6,8-di-C-hexoside **(41)**; apigenin-6-C- (2"-O-deoxyhexosyl) hexoside **(42)**; 8-C-hexosyl apigenin **(43)**; quercetin-3-O-(6"-O-deoxyhexosyl) hexoside **(44)**; tetramethoxydihydroquercetin-3-O-pentoside **(45)**; kaempferol-3-O-(6"-O-deoxyhexosyl) hexoside **(46)**; quercetin-3-O-hexoside (isomers 1 and 2) **(47)**; isorhamnetin-3-O-(6"-O-deoxyhexosyl) hexoside **(48)**; quercetin-3-O-pentoside **(49)**; cinnamtannin B1 **(28)**; kaempferol-3-O-hexoside **(50)**; quercetin-3-O-deoxyhexoside **(51)**; isorhamnetin-3-O-hexoside **(52)**; kaempferol-3-O-pentoside **(53)**; kaempferol-3-O-deoxyhexoside **(54)** (see Table 1).

The fractions which these compounds had been isolated from, showed their high antioxidant activity. The authors of the study have arrived at the conclusion that the extracts, rich in phenolic compounds from Laurus nobilis L. leaves, are of interest from the point of view of searching effective herbal remedies in the prevention and treatment of Alzheimer's and other age-related degenerative diseases.

A study by M. Dias et al. was aimed at a comparative study of cultivated and wild Laurus nobilis L. leaf samples by their nutritional value, some groups of natural compounds, including phenolic ones [57]. For that, a sample of raw materials (air-dried leaves) from cultivated plants was purchased from Ervital in Castro Daire, Portugal. According to the manufacturer, the leaves were collected in 2012. Wild raw materials (fresh leaves) were harvested in the autumn of that year in Bragança, Portugal, and subsequently dried. The both samples were lyophilised to preserve, as far as possible, their native chemical composition for the analysis. Phenolic compounds were determined by HPLC and identified by their UV and mass spectra, retention times and comparison with the standard samples. The phenolic profile of the studied samples was characterised by the presence of flavan-3-ols, flavonols and flavones. The compounds of these groups included: epicatechin hexoside **(55)**, (+)-gallocatechin **(56)**, procyanidin tetramer, (+)-catechin **(57)**, procyanidin dimer, (-)-epicatechin **(58)**, procyanidin tetramer (A- and B-type bonds), procyanidin trimer, luteolin 6-C-glucoside **(59)**, apigenin 8-C-glucoside **(60)**, 2"-O-rhamnosyl-C-hexosyl-apigenin, quercetin 3-O-rutinoside (29), apigenin 6-C-glucoside **(61)**, quercetin 3-O-glucoside **(62)**, quercetin O-hexoside, kaempferol 3-O-rutinoside **(63)**, quercetin O-pentoside, kaempferol 3-O-glucoside **(64)** (see Table 1), isorhamnetin O-rutinoside, quercetin O-rhamnoside, isorhamnetin O-hexoside, kaempferol O-pentoside, isorhamnetin O-pentoside, kaempferol O-hexoside, isorhamnetin O-rhamnoside.

The cultivated raw materials contained phenolic substances in higher concentrations, especially derivatives of flavones and flavonols. However, the flavan-3-ols content was similar in the both samples. It was this group of phenolic compounds that was predominant in the cultivated and wild-growing Laurus nobilis L. Methanol extract and the infusion obtained from the leaf sample of cultivated plants, in addition, showed their higher antioxidant activity.

The studies carried out by these authors later [58], revealed the (*in vitro*) activity of phenolic extracts against human tumour cell lines, as well as bacterial and fungal cells. It was established that the extracts from the samples of wild Laurus nobilis L. leaves, inhibited tumour cell lines stronger (HeLa, MCF7, NCI-H460, and HCT15). Methanol extracts had a higher antibacterial activity. According to the authors, the differences in their biological activity could be associated with different contents of phenolic compounds.

According to the results presented in Table 5, the cultivated samples showed higher concentrations of flavonoids and flavones. On the other hand, methanol extracts were characterised by a high content of flavan-3-ols.

The dried *Laurus nobilis* L. leaves purchased on the market in Saltillo, Coahuila, Mexico, in November 2010,

were investigated for the content of phenolic compounds and the influence of several experimental factors on the processes of their extraction from the raw materials. Among the studied factors, special attention was paid to the ratio of the solid liquid and the solvent concentration [59]. The best results were obtained by ultrasonic extraction of 1 g of a plant sample with 12 ml of 35% ethanol for 40 minutes. The yield of phenolic substances was 17.32 ± 1.52 mg/g. HPLC analysis revealed the presence of two phenolic acids in the extracts - coumaric **(65)** and 2-hydroxycinnamic **(66)**.

A study of the chemical composition of the two leaf and shoot samples of Laurus nobilis L collected in November 2013 in the Crimea in the vicinity of Alushta (1) and the village of Rybachye (2) showed, that they contain carbohydrates, fatty acids, amino acids, and phenolic substances [60]. The authors of the study determined the content of the main groups of biologically active substances, including phenolic compounds, in different samples of shoots and leaves of *Laurus nobilis* L. See Table 6.

As follows from the data presented in Table 6, the content of oxidizable phenols, hydroxycinnamic acids and flavonoids in the leaf samples did not differ significantly. Hereby, the total amount of oxidizable phenols was at least 4.5%, the amount of hydroxycinnamic acids was at least 1.3%, and the amount of flavonoids was at least 0.8%. The data obtained by the authors show, that the content of the studied groups of phenolic compounds is slightly higher in the samples of Laurus nobilis L. leaves in comparison with the shoots. Sample No. 1 of the leaves and shoots of Laurus nobilis L. showed the highest content of phenolic compounds.

The raw materials of the *Laurus nobilis* L. (leaves and fruits), harvested in the Crimea in 2013, was studied by HPLC-UV method [61]. Three compounds of the flavan nature were found out in Laurus nobilis L. leaves. The dominant component was epicatechin **(67)** with its content of 1.29%. In addition, catechin (1.06%) and epigallocatechin (0.40%) **(68)** were found out. In the fruits, 3 compounds of the flavan nature were also established, the dominant components being epicatechin (0.65%) and epigallocatechin (0.51%). The chemical difference between the studied raw materials samples was the presence of catechin in the leaves and gallic acid (0.02%) and epicatechin gallate (69) (0.16%) in the fruits.

The phenolic profile and the antioxidant activity of *Laurus nobilis* L. leaves collected in northern Portugal, the Azores, and Madeira, were analysed by A. Vinha et al. [62]. The dried leaves were used to obtain aqueous, alcoholic and hydroalcoholic (water-ethanol 1: 1) extracts. The phenolic profile of the extracts was determined using HPLC with a diode array detector combined with a mass spectrometer. The results of the study are presented in Tables 7 and 8.

In the study with 2,2-diphenyl-1-picrylhydrazyl, the highest antioxidant activity was detected in alcoholic extract and the lowest one – in aqueous.

CONCLUSION

The data presented in the review, characterize the leaves, fruits, and shoots of the *Laurus nobilis* L. as valuable raw materials for phenolic compounds, such as phenolic acids, flavonoids, proanthocyanidins, etc. Their total amount in the leaves can reach 99.7 g/kg (in terms of gallic acid). In the fruits of *Laurus nobilis* L., anthocyanins are usually accumulated in the quantity up to 217 mg in terms of cyanidin-3-glucoside/g of seed-free raw materials. The quantitative content of these groups of substances varies depending on the place of collection, the source of the raw materials (cultivated or wild plants), the time (phase) of their harvest, the method of drying and extraction from raw materials, etc. According to the results of the studies, the phenolic compounds of *Laurus nobilis* L. exhibit pronounced antioxidant and antiradical activity, have an inhibitory effect on the production of NO, sodium-potassium adenosine triphosphatase, on the tumour cells line (HeLa, MCF7, NCI-H460 and HCT15). They are characterised by an antibacterial action against gram-positive and gram-negative bacteria.

A further, more rigorous research of the Laurus nobilis L. cultivated in Russia, is relevant, and it will make it possible to assess the quality of its raw materials by the content of phenolic compounds and to develop methods for its standardization for this group of active substances. In addition, the development of regulatory documentation for raw materials of *Laurus nobilis* L. will significantly expand the introduction of new medicines based on it, into medical practice.

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AUTHOR CONTRIBUTIONS

All authors have equally contributed to the research work.

CONFLICTS OF INTEREST

The authors of this paper report no conflicts of interest.

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AUTHORS

Dmitry A. Konovalov – Doctor of Science (Pharmacy), Professor, Head of Department of Pharmacognosy, Botany and Technology of Phytopreparation. Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0002-0960-6127. Researcher ID: B-7017-2017. Scopus Author ID: 56436041900. E-mail: d.a.konovalov@pmedpharm.ru

Naida M. Alieva - Senior Lecturer, Department of Normal Physiology, Dagestan State Medical University, e-mail: nasuhov.5@mail.ru