PHYTOCHEMICAL AND PHARMACOLOGICAL PROPERTIES OF SOME SPECIES OF THE GENUS *GALIUM L. (GALIUM VERUM AND MOLLUGO)*

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FITOHEMIJSKE I FARMAKOLOŠKE KARAKTERISTIKE NEKIH VRSTA IZ RODA *GALIUM L.* (BELO I ŽUTO IVANJSKO CVEĆE)

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ABSTRACT

Galium verum L. and Galium mollugo L. are perennial herbaceous plants, belonging to the Rubiaceae family. Several classes of bioactive compounds, such as iridoid glycosides, phenolic compounds, anthraquinones and triterpenes, as well as small amounts of tannins, saponins, essential oils have been isolated from Galium species so far. Plants belonging to this genus have a long history of use in a traditional medicine for the treatment of many diseases and conditions. The main application of G. verum is as diuretic, choleretic and as the treatment for gout and epilepsy. On the other hand, G. mollugo has been used to treat hysteria, epilepsy, as vulnerary. Over the past decades, numerous papers have been published referring to the chemical constituents presented in G. verum and G. mollugo extracts. Additionally, chemical composition and pharmacological effects of G. verum have been investigated, however data related to the effects of G. mollugo is limited. In this review, we summarized the current knowledge on the phytochemical and pharmacological properties of G. verum and G. mollugo. Finally, we proposed directions for future research in this field, which can improve our understanding of the potential health benefits of Galium species.

Keywords: *Galium verum, Galium mollugo, biological activity, chemical composition*

SAŽETAK

Belo i žuto ivanjsko cveće su višegodišnje zeljaste biljke koje pripadaju porodici Rubiaceae. Do sada je iz roda Galium izolovano nekoliko vrsta bioaktivnih jedinjenja, kao što su iridoidni glikozidi, fenolna jedinjenja, antrahinoni, triterpeni, kao i male količine tanina, saponina i etarskih ulja. Biljne vrste iz ovog roda imaju dugu istoriju upotrebe u tradicionalnoj medicini u lečenju mnogih bolesti i stanja. Glavna primena belog ivanjskog cveća je kao diuretik, holeretik i u lečenju gihta i epilepsije. S druge strane, žuto ivanjsko cveće se koristi u lečenju epilepsije i histerije, za zarastanje rana. Tokom proteklih decenija objavljeni su brojni radovi koji se odnose na hemijska jedinjenja prisutna u ekstraktima žutog i belog ivanjskog cveća. Dodatno, hemijski sastav i farmakološki efekti belog ivanjskog cveća su proučavani, dok su podaci o efektima žutog ivanjskog cveća ograničeni. U ovom preglednom radu smo rezimirali trenutna saznanja o farmakološkim i fitohemijskim karakteristikama žutog i belog ivanjskog cveća. Konačno, predložili smo smernice za buduća istraživanja u ovoj oblasti, koja bi mogla poboljšati naše razumevanje potencijalnih zdravstvenih koristi roda Galium.

Ključne reči: *belo ivanjsko cveće, žuto ivanjsko cveće, biološka aktivnost, hemijski sastav*

INTRODUCTION

Galium genus belongs to the *Rubiaceae* family and comprises about 400 herbaceous plant species, 145 of which are distributed in Europe (1). Furthermore there are 37 species from *Galium* genus distributed in Serbian flora (2). Among them, the herb Lady`s Bedstraw (*G. verum* L.) is renowned for the most frequent use in traditional medicine (3). It is common throughout Europe, North Africa and Asia, tropical Asia and Europe, but it can occur in southern Canada and northern U.S. In addition, *G. mollugo* (hedge bedstraw or false baby's breath) is widely distributed in Europe and North Africa and it is naturalized in the Russian Far East, New Zealand, Norfolk Island and much of North America (4).

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Descripiton

G. verum L. is a perennial herbaceous plant, with elongated stems growing to 60-120 cm. Leaves are glossy and dark green, while flowers are golden yellow, grouped in many-flowered panicles. The aerial parts of this plant are collected during dry and sunny days of the blooming period. Its golden yellow *flowers* are present from *June* to *September.* It occurs at elevations between sea level and 2.600 m, at mountain meadows and temperate grasslands.

Galium mollugo L. is a perennial herb, with the stems growing to 15–100 cm, with bright green leaves and white to greenish white flowers. The *flowering* period extends from May to *September and arterial parts are collected during dry and sunny days of the blooming period (2-4).*

Since both *G. verum* and *G. mollugo* have a perennial habit they can be easily confused. What make them differ are stems, which are thinner and firmer in case of *G. verum*, while the panicles in *G. mollugo* are looser, almost leafless (4).

Chemical constituents

Several kinds of bioactive compounds have been isolated from *Galium* species so far. Previous phytochemical investigations of the *G. verum* and *G. mollugo* species reported the presence of iridoid glycosides, phenolic compounds, anthraquinones and triterpenes, as well as small amounts of tannins, saponins, essential oils, waxes, pigments and vitamin C (3).

Iridoids

It's been known that both *G. verum and G. mollugo* are rich in iridoids (Table 1). Secogalioside is marked as an important chemotaxonomic marker of the *G. mollugo* group (1).

Table 1. Iridoids in *G. verum* and *G. mollugo* species

Chemical name	Source *G. verum* References	Source *G. mollugo* References
Asperuloside	*Bojthe-Horvath K et al* [5,6] *Demïrezer* [7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
Monotropein	*Bojthe-Horvath K et al* [5,6] *Demïrezer LO* [7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
Scandoside	*Bojthe-Horvath K et al* [5,6]	*Iavarone C*[8] *Uesato S*[9]
Geniposidic acid	*Bojthe-Horvath K et al* [5,6]	*Uesato S*[9]
Deacetylasperulosidic acid	*Bojthe-Horvath K et al* [5,6] *Demïrezer LO*[7]	*Mitova MI*[1]
Asperulosidic acid	*Bojthe-Horvath K et al* [5,6] *Demirezer LO*[7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
6-o-epi-acetylscandosid	*Demirezer LO*[7]	*Nf*
Daphylloside	*Demirezer LO*[7]	*Nf*
Apigenine glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Luteoline glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Diosmetin glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Deacetyl-daphylloside	*Demirezer LO*[7]	*Nf*
6-O-epi-acetylscandosid	*Demirezer LO*[7]	*Nf*
Loganin	*Mitova MI*[1]	*Iavarone C*[8]
Secogaliosid	*Mitova MI*[1]	*Uesato S*[9]
6-acetylscandoside	*Mitova MI*[1]	*Mitova MI*[1] *Iavarone C*[8]
Galioside	*Nf*	*Mitova MI*[1] *Uesato S*[9]
Mollugoside	*Nf*	*Mitova MI*[1]
Secogalioside	*Nf*	*Mitova MI*[1] *Uesato S*[9]
Gardenosidic acid	*Nf*	*Uesato S*[9]
Scandoside methyl ester	*Nf*	*Iavarone C*[8] *Uesato S*[9]
Daphylloside	*Nf*	*Iavarone C*[8] *Uesato S*[9]
10-hydroxymorroniside	*Nf*	*Uesato S*[9]
10-hydroxyloganin	*Nf*	*Iavarone C*[8]

**Nf*-not found so far

Table 2. Phenolic compounds in *G. verum* and *G. mollugo* species

Chemical name	Source *G. verum* References	Source *G. mollugo* References
Isorhamnetin	*Zhao C et al*[10,11] *Matei AO et al* [12]	*Nf*
Isorhamnetin 3-O-α-L-rhamnopyranosyl-(1–6)-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Kaempferol	*Zhao C et al*[10,11] *Vlase L*[15]	*Nf*
Quercetin	*Zhao C et al*[10,11]	*Nf*
Diosmetin	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-β-D-xylopyranosyl-(1–6)-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-α-L-rhamnopyranosyl-(1-2)-[β-d-xylopyranosyl-(1-6)]-β-d-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
3,5,7,3′,4′,3″,5″,7″,3‴,4‴-decahydroxyl-[8-CH(2)-8″]-biflavone	*Zhao C et al*[10,11]	*Nf*
Quercetin	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[15] *Matei AO et al*[12]
Quercetin-3-O-β-D-glucopyranoside	*Zhao C et al*[11]	*Nf*
Fisetin	*Matei AO et al*[12]	*Nf*
Chrysin	*Matei AO et al*[12]	*Nf*
Catechin	*Matei AO et al*[12]	*Nf*
Epicatechin	*Matei AO et al*[12]	*Nf*
Coumaric acid	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[15]
Ferulic acid	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[16]
Hesperidin	*Matei AO et al*[12]	*Nf*
Astragalin	*Demirezer LO*[7] *Tamas M*[13]	*Demirezer LO*[7] *Tamas M*[13]
Rutin	*Demirezer LO*[7] *Matei AO et al*[12] *Tamas M*[13] *Vlase L*[15]	*Tamas M*[13] *Vlase L*[15]
Hyperozide	*Tamas M*[13]	*Tamas M*[13]
Rutoside	*Tamaș M et al*[13]	*Tamaș M et al*[13]
Hispidulin	*Mocan A et al*[14]	*Mocan A et al*[14]
Chlorogenic acid	*Matei AO et al*[11] *Tamas M*[13] *Mocan A et al*[14]	*Tamas M*[13] *Mocan A et al*[14]
Caffeic acid	*Matei AO et al*[12] *Tamas M*[13] *Mocan A et al*[14]	*Tamas M*[13] *Mocan A et al*[14] *Vlase L*[15]
Luteoline	*Nf*	*Vlase L*[15]
Chalcone	*Shafaghat A*[16]	*Nf*

Phenolic compounds

Phytochemical investigation of *G. verum L.* has led to the isolation of several phenolic compounds in *G. verum* and *G. mollugo* extracts (Table 2). Chemical analysis of ethanolic extracts [30, 50 and 70% (w/v)] of *G. verum* was observed and the results indicate that concentration of certain phenolic depends on the solvent (12). Qualitative differences in the flavonoid fractions between *G. verum* and *G. molugo* species exist, suggesting that the content of the flavonoids is about three times higher in *G. verum* (13). Regarding the amount of phenolics obtained by different extraction techniques (maceration, reflux and ultrasonic extraction), it was shown that the highest amount of phenolics from *G. mollugo* extracts has been obtained by the reflux extraction. Authors explained this fact by oxidation and degradation of some bioactive compounds during sonication of the aqueous solution. In addition, increased solubility of phenols and flavonoids in the extracting solvent at higher extraction temperatures may be an explanation for such composition of the extracts (17).

Terpenes and anthraquinones

Data suggests the presence of triterpenic saponins in *Gallium* species (18). However there is a lack of data referring to the amount of terpens in *G. verum* or *G. mollugo*. Two monoterpene glycosides, such as betulalbuside A and (2E)-2,6-dimethyl-2,7-octadien-1,6-diol-6-O-β-glucopyranoside were isolated from the aerial parts of *G.verum* (7). In the ethanolic extract of *G. verum* L 1,3-dihydroxy-2-methylanthraquinone, physcion, 2-hydroxy-1,3dimethoxyanthraquinone and 2,5-dihydroxy-1,3-dimethoxyanthraquinone were identified (19). It's been shown that anthraquinones are located in the vacuole of *G. mollugo* (20). In addition, anthraquinones production from *G. verum* lines of calus was proven as well (21). Unfortunately, data regarding the presense of anthraquinones and triterpenes in this *Galium* species is limited, thus suggesting that they are probably present in a smaller quantities compared to other bioactive compounds.

Mineral composition

A significant chemical compounds identified in white lady's bedstraw are certainly minerals such as potassium, calcium and magnesium (22, 23). Study which examined mineral composition of the extracts of *G. mollugo* flowers obtained by maceration, extraction under reflux and ultrasonic extraction, using *atomic absorption spectrometry, suggested that t*he *highest calcium and magnesium yield* could be *achieved* at the *ultrasonic extraction, while type of extraction didn't affect K yield (23).*

Phytosterols

Phytosterols, known as plant sterols structurally similar to cholesterol, may also be found in *Galium* species. It's been reported that *G. mollugo* was richer in β-sitosterol (19.02 ± 7.24 μg/g) and campesterol (15±0.08 μg/g) than *G. verum* (85.46 ± 1.24 μg/g for β-sitosterol and 9.86 ± 0.04 μg/g for campesterol) (14).

Essential oil

Essential oil obtained by hydro-distillation from the aerial parts of *G. verum* contains ß-caryophyllane, caryophyllene oxide, germacrene D, terpinene, benzyl alcohol, squalene and cis-3-Hexen-l-ol (24, 25). On the other hand, essential oil from the aerial parts of *G. mollugo* is yellow-green oil which was rich in palmetic acid, tetradecanal and ethyl linoleolate (26).

***G. verum* and *G. mollugo* usage**

Galium species have been traditionally used for the treatment of many diseases and conditions. Furthermore they are renowned for its usage in milk coagulation due to an enzyme in their chemical composition and that's the reason for knowing this plant as "Yogurt herb" (3, 14, 27). In Scotland the plant is still used in cheese manufacturing. Since the coumarin scent of the plants acted as a flea killer, dried plants were widely used to stuff mattresses (3, 27). Furthermore, *G. verum* may serve as a food additive and yellow and red pigments presented in its aerial parts and roots allow usage of this plant in dyeing (10). However there is a limited number of studies which examined the effects of *G. verum* and *G. mollugo* extracts both in animal models and humans.

Pharmacological effects of *G. verum* and *G. mollugo*

Studies which evaluated the effects of *Galium* species predominantly were conducted in Asian people. This is expected since traditional medicine is more present in their culture and everyday life compared to Europe and USA continents (27). *G. verum* has been studied both chemically and pharmacologically, however there is a little data related to the effects of *Galium mollugo* (17).

Anticancer effects

Recommendations for using *G. verum* in the treatment of tongue cancer are supported by the reports of patients with tongue and larynx carcinome successfully treated with the tea of this plant. *G. verum* decoction was proved to inhibit the chemo-sensitive and -resistant laryngeal carcinoma cell lines growth, thus suggesting its possible concomitant therapeutic use for oral or head and neck cancer (27). *Hartwells'* survey indicate that *G.verum* has been traditionally used in Europe and Northern America for the treatment of cancerous ulcers or breast cancer (28). In support of that, there is a data that its ethanolic extract may inhibit the proliferation of human breast cancer cells and induce cell death by apoptosis. Furthermore diosmetin, a flavon, extracted from the traditional Chinese herb *G. verum* L was tested on cervical cell lines and it was shown that it inhibit the tumor growth and protect tumor-induced apoptosis of thymus (29). To our knowledge there are no studies which proved anticancer effects of *G. mollugo* species.

Effects on central nervous system

The aerial parts of *G. verum* were traditionally used as sedative (3, 30, 31) and that was confirmed by an ethnobotanical study on the usage of wild medicinal herbs from Central Serbia (32). It's been proposed that chemical compounds such as iridioides (asperuloside) are responsible for sedative effects of *Galium* species (31). Upper herbaceous parts of *G. verum* have been renowned for beneficial effects on nervousness and phobias (3). Furthemore, both *G. verum* and *G. mollugo* species have been used in traditional medicine in the treatment of epilepsy and hysteria (14, 33, 34). There is an evidence that *G. mollugo* is used as a nerve relaxant (34). Hispidulin, which is proven benzodiazepine

receptor ligand, was recently discovered in some *Galium* species and may be responsible for the anticonvulsive effects of these plants (15, 35).

Effects on gastrointestinal, renal, hepatobiliary and urinary system

G. verum tea has diuretic effect and it may contribute to the cure of pyelitis or cystitis (14, 30, 33). It is effective in cases of bladder and kidney irritation, kidney stones and as anticolic as well (33, 36). *G. verum* may be used as spasmolytic, against diarrhea and in the treatment of some stomach complaints (3, 14, 17). In addition, upper herbaceous parts of *G. verum* exert effects on liver disorders and acts as choleretics and cholagogue (3, 7). In China it has been used to treat hepatitis (37). There is little data about the pharmacological effects of *G. mollugo* on the function of these systems, but taking into consideration similar chemical composition, we may assume that this species exert similar activity to *G. verum.*

Other pharmacological effects

It's been reported that both *G. verum* and *G. mollugo* may be useful in the treatment of skin disorders, exogenous treatment of psoriasis or wound healing (3, 27, 32). In addition *G. verum* is effective as diaphoretic and depurative, while *G. mollugo* as antiscorbutic (3, 30, 34). Among various therapeutic properties of these species, *G. verum* herba has beneficial effects on cardiovascular diseases, treatment of gout and rheumatic diseases in folk medicine (3, 17). *Galium verum* extract applied to the animals exposed to anakinetic stress led to a significant stimulation of secretory activity of thyroid and ovary, and to an increase in adrenal and glucocorticoid hormone synthesis (31, 38).

Antioxidant activity

There is an evidence that plants from *Gallium* genus possess natural antioxidants. Extracts from aerial parts of *G. verum* express very strong scavenger activity in a dose dependant manner. That antioxidant activity was determined via the neutralization of 2,2-diphenyl-1-pycrylhydrazyl (DPPH) radicals, hydroxyl (OH^-) radicals, hydrogen peroxide (H_2O_2) and inhibition of lipid peroxidation (3). These results are confirmed by several authors, thus qualifying *G. verum* as a promising natural source of antioxidants (15, 30, 39). Other researchers revealed that methanol extract had greater antioxidant activity than its water extract, while examining *G. verum* aqueous and methanolic extracts in the range 50-500 mg/L (39). Furthermore there was an investigation reporting that compounds found in methanol extract of *G. verum* exerted riboflavin-originated superoxide and xanthine-originated superoxide quenching activities (40). By comparing the antioxidant potential of different extracts, such as aqueous, 30%, 50% and 70% alcoholic, it was noticed that the highest potential may be expected from 50% alcoholic *G. verum* extract (41). Methanolic extract of *G. verum* exerted great antioxidant potential in tested models which included DPPH and nitric oxide radical scavenging, reducing power and H_2O_2 scavenging (42).

Antioxidant activity of aqueous-ethanolic *G. mollugo* extracts was revealed as well. It's important to emphasize that the activity was changing dependently of the extraction technique applied, where extracts obtained by extraction with reflux showed the best antioxidant activity (17). There is a data referring to the antioxidant potential of *G. mollugo* tested and proven by ferric ion reducing antioxidant power (FRAP) and trolox equivalent antioxidant capacity (TEAC) assays (43). Another study which aimed to compare the antioxidant potential of four *Galium* species suggested that *G. verum* extract exhibited higher antioxidant capacity compared to *G. mollugo* extract (15). Phenolic compounds isolated from *G. mollugo* may protect human fibroblast cells against oxidative stress (44).

Antibacterial and antifungal activity

Galium species have been used in the folk medicine for the treatment of infectious diseases, however antimicrobial activity of these plants is poorly reported. It was shown that chloroform extract of *G. verum* express antibacterial activity in comparison to aqueous and alcohol (70%) extracts, which possess no activity. In addition, *Candida albicans* was generally insensitive to the extracts of this plant. Confirmed antimicrobial activity of *G. verum* predominantly refers to its efficiency against Gram-positive microorganisms and less efficiency in reference to Gram-negative strains (45). Other authors noticed that *G. verum* and *G. mollugo* extracts exhibited effects mainly against the Gram-positive bacteria (*S. aureus, L. monocytogenes*) and low activity against Gram-negative bacteria (*S. typhimurium, E. coli*). Ethanolic extracts of these two G. species showed a weak antifungal capacity against *C. albicans* (46). Furthermore neither chloroform nor methanolic extract of *G. verum* has inhibitory effect against both clinical and standard strains of *Candida* spp (47). It may be hypothesized that the lack of antifungal activity of these plants may be the consequence of the insufficient quantity of compounds responsible for that activity.

CONCLUSION

Numerous studies proved that *G. verum* and *G. mollugo* contain chemical compounds with high therapeutic potential, which may be pharmaceutically exploited. Despite the centuries of successful traditional use in the treatment of many diseases, the number of studies referring to the effects of *G. verum* and *G. mollugo* is limited. This review provides available evidence on these two plants and may help to those intending to research further on these topics. Further researches regarding the effects of *G. verum* and *G.*

mollugo are necessary to make them a possible candidate for medicinal product.

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