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Revealing the reviving secret of the white dead nettle (*Lamium album* L.)

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Abstract *Lamium album*, commonly known as white dead nettle or non-stinging nettle is a flowering herbaceous plant, native throughout Europe, Western Asia and North Africa. From ancient times this plant has been endowed with revival, curative and culinary virtues. In the past, in the traditional and folk medicine white dead nettle has been used mainly for its anti-inflammatory, astringent and anti-septic activity. Nowadays significant amount of knowledge on the efficacy of extracts and raw material of *L. album* is accumulated and a number of health-related beneficial activities have been scientifically proven. In vitro analyses conducted in various model systems have demonstrated antiviral, antimicrobial, antioxidant, anticancer, cytoprotective, wound healing and other important pharmacological effects. The present review summarizes the recent information on the phytochemical features of this pharmacologically important species. The findings on the chemical composition, biological activities and the pharmacological properties underlying the revival secret of white dead nettle are described and discussed in the view of potential applications for treatment of human diseases. Trends for further research are outlined.

Keywords Iridoids · *Lamium album* · Pharmacological properties · Phenylethanoid glycosides · Terpenes

Introduction

The genus *Lamium* (Family: Lamiaceae alt. Labiatae) comprises about 40 annual and perennial herbaceous species native to Europe, Asia and North Africa. *Lamium album* L. is a perennial herb growing to 50–100 cm tall, with green, four-angled stems. The leaves are long, triangular with rounded base, serrated margin and soft hairs. The flowers are white with two lips and are positioned on the upper part of the stem in whorls of six to twelve flowers. *L. album* is commonly known as white dead nettle owing its name to "nettle" because phenotypically it appears similar to the stinging nettle (*Urtica dioica*). However, unlike *U. dioica*, the hairs of *L. album* are not stinging which makes it harmless as if being "dead" (Yalçin and Kaya 2006). It is believed that this superficial resemblance has evolved as a survival measure. Whereas the true nettle is defended by its power of stinging, the dead nettle is protected by its likeness to the others. It is

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suggested that as the two species are commonly found growing together the similarity may serve as a protection against browsing quadrupeds and leaf-eating insects (Grieve 1994).

In ancient times, white dead nettle has been considered as a mood and vitality enhancer. It has had a reputation of being able to make the heart merry, to drive away melancholy and to revive vital spirits (Chevalier 2001). *L. album* has also been used as famine food, as alternative nourishment mostly during the specific decades of starvation in different countries in Europe, China and Japan (Luczaj 2008; Turner et al. 2011). The young shoots, leaves and flowers of this plant are edible and can be consumed raw or cooked. Nowadays, the consumption of white dead nettle is primarily associated with health benefits and is used for preparation of teas and food supplements. For e.g. in some culinary recipes it is applied for confection of several dishes including omelets, stews and roasts and as specific ingredient of local dishes in the Mediterranean and surrounding areas (Heinrich et al. 2006). Non-stinging nettle is also a base component of famous vegetarian dishes such as "White Dead Nettle Frittata", "White Dead Nettle Feta and Watermelon Salad" and "Dead nettle soup" (Pereira et al. 2012). In particular, the consumption of food supplements enriched with *L. album* extracts are claimed to detoxify the organism, to prevent menstrual disorders, abdominal inflammation and musculoskeletal diseases (Xu 2008) and, to improve fat metabolism (Ninomiya et al. 2006).

In the traditional and folk medicine white dead nettle is also known with its anti-inflammatory, astringent and anti-septic activity and is especially utilized in menorrhagia, uterine hemorrhage, vaginal and cervical inflammation and, leucorrhoea treatment. It is often called the medicine of women afflictions (Bremness 1995). Additionally, *L. album* has mucolytic and antispasmodic activity, making it effective in chronic bronchitis or pharyngitis. Moreover, the dried flowers are applied in case of skin inflammation, alimentary or urinary tract diseases and are beneficial for the whole organism, facilitating the removal of harmful metabolic products (Paduch et al. 2007).

In the ancient times the people have used natural ingredients merely based on empirical evidence and the folk medicine recipes have been developed without scientific knowledge on the efficacy of the used plant preparations and about their active compounds and mode of action. Currently, the knowledge is greatly expanded and scientifically validated providing more profound understanding of the beneficial properties of the natural products. An increasing body of scientific data now demonstrates the wide spectrum of therapeutic activities of *L.album* and most of the various biologically active substances in this plant have been identified (Alipieva et al. 2007; Paduch et al. 2007; Zhang et al. 2009; Pereira et al. 2012). The available findings provide basis for further studies and clinical research and for more controlled processing and applications of white dead nettle.

In the present review the chemical composition and the main biological and pharmacological properties of the compounds underlying the revival magic of this ethnomedicinally and pharmacology important species are described and discussed in the view of the latest discoveries.

Chemical composition

The medicinal properties of *L. album* and its traditional usage have attracted significant attention and this has led to intensive phytochemical investigations. White dead nettle expresses a wide spectrum of therapeutic activities which are attributed to a variety of biologically active substances such as iridoids, flavonoids, phenolic acids, isoscutellarein derivatives, terpenes, phytoecdysteroids and essential oils. In this part of the review the chemistry of identified metabolites and some of their effects are described.

Iridoids

Iridoids form a large group of naturally occurring monoterpenes and are the most prominent compounds in *Lamium* species. They are usually present as glycosides. *In vitro*, in vivo and clinical studies have demonstrated a broad range of biological activities in iridoids rich plants. These include anti-arthritic, anti-inflammatory, antibacterial, anticancer, antioxidant, antiviral, immunomodulatory, wound healing and neuroprotective activities (Ghule et al. 2012). One of the earlier reports on the phytochemical properties of *L. album* revealed the major iridoid glycoside for which the name lamiridoside (lamalbid) **(1)** was proposed (Eigtved et al. 1974) (Fig. 1). Later, in Bulgarian population of *L. album* lamiol **(5)**,

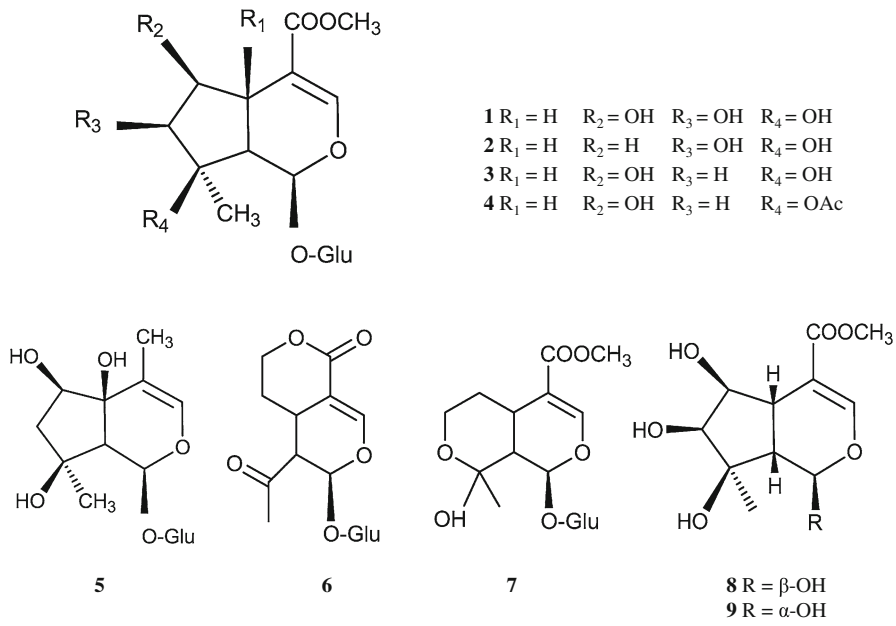


Fig. 1 Iridoids from *Lamium album* L

Ac - Acetyl unit; Glu - Glucosyl unit

caryoptoside **(2)**, shanzhiside methyl ester **(3)** and barlerin **(4)** were identified (Alipieva et al. 2003a, 2003b 2006 and 2007) whereas in the Danish population albozid A **(6)** and albozid B **(7)** (Damtoft 1992) and, two new isomers lamiridozin A **(8)** and B **(9)** with antiviral activity were isolated (Zhang et al. 2009). The secoiridoid glucosides albosides A and B are the only examples of secoiridoids reported from a plant belonging to the genus *Lamium*. Alboside A has a structure of sweroside-type, whereas alboside B is a morroniside-type secoiridoid glucoside (Yalçin and Kaya 2006).

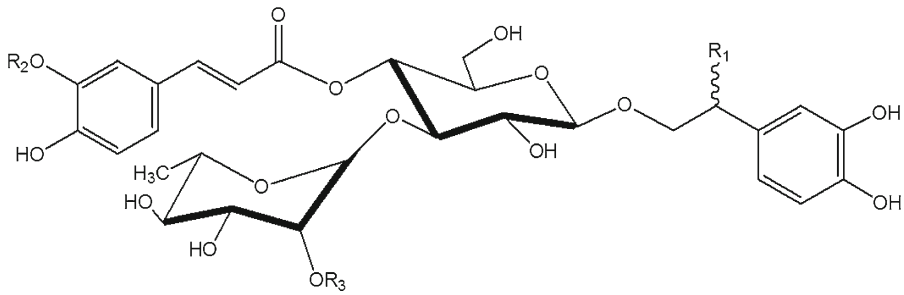
Iridoids are also recognized as valuable taxonomic markers of the genus. In *L. album, L. amplexicaule, L.garganicum, L. maculatum, and L. purpureum* 11-$COOCH_3$ iridoids as lamalbide, shanzhiside methyl ester and barlerin were found whereas 11-CH_3 iridoids have more restricted distribution. Some of the iridoids are specific for single species and could be considered as characteristic features. For example, caryoptoside was determined as characteristic for *L. album* and sesamoside for *L. garganicum* (Alipieva et al. 2007).

Phenolic compounds

Phenolic compounds are widespread in plants and express multitude of biological activities. In the aerial part of *L. album* three phenylethanoid glycosides, verbascoside (acteoside) **(10)**, isoverbascoside **(12)**, and lamalboside **(11)** were identified (Budzianowski and Skrzypczak 1995; Pereira et al. 2012) (Fig. 2). In purified ethanol extract of flowers, leaves and stems from *L. album*, derivatives of unusual flavone isoscutellarein were found to represent approximately one-third of the total phenolics quantified (Pereira et al. 2012). Isoscutellarein-7-*O*-allosyl (1 → 2) glucoside **(13)**, isoscutellarein-7-*O*-(6-*O*-acetylallosyl) (1 → 6) glucoside **(14)**, and its structural isomer, 4′-*O*-methylisoscutellarein-7-*O*-allosyl (1 → 2) glucoside **(15)** and 4′-*O*-methylisoscutellarein-7-*O*-(6-*O*-acetylallosyl) (1 → 2) glucoside **(16)** were described for the first time in genus *Lamium* (Fig. 3). Besides, the isoscutellarein derivatives glycosides of common flavones, namely luteolin-7-*O*-glucoside, apigenin-7-*O*-glucoside, apigenin-7-*O*-rutinoside and the flavanone naringenin-7-*O*-rutinoside were also reported (Pereira et al. 2012).

Large amount of flavonoids in forms of glycosides (rutin, isoquercitrin, tyliroside) and aglycones (quercetin) and phenolic acids (protocatechuic, chlorogenic, vanillic, caffeic, coumaric, and ferulic acids) have been found in methanol and ethyl acetate extracts from flowers of *L. album* (Paduch et al. 2007). Epidemiological studies suggest that dietary intake of flavonoids are associated with a reduced risk of cancer (O'Prey et al. 2003). Moreover, flavonoids uptake in some

Fig. 2 Phenylethanoid glycosides from *Lamium album* L



10 $R_1 = H$ $R_2 = H$ $R_3 = H$
11 $R_1 = H$ $R_2 = H$ $R_3 = \beta$-galactopyranosyl

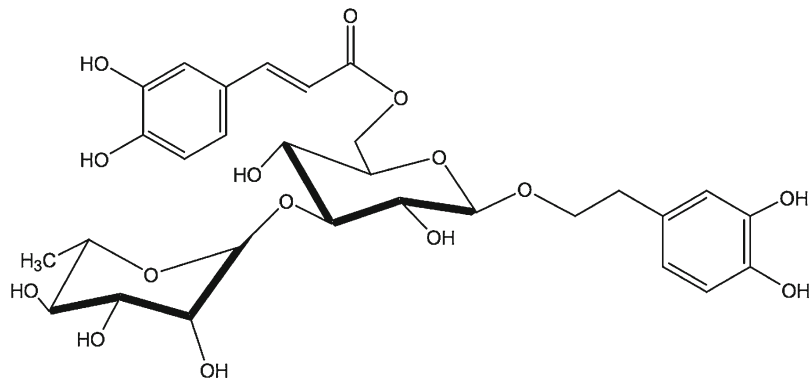


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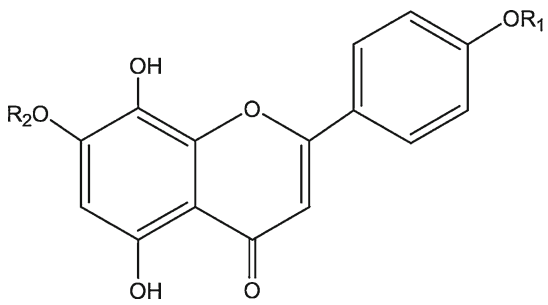
Fig. 3 Isoscutellarein derivatives identified in *Lamium album* L



13 $R_1 = H$ R_2 = Allo-Glu
14 $R_1 = H$ R_2 = Ac-Allo-Glu
15 $R_1 = CH_3$ R_2 = Allo-Glu
16 $R_1 = CH_3$ R_2 = Ac-Allo-Glu

Allo - Allosyl unit; Glu - Glucosyl unit; Ac - Acetyl unit

cases has been linked to protection of normal human skin fibroblasts against oxidative stress-induced cell injury (Spencer et al. 2004).

Phytoecdysteroids

Phytoecdysteroids are insect hormone analogues synthesized in plants for defense against phytophagous insects. These compounds imitate hormones which are involved in molting process in arthropods. Investigations on plant phytoecdysteroids in aerial part of *L. album* revealed four ecdysteroids: abutasterone **(17)**, inokosterone **(18)**, polypodine B **(19)** and pterosterone **(20)** (Fig. 4) (Savchenko et al. 2001). Higher level of ecdysteroids has been established in young leaves and shoot apex in comparison to mature stem. In the latter the concentration of these metabolites was dramatically lower. This might be related to the fact that younger vegetative plant organs are more vulnerable to insect attack (Savchenko et al. 2001).

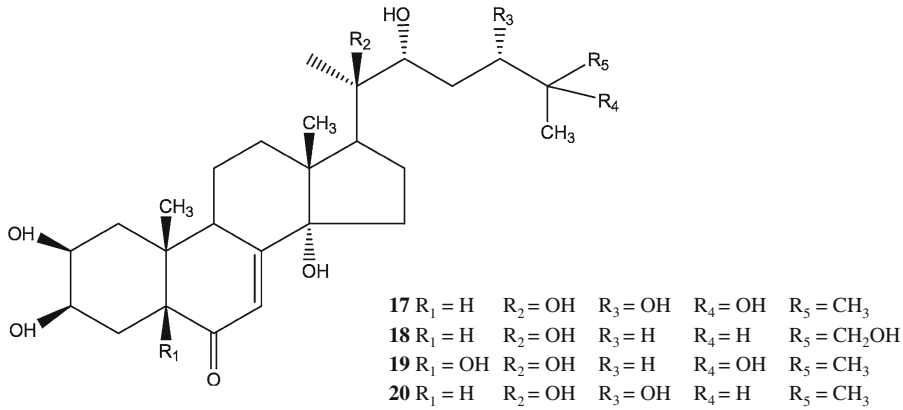


Fig. 4 Phytoecdysteroids from *Lamium album* L

Phytoecdysteroids display a wide array of beneficial pharmacological effects on vertebrates. These compounds stimulate protein synthesis and immune response, reduce the concentration of cholesterol and glucose in blood vessels and have antimutagenic, antioxidant and wound healing activity. Plant extracts containing ecdysteroids are included in more than 140 food supplements (Lafont and Dinan 2003).

Terpenes

From white dead nettle the hemiterpene glucoside hemialboside **(21)** has been isolated (Fig. 5) (Damtoft and Jensen 1995). Triterpenes ursolic acid **(22)** and β-amyrin **(23)** were established in methanol, ethyl acetate and heptane extracts of *L. album* flowers. Particularly heptane extract contained large amount of these metabolites (Paduch et al. 2007). Wojciak-Kosior et al. (2013) compared the classical techniques such as maceration (ME), Soxhlet (SE) and heat reflux extraction (HRE) with the modern techniques ultrasonic extraction (UE), microwave-assisted extraction (MAE) and accelerated solvent extraction (ASE) for their efficiency for extraction of oleanolic and ursolic acids from flowers of *L. album*. These authors found that the highest concentration of ursolic acid (111.2 ± 1.7 μg/g) was obtained through MAE in closed system for 10 min and 100 % of generator power. Oleanolic acid (22.2 ± 0.4 111.2 ± 1.7 μg/g) was better extracted at milder conditions of 30 % generator power for 30 min.

Essential oils

Although the plants from family Lamiaceae are known to contain high amount of essential oils, the content of these compounds in species from genus *Lamium* belonging to subfamily Lamioideae is relatively low. The yield of essential oils obtained from fresh flowers of *Lamium* plants vary between 0.01 and 0.31 % (Flamini et al. 2005). In a comparative study on four *Lamium* species from Bulgaria, the essential oils obtained from *L. album, L. purpureum, L. garganicum*, and *L. maculatum* flowers collected from nine populations were analyzed by GC/MS. A similarity of the volatile profile of all samples was found. Qualitative and quantitative differences in oil composition of the plants collected from different locations were observed. All studied samples contained significant amounts of hydrocarbons with C_{12} to C_{31} carbon atoms mainly with straight chains and fully saturated. Unusual high concentrations of the terpenoid squalene were established in all analyzed plants (Alipieva et al. 2003a, 2003b). Squalene is a flower attractant for pollinating insects and repellent against ants and possesses significant biological activity as bactericidal, anti-tumor and immunostimulant (Dutton et al. 2002).

The micropropagation techniques allow plant multiplication in in vitro conditions followed by adaptation *ex vitro* and this approach is widely applied for production of valuable substances (Kirakosyan et al. 2004; Dimitrova et al. 2011). In a study undertaken in our laboratory the essential oil content in leaf extracts

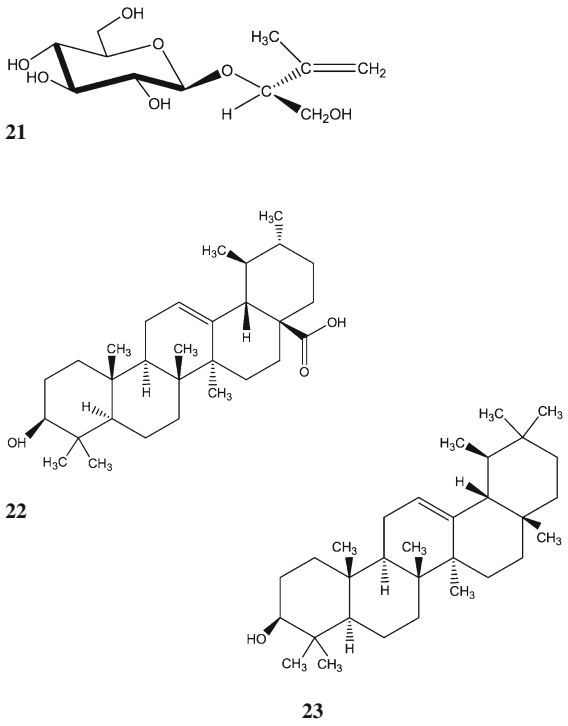


Fig. 5 Terpenes from *Lamium album* L

from in situ, in vitro and *ex vitro* grown plants was analyzed. A total of 130 metabolites were detected with biggest portion of hydrocarbons (C_8–C_{27}) and terpenes. The in situ grown plants contained 45 hydrocarbons. Following in vitro cultivation the content of these compounds decreased about two-times reaching 24 and 19 after *ex vitro* adaptation. While the content of many of the compounds found in in vitro grown plants decreased in comparison to in situ grown ones, there were some that increased during micropropagation. Importantly, the in situ plants were characterized with accumulation of long chain alkanes (nonadecane; heneicosane; heptadecane; tricosane), whereas shorter hydrocarbons such as octane and undecane were found both in in vitro and *ex vitro* plants (unpublished data). In the oil from in situ plants 60 terpenes were detected whereas micropropagation resulted in decrease in in vitro and *ex vitro* plants—44 and 35 compounds, respectively. During in vitro cultivation terpene composition also changed. The main sesquiterpenes detected in the in situ grown plants were germacrene D (6.9 %) and β-caryophyllene E (1.1 %). In in vitro and *ex vitro* plants very high accumulation of these compounds was observed—the germacrene D reached 44.1 and 46.7 %, respectively, and the portions of β-caryophyllene E were 13.0 and 6.5 %, respectively (unpublished data). Several biological activities such as anti-inflammatory, antibiotic, antioxidant, anticancer and local anesthetic activities are attributed to β-caryophyllene (Legault and Pichette 2007). It has been suggested that germacrene D may have deterrent effects against herbivores and it has been reported to exhibit insecticidal activity against mosquitoes, as well as repellent activity against aphids and ticks (Birkett et al. 2008).

Bioactivity and pharmacological effects

Lamium album is widely used herb in folk medicine. Here the scientific advantages in understanding the biological activities of *L. album* extracts and the major pharmacological properties such as antiviral, antimicrobial, antioxidant, cytoprotective, anticancer and anti-inflammatory are presented (Fig. 6).

Antiviral activity

In the recent years, an intensive search for natural products applicable for treatment of patients infected with hepatitis C virus (HCV) has been going on. HCV causes liver problems as cirrhosis and cancer worldwide. The current treatment for HCV relies on interferon-based therapy which, however, appears inefficient for nearly half of the HCV-infected patients. The efficacy of this therapy depends on strain genotype and is often accompanied with unfavorable side effects such as depression, psychoses, and extreme fatigue (Davis et al. 1998). An herbal based commercial product has been proven as effective in the treatment of HCV infections in patients who did not respond to standard interferon treatment. Aqueous extract of *L. album*, a component of the commercial preparation, showed anti-HCV entry activity of 50 % inhibition compared to a negative control against the HCV pseudoparticles infection at concentration of 100 μg/ml (Zhang et al. 2009). Workup of a methanol extract from *L. album* flowers led to the isolation of lamalbid as a major component, that however, was inactive against HCV. In contrast, lamiridosins A/B were found as major constituents in the extract of the commercial aqueous sample of *L. album*. These

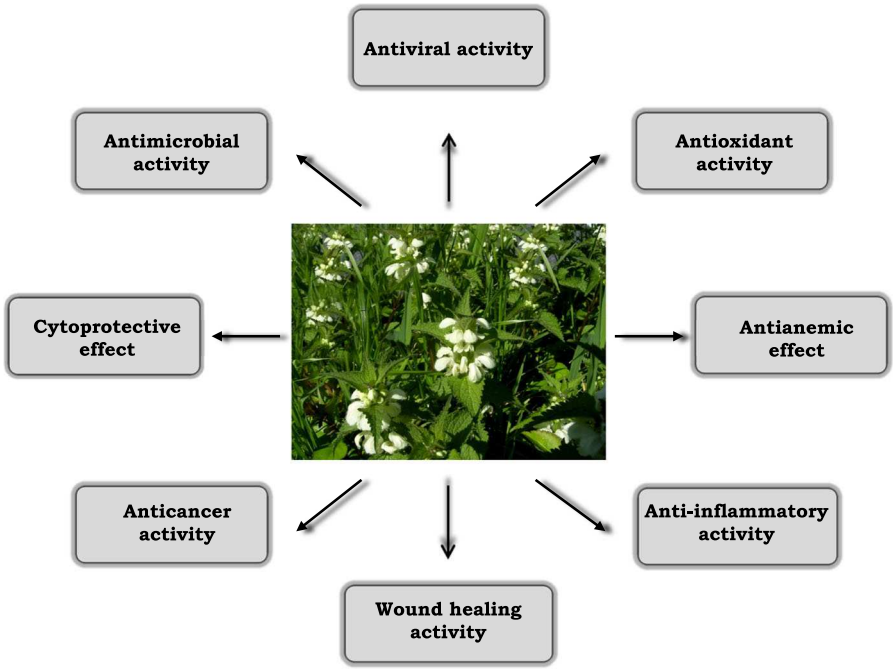


Fig. 6 Pharmacological effects of *Lamium album* L

iridoid aglycone epimers exhibited significant inhibition against HCV entry with an IC_{50} value of 2.31 μM and they were noncytotoxic to the Hep G2 2.2.15 cells at a concentration of 50 μg/ml. Interestingly, lamiridosins A/B were not found in the methanol extract of *L. album*.The difference between methanol and aqueous extracts was suggested to be due to the presence of a glycoside moiety which is subjected to enzymatic hydrolysis of the aglycone epimers (lamiridosins A/B) by naturally existing enzymes in the plant matrix during the maceration/extraction process using water as the solvent. Methanol, on the other hand, inactivated the associated hydrolytic enzymes in the plant matrix, resulting in preserved intactness of the molecule of lamalbid. Additional tests for determining the specificity of lamiridosins A/B action toward HCV revealed that the epimeric mixture is rather a selective antiviral agent against HCV than universal inhibitor of viral entry (Zhang et al. 2009). These authors performed screening for lamiridosins structurally related compounds and discovered additional entry inhibitors of HCV activity that could be applied for more efficient anti-HCV treatment. However, further study of the structure and activity relationships are needed to better establishing the anti-HCV activity of natural iridoids.

Herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) are other widespread human pathogens for which licensed anti-herpetic drugs are available but their continuous use results in development of resistant strains (Bacon et al. 2003). On the other hand, compounds with natural origin that are characterized with more complex chemical structure are found to delay the occurrence of strain resistance and to have lower cytotoxicity (Newman and Cragg 2007; Istatkova et al., 2012). The antiviral activity of chloroform extracts from in situ and in vitro propagated *L. album* plants has been demonstrated by significant inhibition of HSV-1 and HSV-2 replication in Madin-Darby Bovine Kidney (MDBK) cells with an IC_{50} values of 668 and 552 μg/ml, respectively without apparent cytotoxicity (Todorov et al. 2013). When the chloroform extracts were applied at maximal tolerated concentrations (1.2 and 1 mg/ml, respectively), the virus replication was suppressed over 90 %. This demonstrates that *L. album* could be a promising source of natural antiviral substances with potential use in medicine. However, further investigations on metabolic profile of in situ and in vitro cultivated *L. album* plants and identification of active agents in the extracts which contribute to such activity are needed.

Table 1 Biological activities of pure compounds and *Lamium album* L. extracts in in vitro model systems

Extract or pure vcompaunds	Concentration	Model system or assay	Effect	References
Aqueous extract	100 μg/ml	Huh 7 (hepatocyte derived cellular carcinoma cell line)	Anti-Hepatit C virus entry activity	Zhang et al. (2009)
Lamiridosins A/B	IC_{50} 2.31 μM	Hep G2 2.2.15 (human hepatoma cell line)	Anti-Hepatit C virus entry activity	Zhang et al. (2009)
Chloroform extract	IC_{50} 668 μg/ml	MDBK (Madin-Darby Bovine Kidney cell line)	Inhibition of replication of *Herpes simplex* viruses type 1 and type 2	Todorov et al. (2013)
Chloroform extract from in vitro cultivated plants	IC_{50} 552 μg/ml	MDBK (Madin-Darby Bovine Kidney cell line)	Inhibition of replication of *Herpes simplex* viruses type 1 and type 2	Todorov et al. (2013)
Aqueous fraction of hydro-alcoholic extract	IC_{50} 280 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Trouillas et al. (2003)
Butanol fraction of methanol extract	IC_{50} 9.9 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Budzianowski and Budzianowska (2006)
Methanol extract	IC_{50} 1 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Matkowski and Piotrowska (2006)
Methanol extract from in vitro cultivated plants	IC_{50} 194 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Valyova et al. (2011)
Ethanol extract from in vitro cultivated plants	IC_{50} 274 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Valyova et al. (2011)
Ethanol extract	IC_{50} 11.2 μg/ml	DPPH free radical scavenging test	DPPH antiradical activity	Pereira et al. (2013)
Ethanol extract	50 μg/ml	Hep G2 (HB-8065) (Human hepatoblastoma cell line)	Decrease ROS production	Pereira et al. (2013)
Ethanol extract	MIC 250 mg/ml	Liquid dilution analysis	Antimicrobial activity against *Bacillus cereus* and *Staphylococcus aureus*	Kokoska et al. (2002)
Chloroform extract	MIC 313 μg/ml	Diffusion analysis	Antimicrobial activity against *Enterococcus faecalis, Staphylococcus aureus, Proteus hauseri, Pseudomonas aeruginosa*	Chipeva et al. (2013)
Aqueous fraction of hydro-alcoholic extract	500 μg/ml	B16 cell line derived from C57BI/6 mouse spontaneous skin tumor cells	Antiproliferative activity	Trouillas et al. (2003)
Ethyl acetate extract	IC_{25} 188 μg/ml	HSF (human skin fibroblasts cells)	Antiproliferative activity	Paduch et al. (2008)
Methanol extract	IC_{50} 800 μg/ml	A549 (cancer lung cell line)	Cytotoxic activity, reduction of cell adhesion	Moskova-Doumanova et al. (2012)
Chloroform axtract	IC_{50} 500 μg/ml	A549 (cancer lung cell line)	Cytotoxic activity	Moskova-Doumanova et al. (2012)
Ethanol extract	50 μg/ml	Hep G2 (HB-8065) (human hepatoblastoma cell line)	Cytoprotective activity	Pereira et al. (2013)

Table 1 continued

Extract or pure vcompaunds	Concentration	Model system or assay	Effect	References
Verbascoside	50 μg/ml	Hep G2 (HB-8065) (human hepatoblastoma cell line)	Cytoprotective activity	Pereira et al. (2013)
Aqueous fraction of hydro-alcoholic extract	IC_{50} 1500 μg/ml	Lipoxygenase assay	Anti-inflammatory activity	Trouillas et al. (2003)
Heptane extract	20 μg/ml	10.014 pRSV-T (human corneal cell line)	Anti-inflammatory activity; down-regulation of sICAM-1 exspression	Paduch and Wozniak (2012)

Antimicrobial activity

Due to undesirable side effects of the antibiotics and the growing resistance that pathogenic microorganisms develop against these agents, recent attention has been paid to plant derived extracts and harmless biologically active compounds. Herbal based antimicrobials have enormous therapeutic potential. They are effective in the treatment of infectious diseases and in mitigating many of the side effects that are often associated with synthetic antimicrobials (Kokoska et al. 2002). Crude ethanol extract from rhizome of *L. album* were shown to possess antimicrobial activity against *Bacillus cereus* and *Staphylococcus aureus* (Kokoska et al. 2002) (Table 1). Recently, more detailed analysis on the antimicrobial activity of 18 different extracts from in situ and in vitro *L. album* plants have been performed (Chipeva et al. 2013). The extracts were obtained by using four different solvents (methanol, ethanol, water and chloroform). All used extracts demonstrated antibacterial activity on the tested bacteria strains (*Bacillus subtilis*, *Enterobacter aerogenes*, *Enterococcus faecalis, Escherichia coli*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Proteus hauseri*, *Pseudomonas aeruginosa*, *Salmonella enterica*, *Staphylococcus aureus*, *Staphylococcus epidermidis*) with minimum inhibitory concentration (MIC) ranging from 10 to 0.313 mg/ml. Gram-positive bacteria were found more sensitive than Gram-negative bacteria. Methanol and ethanol leaf extracts from in vitro propagated *L. album* possessed a broader spectrum of antibacterial activity than those obtained from in situ plants. The lowest MIC towards *E. faecalis*, *S. aureus*, *P. hauseri*, and *P. aeruginosa* was achieved by chloroform extracts from in situ plants (Chipeva et al. 2013).

Antioxidant activity

Oxygen free radicals are involved in pathophysiology of many diseases, including inflammation and cancer. Antioxidant and free radical scavenging activities of the medicinal plants are mainly attributed to their phenolic contents like flavonoids and phenylpropanoids. A possible correlation between antioxidant efficiency and phenolic composition of *L. album* extract has been reported by Trouillas et al. (2003). The antioxidant tests were carried out on the basis of the scavenging activity of the synthetic stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical, and two oxygen radicals naturally produced in the cells - superoxide radicals and hydroxyl radicals, which at elevated levels are toxic for the cell. The aqueous fraction of hydro-alcoholic extract from *L. album* exhibited weak antioxidant activity in comparison to reference molecules such as vitamin E and quercetin. However, among all tested aqueous fractions from 16 medicinal plants, the extract from *L. album* expressed moderate scavenging effect on DPPH radicals (IC_{50} = 280 μg/ml) and superoxide radicals (IC_{50} = 1.25 mg/ml) while in the case of hydroxyl radicals a weaker activity was observed ((IC_{50} = 530 μg/ml). Antioxidant effect of the extract is a result of a mixture of molecules with different activities. This makes difficult to speculate that the most active molecules in the extract may be characterized with lower antioxidant potential in comparison with purified molecules of vitamin E and quercetin. More detailed analysis for correlation between anti-DPPH activity and phenolic compounds was performed in methanol extract from *L. album* flowers Budzianowski and Budzianowska (2006). Chloroform, butanol and aqueous fractions of the methanol

extract were examined. The butanol fraction was found most enriched in phenolic compounds and significant DPPH antiradical activity (Table 1) that was nearly equal to the known antioxidant butylated hydroxyanisole ($IC_{50} = 9.1$ μg/ml) was observed. It is assumed that phenolic compounds like flavonoids and caffeic acid derivatives are responsible for the antiradical properties of the butanol fractions from *L. album* flowers.

Methanol extract of *L. album* was also reported to exhibit great DPPH radical scavenging properties ($IC_{50} = 1$ μg/ml) (Matkowski and Piotrowska 2006). Additional in vitro analyses including phosphomolybdenum method for determination of total antioxidant activity and lipid peroxidation assay showed variation in the antioxidative potential of the examined herb. This indicates the complexity of involved mechanisms and supports the necessity of combining several assays in studying the antioxidant potential of medicinal plants. Correlation of total phenolic and flavonoid contents with antioxidant capacity in plants grown at in situ and in vitro conditions was established (Valyova et al. 2011). The highest total phenolic and flavonoid content was detected in methanol and ethanol extracts from in situ plants, which showed also good radical scavenging activity unlike extracts from micropropagated plants which were characterized with weak antioxidant capacity (Table 1). However, further efforts need to be invested to establish optimal conditions that promote biosynthesis and accumulation of antioxidant compounds in in vitro cultivated *L. album* plants.

Very recent work of Pereira et al. (2013) confirmed that purified ethanol extract of *L. album* plants possess not only DPPH scavenging ability but it could also decrease reactive oxygen species (ROS) production in potassium dichromate-stimulated human hepatoblastoma Hep G2 cell model (Table 1). The antioxidant activity of ethanol extract was attributed to the content of polyphenols, and the use of individual polyphenol compounds determined in the extracts or their mixtures could simulate the antioxidant effect and showed cytoprotective effect against potassium dichromate induced toxicity. Among the phenolic compounds in purified ethanol extract from *L. album* the amount of verbascoside and its derivatives represented nearly 56 %, whereas the remaining constituents included isoscutellarein glycosides and 7-O-derivatives of naringenin, apigenin and luteolin. Despite their minor abundance in the purified ethanol extract in comparison to verbascoside (54 % total phenolics), they exhibited almost twice of its capacity for decreasing potassium dichromate-stimulated increment of ROS levels. ROS overproduction results in oxidative stress that is associated with aging and diseases such as cardiovascular, neurodegenerative, inflammatory disorders, and cancer. Each of the identified phenolic compounds in *L. album* extracts was shown to reduce ROS production in stressed human hepatoblastoma Hep G2 cells and therefore these biologically active molecules may find potential therapeutic applications towards the prevention of degenerative and neoplastic diseases.

Cytoprotective activity

The different extracts from *L. album* flowers, such as methanol, ethyl acetate and heptane have been tested for their toxicity and ability to stimulate growth of human skin fibroblasts (HSF) in vitro (Paduch et al. 2007). In toxicity analysis performed with 1×10^5 cells/ml for 24 h of incubation slight cytotoxic effect of the extracts in the range of applied concentrations (25–175 μg/ml) was observed. However, longer exposition (between 24 and 72 h) of culture with low cell density ($2x10^4$ cells/ml) to methanol and ethyl acetate extracts at concentrations greater than 125 μg/ml resulted in significant cytotoxicity. At concentration of 25 μg/ml the cells remained unaffected. Strikingly, when the cells were incubated with heptane extract, relatively high viability (>60 %) of cells was observed and the mitochondrial dehydrogenase activity, measured by MTT assay was gradually increasing with the time. Skin fibroblasts proliferation is considered as the most important initial stage of tissue repair which suggests possible application of heptane extract of *L. album* in wound healing treatments. To this respect, it is important to have knowledge about the content of biologically active compounds in the *L. album* extracts that could be applied for developing formulation for wound healing. Paduch et al. (2007) determined presence of flavonoids, phenolic acids, iridoids and terpenes in methanol and ethyl acetate extracts. However, in the heptane extract only triterpenes were found and experimental data demonstrated that these compounds have limited toxicity during prolonged incubation of HSF cells. This suggests that they may contribute to wound healing effect. On the other hand,

methanol and ethyl acetate extracts exerted time- and concentration-dependent cytotoxic effects on HSF cells. Paduch et al. (2008) performed more detailed investigation to elucidate the cytotoxic activities of these two *L. album* extracts. They found that methanol extract contained large amounts of flavonoids in the form of glycosides, and aglycones, protocatechuic, chlorogenic, vanillic, caffeic, coumaric and ferrulic acids. In ethyl acetate extract few flavonoids, mainly in the form of aglycones and traces of vanillic and caffeic acids were established. In both extracts ursolic acid and β-amyrin were present. Ethyl acetate extract had stronger anti-proliferative activity on HSF cells (2×10^4 cells/ml) than the methanol extract. The anti-proliferative activity may be associated with different amount of the flavonoid quercetin and triterpene ursolic acid present in the extracts that are suggested to block the cell cycle progression in G1 phase and to trigger apoptosis (Hsu et al. 2004; Jakubowicz-Gil et al. 2005). Ethyl acetate extract limited HSF cell proliferation more effectively than the methanol one, eventually because it contained significantly higher quantities of ursolic acid. The ethyl acetate samples influenced cell-to-cell adhesion complexes when applied at higher concentrations and at prolonged exposure, while treatment with methanol extracts affected cytoskeleton organization and F-actin filament polymerization but did not result in disturbed intercellular interaction (Paduch et al. 2008). This is only one of the possible explanations but active components of plant extracts may also influence other mechanisms closely associated with cytoskeleton organization and related to cell viability. The lower anti-proliferation activity of methanol extract could be due to the higher content of phenolic compounds such as caffeic acid considered as a superior antioxidant with high radical scavenging activity (Gülçin 2006). However, these phenolics were not detectable in ethyl acetate extract and no free radical reduction was found. The available information indicates that methanol extract of *L. album* appears non-toxic and expresses antioxidant activity in short time of incubation with HSF cells. Hence, after careful justification of exposure time and specimen concentration, *L. album* extracts could be taken into consideration for their potential use as components of wound healing and skin protective formulations.

Cytoprotective effect of purified ethanol extracts of *L. album* plants has been demonstrated against potassium dichromate-induced acute toxicity (the chemical applied at 200 μM for 6 h) or long-term toxicity (2 μM for 72 h) in hepatoblastoma Hep G2 cell model (Pereira et al. 2013). It is described that the extract exerted a significant protection against the cell viability decrement (about 30 %) under acute and long-term toxic conditions. The cytoprotective effect of *L. album* ethanol extract seems related to the presence of the major phenol compound verbascoside (50 μg/ml) that counteracted by 49 % the decrease in cell reducing activity induced by 200 μM potassium dichromate. The involved mechanism of cytoprotection of verbascoside is rather independent from its ROS scavenging action whereas other polyphenols as naringenin, apigenin and luteolin dominate with higher antioxidant potential. Hence, further studies are awaited to elucidate the processes targeted by verbascoside. It is known that potassium dichromate-induced cytotoxicity triggers apoptosis through a cascade of cellular processes, including gene expression and DNA breakdown (He et al. 2007; Son et al. 2010). The inhibition of some cell death events has been previously associated to verbascoside (Fu et al. 2008) and suggested to underline the cytoprotective action of *L. album* extract.

Anticancer activity

Trouillas et al. (2003) reported significant antiproliferative effect of aqueous fraction of hydro-alcoholic extract from *L. album* (500 μg/ml) on B16 cell line derived from C57BI/6 mouse spontaneous skin tumor cells. Although the molecular components of aqueous fraction were unknown, it has been suggested that compounds with antioxidant activities, especially phenolic compounds, could inhibit tumor promotion and cell proliferation.

The cytotoxic effect of extracts from in situ and in vitro-grown *L. album* plants was tested on A549 cancer lung cell line (3×10^4 cell/ml) after 24 and 48 h of cultivation (Moskova-Doumanova et al. 2012; Topouzova-Hristova et al. 2012). A series of concentrations (0.25, 0.50, 1.0, 2.5 and 5.0 mg/ml) of methanol and chloroform extracts and combination between two extracts were explored. All extracts showed cytotoxic effect (Table 1), except methanol and chloroform extracts in concentrations of 2.5 and 0.5 mg/ml, respectively. Methanol extract in concentration 4.5 mg/ml exhibited strongest effect on cell

adhesion and after 6 h, around 50 % of cells remained unattached, which is crucial for preventing further metastasis of tumor cells. Authors suggested that reduced adhesion could be due to affection of integrins, which are a family of transmembrane proteins involved in the cell adhesion and migration, or due to disruption of membrane phospholipids. After 48 h incubation separately with methanol and chloroform extracts in different concentrations, general G2-phase arrest of the cell division progression was observed, whereas in the presence of combined methanol/chloroform extracts only small amount of apoptotic cells was noticed. Comparison of cell lines with normal and cancerous origin showed that treatment with combined methanol/chloroform extracts exhibited the most powerful anticancer effect, while individual treatments with methanol or chlorophorm extracts caused weaker activity (Topouzova-Hristova et al. 2012), suggesting the presence of synergisms on the mentioned beneficial properties of the extracts. The number of cancer A549 cells after treatment with combined extracts decreased and many cells displayed morphological changes such as chromatin clustering, nuclear fragmentation, and reduced volume of the cytoplasm and disturbances of membrane integrity associated with progression of cell death. It should be noted that *L. album* extracts selectively inhibited the development of tumor cells and did not affect the normal cells.

Anti-inflammatory effect

In a bioassay system the anti-inflammatory activity of aqueous fraction of hydro-alcoholic extract from *L. album* (IC_{50} 1,500 μg/ml) has been demonstrated by significant inhibition of soybean lipoxygenase activity that generates important mediators of inflammation (Trouillas et al. 2003). This effect was suggested to be mediated by phenolic compounds such as caffeic acid derivatives and ursolic acid acting as lipoxygenase inhibitors. The phenolic compounds could also serve as scavengers of reactive free radicals which are produced during the inflammation process. Accordingly, good correlation has been observed between inhibition of lipoxygenase and scavenging activity against DPPH and superoxide radicals (Trouillas et al. 2003). Although the exact biologically active molecules are still to be identified, there are several reports supporting the anti-inflammatory effect of *L. album* extracts in specific functional disorders. The cell adhesion molecules are important to keep the homeostasis of plethora of vital cellular responses. The glycoprotein intercellular adhesion molecule-1 (ICAM-1) is synthesized in the epithelial ocular tissues. It is signal molecule with essential role in different eye inflammatory diseases. The soluble ICAM-1 (sICAM-1) which results from enzymatic cleavage and shedding of the membrane-bound ICAM-1 form is increased in patients with ocular inflammatory and allergic reactions, and serves as indicator of inflammatory processes in eyes (Gao et al. 2004). Treatments of 10.014 pRSV-T human corneal cells with heptane extract from *L. album* flowers in concentration 8 and 20 μg/ml resulted in concentration-dependent decrease of sICAM-1 in human corneal cells (10.014 pRSV-T cell line), while ethanol extracts resulted in sICAM-1 increase and ethyl acetate extracts did not cause changes (Paduch and Wozniak 2012). The data suggest the implication of *L. album* extracts in eye drop products that can inhibit inflammation in eye-related diseases.

In addition to the already above described effects, oil extracts from *L. album* plants have been shown to exhibit antianemic effect in models of hemolytic and iron-deficiency anemia in white mongrel male rats, following oral administration of 1 ml/kg of the extract per day, for up to 12 weeks (Petukhova et al. 2008).

White dead nettle extracts have multifarious biological activity (Fig. 6) and are widely used in traditional folk medicine. It should be noted, however, that some of the pharmacological effects occur at considerably high concentrations and therefore need to be treated with caution. More precise characterization of the plant extracts by using some modern platforms (including metabolomics) for comprehensive metabolite profiling and fingerprinting should be applied. The available in vitro investigations are still insufficient to fully determine the pharmacological effects and in vivo and clinical trials are as well required to justify the proper medicinal use of this plant.

Conclusions and future perspectives

The health promoting effects of *L. album* are widely recognized. Its traditional usage in folk and official medicine has attracted significant attention and has led

to intensive phytochemical and biological activity investigations. In ancient times, white dead nettle had been considered as a magic plant capable of solving numerous human infirmities. In the recent decade, significant number of studies have been carried out in search for metabolites responsible for the beneficial properties and various organic compounds belonging to the groups of iridoids, phenylethanoid glycosides, flavonoids, phenolic acids, isoscutellarein derivatives, terpenes have been identified. Pharmacological researches have proven valuable cytoprotective, antioxidant, antiviral and anti-inflamatory effects of the substances. Numerous bioactivity studies have been conducted on the application of water and organic solvents extracts from the aerial part of *L. album*, but the synergistic effects of the different compounds have been poorly investigated. Thus, an effort should be invested in order to obtain more profound information on these effects. Furthermore, the mode of action and molecular targets of the biologically active compounds isolated from white dead nettle are still largely unknown. Here we have summarized the recent findings on the chemical and pharmacological properties that seem to underline the revival secrets of *L. album*. The current review provides up-to-date information on chemical composition of biologically active metabolites found in *L. album* and contributes to better understanding of their pharmacological effects.

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