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REVIEW

Leonurus cardiaca L. (Motherwort): A Review of its Phytochemistry and Pharmacology

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***Leonurus cardiaca* is a perennial plant indigenous to central Europe and Scandinavia, but it is also found in the area spanning temperate Russia to central Asia. It has been introduced to North America and has become established locally in the wild. Motherwort (*Leonuri cardiacae herba*) consists of aerial parts of *Leonurus cardiaca* gathered during the flowering period, dried at 35 °C and, according to European Pharmacopoeia 7th edition, should contain a minimum of 0.2% flavonoids, expressed as hyperoside. Compounds belonging to the group of monoterpenes, diterpenes, triterpenes, nitrogen- containing compounds, phenylpropanoids, flavonoids and phenolic acids, as well as volatile oils, sterols and tannins, have been identified in motherwort. Traditionally, extracts of the herb have been used internally, mainly for nervous heart conditions and digestive disorders. However, they have also been used for bronchial asthma, climacteric symptoms and amenorrhoea, as well as externally in wounds and skin inflammations. Mild negative chronotropic, hypotonic and sedative effects can be attributed to the herb and preparations thereof. Pharmacological studies have confirmed its antibacterial, antioxidant, anti-inflammatory and analgesic activity, as well as its effects on the heart and the circulatory system. Sedative and hypotensive activity has been demonstrated in clinical trials. Copyright © 2012 John Wiley & Sons, Ltd.**

Keywords: motherwort; *Leonurus cardiaca* L; pharmacology; phytochemistry.

INTRODUCTION

Leonurus cardiaca belongs to the genus *Leonurus*, family Lamiaceae, formerly Labiatae. It is a perennial herb widespread in Europe, commonly found in rural areas throughout the lowlands and foothills, as well as in East Asia to the Himalayas and eastern Siberia, northern Africa and North America. Motherwort (*Leonuri cardiacae herba*) consists of the aerial parts of *Leonurus cardiaca* gathered during the flowering period and dried at 35 °C and, according to European Pharmacopoeia 7th edition, should contain a minimum of 0.2% flavonoids expressed as hyperoside. In the aerial parts of *Leonurus cardiac*, there are compounds belonging to the group of terpenes: monoterpenes (irdoids), diterpenes (of clerodane, furanolabdane and labdane types), triterpenes (ursolic and oleanolic acids), nitrogen-containing compounds (leonurine, stachydrine), phenylpropanoids (lavandulifolioside), as well as flavonoids, phenolic acids, volatile oils, sterols and tannins.

Antihypertensive and heart-strengthening effects are attributed to motherwort, such as the facilitation of coronary blood flow, and a calming effect in nervous and functional heart disorders (Bradley, 1992; Wichtl, 2004). Traditionally, it is used in nervous heart conditions and as an aid in hyperthyroidism because it relieves the heart palpitations and tachycardia associated with hyperthyreosis. Furthermore, it is applied in digestive disorders, bronchial asthma, climacteric symptoms and amenorrhoea, as well as externally in wounds and skin inflammations. Mild negative chronotropic, hypotonic and sedative effects can be attributed to the herb and preparations thereof. In order to obtain positive results, long-term use, even for a few months, is necessary. The sedative activity is comparable to the effect induced by administration of preparations of valerian root *Valeriana officinalis* (Mścisz and Gorecki, 1997; Blumenthal *et al*., 2000; Weiss and Fintelmann, 2000). The alkaloids, leonurin and stachydrin, are probably responsible for such effects on the nervous system as well as the herb's ability to lower blood pressure (Bradley, 1992). In addition, there are traditional applications for gynaecological disorders, particularly nervous symptoms associated with the period of menopause and menstrual disorders (painful or absent menstruation) (Blumenthal *et al*., 2000). A spasmolytic effect on the smooth muscles of the gastrointestinal tract justifies the use of the raw material in spastic colic, which results in the weakening of intestinal motility, manifested as digestive disorders, bloating, abdominal pain and recurrent constipation. Due to the presence of tannins which act astringently on mucous membranes, motherwort can be used in mild diarrhoea. In folk medicine, motherwort is sometimes regarded as a diuretic, hypoglycaemic and anti-epileptic drug (Weiss and Fintelmann, 2000).

Externally, infusion of the raw material is recommended as a rinse for wraps and wounds, skin abrasions and burns.

Motherwort is mainly used in European medicine, but the aerial parts, as well as the ripe dried fruits of other *Leonurus* species: *L. japonicus* HOUTT (syn. *L. sibiricus* L.), are used in traditional Chinese medicine, and the range of their applications is concerned with heart palpitations caused by hyperthyroidism or hormonal changes during menopause (Bradley, 1992).

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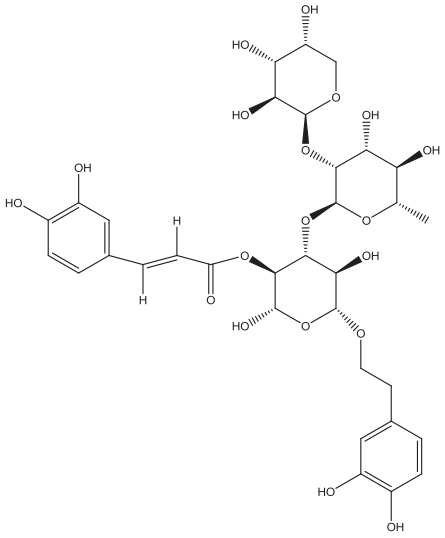
Plant constituents

Compounds belonging to different chemical groups have been identified in the *Leonuri cardiacae herba* (Fig. 1).

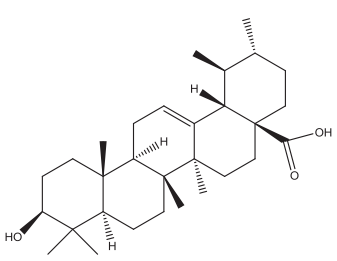
Terpenes are represented by monoterpenosides (iridoids): leonuride (= ajugol = 4-deoxyharpagid), ajugoside, galiridoside, reptoside (Weinges *et al*., 1973; Wichtl, 2004), bitter diterpenoids of clerodane (Brieskorn and Hofmann, 1979) and of the labdane-type: leocardin (an epimeric mixture of 15-O-ethylleopersin C, 15-O-methylleopersin C, together with the isomer of α-15-epi-O-methylleopersin C) (Malakov *et al*., 1985; Agnihotri *et al*., 2008), furanolabdane derivatives related to marrubiin: leosibiricin (2.6–3.2 mg/g fresh weight), 19-acetoxypregaleopsine (Knöss and Zapp, 1998; Papanov *et al*., 1998) and triterpenes: ursolic acid (0.26%), oleanolic acid, corosolic acid, euscaphic acid and ilelatifol D (Janicsák *et al*., 2006; Ali *et al*., 2007).

The nitrogen-containing compounds are pyrrolidine-type alkaloids: stachydrine (0.5–1.5%), and stereoisomers of 4-hydroxystachydrine: betonicine and turicin (Romanowski, 1960), imines guanidine derivative: leonurine = syringic acid ester and 4-guanidino-1-butanol (0.0068%) (Gulubov and Chervenkova, 1970), and amine choline (Reuter and Diehl, 1970). Other constituents include flavonoids, particularly quercetin and kaempferol O-glycosides: rutin, hyperoside, quercitrin, isoquercitrin, astragalin, as well as apigenin: 7-, 5-, 4'- O-glycosides, and quinqueloside = 4'-*p*-coumaroyl-apigenin-7-glucoside; flavonoid C-glycosides: vitexin and isovitexin; free aglycones (quercetin, kaempferol, genkwanin); genkwanin is proposed as a chemotaxonomic marker of the Leonurus genus (Schultz and Alhyane, 1973; Kartnig *et al*., 1985; Bernatoniene *et al*., 2009).

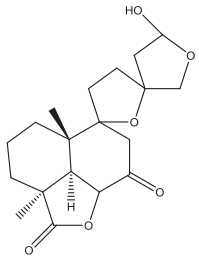
The phenolic compounds include phenylpropanoid glycosides: lavandulifolioside: arabinoside of verbascoside



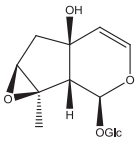
Lavandulifolioside



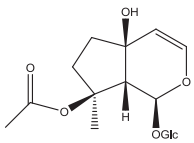
Ursolic acid



Leocardin

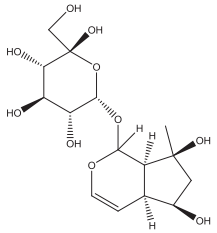


Galiiridioside

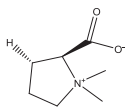


Reptoside

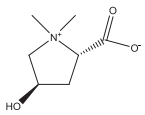
Figure 1. Structures of some of the chemical compounds isolated from *Leonurus cardiaca*.



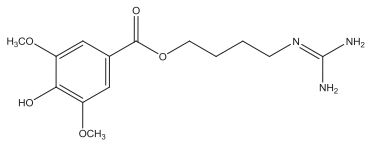
Ajugol



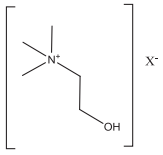
Stachydrine



Betonicine and turicine (stereoisomers)



Leonurine



Choline

Figure 1b. (Continued)

= acteoside (1%) (Miłkowska-Leyck *et al*., 2002) and phenolic acids: chlorogenic, rosmarinic, caffeic, *p*-coumaric, *p*- hydroxybenzoic, vanillic, ferulic acid, as well as phenolic glycoside: caffeic acid 4-rutinoside (0.1%) (Tschesche *et al*., 1980; Bernatoniene *et al*., 2009; Wojtyniak, 2011).

The volatile oils (0.02%) mainly contain sesquiterpenes: germacrene D (28.3–32.0%), epicedrol, β-caryophyllene (7.0–8.9%), α-caryophyllene = α-humulene (6.5–8.8%), spatulenol and monoterpenes: α-pinene (0.5–1.0%), dehydro-1,8 cineole (Mockutë *et al*., 2005; Morteza-Semnani *et al*., 2008).

Sterols (0.02%) are represented by β-sitosterol and stigmasterol (Senatore *et al*., 1991) while the structural formula of tannins (5–9%) has not been identified (Hänsel *et al*., 1993).

Pharmacological activity

Pharmacological studies have confirmed antibacterial, antioxidant, anti-inflammatory and analgesic activity, as well as the effects of the herb on the heart and circulatory system. Sedative and hypotensive activity has been demonstrated in clinical trials.

The use of motherwort is mainly based on traditional indications as pharmacological studies are limited.

Antimicrobial activity

The labdane-type diterpenes are probably responsible for the antimicrobial activity of motherwort. A chloroformic extract of motherwort leaves, rich in diterpenes, inhibited the growth of *Staphylococcus aureus* (Sattar *et al*., 1995) whereas a chloroformic fraction of a methanolic extract of its aerial parts showed activity against the multiresistant strain of *Plasmodium falciparum* (Tasdemir *et al*., 2005). A fraction obtained from the chloroformic extract, containing labdane-type diterpenes: 15-O-ethylleopersin C, 15-O-methylleopersin C and its isomer: α-15-epi-O-methylleopersin C, was also active against this strain (Agnihotri *et al*., 2008). An aqueous extract of motherwort almost completely inhibited the development of the tick-borne encephalitis virus in cell cultures, causing greater life expectancy of virus-infected mice and thus proving the induction of immunity (Fokina *et al*., 1991).

Antioxidant activity

Extracts from motherwort demonstrated antioxidant activity in several in vitro studies. Polyphenolic compounds, mainly flavonoids (rutin) and derivatives of hydroxycinnamic acid (Matkowski and Piotrowska, 2006, 2008; Masteiková *et al*., 2008; Bernatoniene *et al*., 2009; Jafari *et al*., 2010) may be responsible for this effect.

Analgaesic and anti-inflammatory activity

In the 'hot plate' test (53 °C), a water-ethanolic extract of motherwort reduced the perception of pain in mice (Szõcs *et al*., 1999). The fraction of the extract, containing furanolabdane type diterpenes as well as isolated diterpenes, inhibited abdominal cramps caused by acetic acid more effectively than the parallel-given aspirin or acetaminophen (Brand *et al*., 1999). Ursolic acid, isolated from motherwort, in a model of respiratory burst of neutrophils in vitro had stronger anti-inflammatory activity than indomethacin and acetylsalicylic acid when used as a positive probe (Ali *et al*., 2007).

Neuroprotective effect

The neuroprotective effect of synthetic leonurine on nerve cells in an ischaemic stroke model (in vivo, in rats) was demonstrated by a reduction of the stroke area, and motor and behavioural changes indicating brain injury. In the study group, a lower level of generation of reactive oxygen species (ROS), less damage within the mitochondria, decreased proapoptopic Bax protein expression, increased expression of anti-apoptopic Bcl-2 protein (involved in the signalling pathways for the programmed death of the cell) and a limited outflow of cytochrome C from mitochondria were achieved. Thus, the neuroprotective effect of leonurine is mainly due to the reduction of ROS formation, by virtue of which proper functioning of mitochondria is maintained and, consequently, inhibition of apoptosis takes place. The investigation suggests that leonurine could be useful in preventing and treating ischaemic strokes due to its antioxidant and apoptopic mechanisms (Qi *et al*., 2010).

Cardiovascular activity

Intracoronary administration of a *Leonurus cardiaca* refined extract to isolated rabbit hearts reduced left ventricular pressure and increased coronary blood flow, lengthened Q-T and P-Q intervals, increased the basic cardiac cycle and activation recovery interval and led to the inhibition of the inward calcium current (blocking ICa.L) and the inward potassium current (IK.r) which are responsible for depolarisation and repolarisation, respectively. The extract lengthened the duration of the action potential and the activation time of the inward depolarising sodium and potassium currents (If) in pacemaker cells of the heart conduction system. The study showed the multidirectional activity mechanism of the extract from motherwort on the heart, corresponding to the activity of class III antiarrhythmic drugs, which justifies its use in tachycardia (Ritter *et al*., 2010).

The potential effect of lavandulifolioside, obtained from a butanol extract of motherwort, on the blood pressure of normotensive rats, and the work on rat hearts isolated from another group of these animals and the effect of the butanolic extract on the heart were investigated. Both lavandulifolioside and the butanol extract decreased the heart rate, lengthened the duration of P-Q and Q-T intervals and QRS complex and decreased coronary outflow. This is in contrast to the experiment carried out by Ritter *et al*. (2010). The contradictory results may have arisen from variations in the preparation of the extracts. An intravenous injection of 77 mg/kg of lavandulifolioside decreased the systolic blood pressure by 13–15% and diastolic blood pressure by 16–19%. Furthermore, the antihypertensive activity lasted 60 min (Miłkowska-Leyck *et al*., 2002).

The aqueous extract of a variety of motherwort collected in Romania (*Leonurus quinquelobatus*) antagonised

(150 mg/kg) the pressor activity of norepinephrine given intravenously to dogs a total of two times in continuous perfusions (10 μg/kg/min) (Rácz and Rácz-Kotilla, 1989).

Leonurin, isolated from motherwort and obtained by synthesis, showed a protective effect on the myocardium in the ischaemia-induced damage model in rats (in vivo) by reducing lipid peroxidation and apoptosis. The compound was administered intraperitoneally in two doses: 7.5 and 15 mg/kg/day for seven days preceding the ligation of the left coronary artery, which resulted in ischaemia and myocardial infarction. Leonurine (15 mg) diminished the levels of two enzymes: lactate dehydrogenase and creatine kinase, of which increased levels in blood serum indicate damage to the heart. As a result, low values of malonic dialdehyde, originating from lipid peroxidation, and high concentrations of superoxide dismutase, participating in the protection against reactive forms of oxygen, as well as a decrease in proapoptopic Bax gene and protein expression and increased expression of anti-apoptopic protein Bcl-2 were observed (Liu *et al*., 2010).

Results of old studies (1949) on various preparations of motherwort (tincture, alcoholic liquid extract, dry extract and infusion) used in a group of 100 patients (aged 18–65) suffering from nervous cardiovascular conditions, hyperthyroidism, atherosclerosis and heart diseases, and hypertension were published. After 3–4 days of treatment with tablets containing liquid and dry extracts, reduced palpitations and sensations of tightness in the heart area, and weakened tachycardia and nervous excitability in people suffering from hyperthyroidism were observed. The best results of the treatment with motherwort preparations were obtained in the group suffering from nervous heart conditions and hyperthyroidism. In the patients with essential hypertension, after 8–10 days of treatment, there was a decrease of 8–20 mmHg in blood pressure, and headaches and dizziness were alleviated. However, in cases with heavy heart ailments, therapy with preparations of motherwort proved to be ineffective (Rossyjskij, 1949).

Sedative activity

The sedative activity of tinctures of motherwort and valerian root was compared in a study on rabbits, which had electrodes placed on their hind legs. An increase in the measured values of direct current intensity, necessary to cause a contraction of the flexor muscles after administration of the tinctures, was noted with a stronger inhibitory effect on the central nervous system exerted by the tincture of motherwort rather than that of valerian root (Polyakov, 1962). A significant sedative effect was observed for a 30% ethanolic extract of motherwort: it prolonged the amount of time the animals spent running through the maze by four, the duration of sleep induced by the barbiturates was increased three times and it reduced spontaneous activity by half (Mścisz and Gorecki, 1997).

Similar observations were applied to an aqueous extract of the aerial parts of a variety of *L. cardiaca (L. quinquelobatus)*, which, after intraperitoneal administration to mice, caused a decrease in motor activity. Provoked by the administration of methylphenidate (20 mg/kg body weight), the effect of increased physical activity was antagonised, ether anaesthesia was prolonged and the convulsive effect of pentetrazol was decreased (Rácz and Rácz-Kotilla, 1989). A butanolic extract from motherwort at a dose of 800 mg/kg reduced spontaneous locomotor activity in mice by 65%. Lavandulifolioside is not responsible for the sedative effect of motherwort since, at doses of 800 and 1600 mg/kg, it reduced the motility of mice only slightly (Miłkowska-Leyck *et al*., 2002).

In a double-blind randomised clinical trial, the sedative effects of tablets containing motherwort (50 mg), valerian root (170 mg), lemon balm leaves (50 mg) and hop pellets (50 mg) were compared with a placebo which comprised identical-looking tablets containing 5 mg of valerian root. The study group included 50 males (average age 45.6 years) suffering from alcohol withdrawal syndrome with sleep disorders (mild to severe insomnia), anxiety and irritability. The patients, divided into two groups, received the preparation an hour before bedtime, once a day, and the next day they were given the placebo. Compared with the placebo, a significant improvement in sleep quality and a decrease in the frequency of awakenings and nightmares proved a mild sedative effect of the product used; however, it caused drowsiness the following day. Motherwort could therefore, to some extent, be helpful in disorders associated with alcohol abstinence (Widy-Tyszkiewicz and Schmida, 1997).

A study to determine if the administration of sedatives, including a tincture of motherwort, decreases the limitation of the ability of the retina to distinguish colours caused by a state of anxiety was also carried out. The experiment involved 26 healthy volunteers with a diagnosed state of nervous anxiety, divided into three groups, and control group consisting of 12 patients without emotional disorders. A decrease in anxiety and an improved ability to distinguish colours, both after the application of tofizopam (benzodiazepine derivative) (10 days) and the tincture of motherwort, were noted, yet the anxiolytic effect of tofizopam persisted longer (up to one month after cessation of use) in comparison with the tincture. The positive effect of the treatment on vision may have resulted from an impact on the GABAergic system in the retina and the brain structures connected with it (Ovanesov, 2005).

In another experiment, 21 young patients (divided into three groups) with mild symptoms of anxiety and depression were administered melatonin, a tincture of motherwort or a placebo for 10 days (10 healthy volunteers constituted the control group). The quality of sleep and emotional state of the patients as well as their retinal function, i.e. the threshold of excitability to light stimuli and the sensomotoric response time of the process of vision, were evaluated before and after the application of the preparations. The administration of melatonin resulted in increased retinal sensitivity to light and an accelerated sensomotoric reaction. The impact on the process of vision after the administration of the tincture of motherwort was statistically insignificant, and sleep quality improved in some patients only. The anxiolytic activity of the tinctures of motherwort was confirmed, but it turned out to be weaker in comparison with that of melatonin (Ovanesov *et al*., 2006).

An oil extract of motherwort (4x300 mg capsules daily for 28 days) was administered to 50 patients with a first (22 patients) and second (28 patients) degree of

hypertension, and symptoms such as anxiety and sleep disorders. In patients with a first degree of hypertension, a reduction in the symptoms of anxiety, emotional instability, headaches and sleep disorders was achieved. After 21 days, there was a significant decrease in and normalisation of blood pressure (from 145/96 to 130/87), and the patients reported they experienced less fatigue, improved mood and activity. However, their reduction in heart rate (from 81.7 to 75.4) was not statistically significant. A considerable drop in blood pressure (from 153/103 to 142/92) in patients with a second degree of hypertension occurred a week later than the first group. The psycho-emotional condition of the patients (anxiety, emotional liability, headache and sleep disturbances) was improved seven days before their blood pressure lowered. The hypotensive, anxiolytic and calming effect may have been caused by iridoids, while the lack of anti-arrhythmic action may have resulted from the absence of alkaloids in the prepared extract (Shikov *et al*., 2010).

Uterotonic activity

Leonurine, present in *L. cardiaca*, but isolated from Chinese motherwort, *Leonurus artemisia*, stimulated muscles from isolated mice uteruses, significantly increasing the strength and frequency of contraction. In a parallel trial, leonurine caused relaxation of the rat portal vein. The effect of uterus shrinking may justify the traditional use of the species of the *Leonurus* genus to facilitate placenta expulsion and the collapse of the uterus after childbirth, while the vasodilating activity may contribute to a reduction of blood stasis and the ensuing ischaemia, thereby causing pain, and thus justifying the use of extract of motherwort in dysmenorrhoea (Yeung *et al*., 1977; Chen *et al*. 2000).

Dosage, contraindications

Commission E recommends daily use (1–3 times) of infusions prepared from 4.5 g of dry motherwort herb in nervous cardiac conditions and as an adjuvant for thyroid hyperfunction. No health hazards or side effects are known if the prescribed therapeutic dosages are administered properly.

Excessive use may interfere with the existing therapy of cardiac disorders, such as cardiac glycosides. Sensitive individuals may experience an allergic reaction. Motherwort is reputed to affect the menstrual cycle. In view of the documented in vitro uterotonic activity, the use of motherwort during pregnancy and lactation should be avoided. It is also not recommended to individuals under 18 years of age (Blumenthal *et al*., 2000).

Summary

Motherwort has a long medicinal tradition. Extracts from the herb have been used internally, mainly in nervous heart conditions and digestive disorders, climacteric symptoms and amenorrhea, as well as externally, in wounds and skin inflammations. Mild negative chronotropic, hypotonic and sedative effects can be attributed to the herb and preparations thereof. Recently, infusions prepared from the dry motherwort herb have been recommended in nervous cardiac conditions and as an adjuvant for thyroid hyperfunction. Compounds belonging to the group of terpenes (iridoids, diterpenes and ursolic acid), alkaloids (leonurin) and phenylpropanoids (lavandulifolioside) may be responsible for the diverse biological activity of *Leonurus cardiaca*; however, the influence of other groups of compounds cannot be excluded. Pharmacological studies have confirmed the valuable cardio- and neuroprotective effects of the extracts from the herb, as well as the uterotonic properties of leonurine and the anti-inflammatory ones of ursolic acid. Compounds present in the herb also show antibacterial, antioxidant, anti-inflammatory and analgaesic activity. Sedative and hypotensive activity has been demonstrated in clinical trials.

The amount of data on the pharmacological activity of *Leonurus cardiaca* is still insufficient to fully determine its effects and to justify the traditional use of the plant. It is particularly important to investigate the effect of the raw material on the human body in controlled clinical trials.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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