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Leonurus sibiricus L. (honeyweed): A review of its phytochemistry and pharmacology

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ABSTRACT

Leonurus sibiricus is a herbaceous plant found in many countries in Asia and America. This plant is widely practiced as a remedy for the treatment of diabetes, menstrual irregularities, and bronchitis. The approval of therapeutic implications of any drugs depends on the well characterized mode of actions of the compounds. The bioactive compounds like diterpenes, triterpenes, flavonoids and phenolic acids in *Leonurus sibiricus* show analgesic, anti-inflammatory, anti-oxidant, anti-atherogenic and anti-hemorrhagic, anti-diabetic, anti-bacterial and allelopathic potency. Interestingly, the expression level of some genes is altered by the crude extract treatments, which are effective against cancers, diabetes and cardiovascular diseases where the molecular mechanisms are yet to be explored. Intriguingly, the extracts significantly induce nitric oxide production by endothelial nitric oxide synthase, a signaling molecule of vasodilation in combination with interferon-γ indicating positive effect on atherosclerosis. Further investigations are required to unlock the effects of bioactive compounds found in extracts at clinical settings.

1. Introduction

Leonurus sibiricus (*L. sibiricus*) is a ubiquitous herbaceous plant grown in crop fields in many countries in Asia and South America [1–5]. This plant belongs to the family of Lamiaceae. It is an annual, biannual or perennial, aromatic, herbaceous plant. The average height is 40–120 cm and it germinates from seed. Lamiaceae family consists of about 236 genera and 6 900–7 200 species. Among all the genera, *Leonurus* contains about 20 species [6] and *L. sibiricus* is one of them, which is called honeyweed or Siberian motherwort in English. It is called Rokdrone in Bengali, Guma in Hindi, Kacangma in Malay, Erva-de-Macaé in Brazil, Marihuanilla in Mexico and marijuana in Spanish. This plant has been used as herbal medicine and culinary ingredients [7]. *L. sibiricus* acts as an effective therapeutic against diabetes, menstrual irregularities, and bronchitis. Studies show that it has medicinal effects on endometritis, myocardial cells and diabetes [8,9]. This plant has widely been using as a source of effluvium to the bees during the process of honey collection in Bangladesh. Based on preliminary information, we summarize the dynamic therapeutic potentials of *L. sibiricus* encouraging scientists to explore the underlying molecular mechanisms and state of the art of mode of actions against diseases. Due to limited studies, little is known about *L. sibiricus* specially the use as therapeutics. We found only one recently partially reviewed article on *L. sibiricus* [10]. To our best knowledge, this will be the first review paper exclusively on

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L. sibiricus, focusing on potential pharmacology and phytochemistry of *L. sibiricus*.

2. Retrieval of published literatures

The authors searched and downloaded the published papers related to *L. sibiricus* from 1982 to 2016 from the different databases like Google Scholar, PubMed, Elsevier, and Springer. The articles in which at least abstract is not in English were not considered for this study. We extracted and gathered the information which is related to its phytochemistry and pharmacology under the different subheadings. All identified chemical compounds were enlisted in tabular form. During the searching of published articles, we did not find any review papers of *L. sibiricus*. So far, we know that this will be the first review paper of *L. sibiricus*.

3. Identification of bioactive compounds

A number of studies show that *L. sibiricus* contains many different pharmacologically important chemical compounds (Table 1).

4. Cytotoxic activity

A number of studies show the beneficiary effects of *L. sibiricus* as a treatment for cancers [20,21] and cardiovascular disease [22]. Compounds like LS-1, LS-2, leonotinin, leonotin, dubiin and nepetaefuran isolated from *L. sibiricus* show a considerable cytotoxic effect against leukemia cells *in vitro* [13]. Interestingly, dry leaves of *L. sibiricus* at low dose (0.5 g/kg body weight) in rats and rabbits did not show any toxic effects while high doses (5.0 and 25 g/kg body weight) showed harmful effects [23,24]. Furthermore, different extraction methods of leaves and roots show cytotoxic effects on brine shrimp [25,26]. These results reveal the potential use of both leaf and root extracts of *L. sibiricus* as wormicide for human. Study shows that labdane type compounds are mainly responsible for the cytotoxicity [27]. A preliminary report shows that transformed root extract of *L. sibiricus* induces the apoptosis in glioma cells by upregulating Bax/Bcl-2–p53 signaling axis [28].

5. Antimicrobial activity

Different chemical extracts of *L. sibiricus* show potential antimicrobial activity. Methanol extract inhibits the growth of *Bacillus subtilis* [29]. The effects of *L. sibiricus* alcoholic extract are notable on Gram-negative and Gram-positive bacteria [30]. Intriguingly, carbon tetrachloride and chloroform extracts show a broad spectrum antibacterial activity than acetone and methanol extracts [1]. Carbon tetrachloride and chloroform extracts inhibit the growth of *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Escherichia coli, Vibrio cholera, Shigella dysenteriae* and *Shigella boydii*. The alcohol extracts do not show any inhibition of the growth of *Escherichia coli* [30]. On the contrary, carbon tetrachloride and chloroform extracts significantly inhibit bacterial growth. Reports show that diterpenes of labdane type compounds isolated from the plants of different family including Lamiaceae show a moderate to strong inhibitory activity on microorganism [27].

6. Analgesic, anti-inflammatory, anti-oxidant, anti-atherogenic and anti-hemorrhagic activity

Methanol extracts of *L. sibiricus* show a significant analgesic effect on mice (dose: 250 and 500 mg/kg body weight). The anti-inflammatory activity is also demonstrated in rats at the dose of 200 and 400 mg/kg body weight [31]. Anti-inflammatory effect of *L. sibiricus* is reported in secretion of inflammatory cytokine like tumor necrosis factor-α and interleukin-6 and interleukin-8 in human mast cell line HMC-1 [32]. The aqueous extracts of *L. sibiricus* show more efficient antioxidant activity than ethanol extracts in three different bioassay systems [33]. The extracts of *L. sibiricus* show not only the antioxidant activity, but also reduce the intracellular reactive oxygen species (ROS) in Chinese hamster ovary cells exposed to hydrogen peroxide. Methanol extract (80% v/v) increases the expression of intracellular antioxidants like superoxide dismutase, catalase and glutathione peroxidase. Liquid chromatography–mass spectrometry/mass spectrometry and high-performance liquid chromatography analyses reveal that the phenolic compounds and flavonoids modulate the antioxidant genes (Figure 1) and repair the oxidative DNA damage [19]. The aerial part of *L. sibiricus* is found to be used for the treatment of menstrual irregularities, amenorrhea, malaria, hypertension and myocardial ischemia [18]. *L. sibiricus* has also clinical implications to reduce the postpartum hemorrhage [34]. In connection with current reports, literature shows the effects of *L. sibiricus* extract for reducing the uterine bleeding in RU486-induced abortion mice [35]. Stachydrine hydrochloride is one of the constituents of *L. sibiricus* which has a function to reduce the uterine bleeding in RU486-induced abortion mice by regulating Th1/Th2/Th17/Treg paradigm [36]. Stachydrine hydrochloride upregulates the mRNA expression of T-bet and RORγt while inhibiting the mRNA expression of GATA-3 and Foxp3 (Figure 1) shows the effects on lowering the uterine bleeding in RU486-induced mice [36]. The isolated leonurine from the methanol extract of *L. sibiricus* shows anti-platelet activity in rabbit [37]. Cardiovascular disease is one of the leading causes of death in the world. Cholesterol, triglyceride and low density lipoprotein (LDL) are generally considered as the risk factors for cardiovascular diseases. Oxidized-LDL is the major risk factor for atherosclerosis which may promote ROS production. Lectin-like oxidized LDL receptor-1, the receptor of LDL, functions to promote the vascular dysfunction connecting to endothelial nitric oxide synthase (eNOS) production in the vessel tissues of human and animals. The suppression of eNOS production in human umbilical endothelial cells (HUVEC) is linked to cardiovascular diseases, hypercholesterolemia and atherosclerosis followed by preeclampsia in pregnant women [22]. Nitric oxide (NO) can be synthesized by the activity of eNOS in vascular endothelial and HUVEC cells, which can act as signaling molecule to prevent the aggregation of blood cells. The aqueous extract of *L. sibiricus* along with recombinant interferon-γ increase the NO production (Figure 1) and tumor necrosis factor-α in mouse peritoneal macrophages [38]. The previous study suggests that *L. sibiricus* has potential effects for reducing atherosclerosis. Furthermore, the ethanol extracts of *L. sibiricus* show the effects in controlling the level of cholesterol, adhesion molecules and ROS *in vivo* as well as lectin-like oxidized LDL receptor-1 *in vitro* [22].

Table 1

A list of compounds isolated from *L. sibiricus*.

Groups	Name of compound	Chemical formula	Source of raw materials	References
Phenols	Leosibirin	$C_{24}H_{34}O_8$	Aerial parts	[11]
	Isoleosibirin	$C_{24}H_{34}O_8$		
	Leosibiricin	$C_{22}H_{28}O_7$		
	Caffeic acid	$C_9H_8O_4$	Root exudates	[12]
Furanoditerpene lactones	LS-1		Aerial parts	[13]
	LS-2			
	Leonotinin	$C_{20}H_{26}O_5$		
	Leonotin	$C_{20}H_{28}O_5$		
	Dubiin			
	Nepetaefuran	$C_{22}H_{25}O_7$		
Labdane diterpenes	Sibiricinone A	$C_{20}H_{30}O_6$	Aerial parts	[14]
	Sibiricinone B	$C_{20}H_{28}O_5$		
	Sibiricinone C	$C_{21}H_{32}O_6$		
	Sibiricinone D and 15-*epi*-sibiricinone D	$C_{21}H_{34}O_5$		
	Sibiricinone E and 15-*epi*-sibiricinone E	$C_{21}H_{34}O_5$		
Phenols	Yimunoside A	$C_{20}H_{30}O_{15}$	Aerial parts	[2]
	Yimunol A	$C_{12}H_{16}O_7$		
	4-Hydroxythiophenol	C_6H_6OS		
	Syringic acid	$C_9H_{10}O_5$		
	Apigenin	$C_{15}H_{10}O_5$		
	Luteolin-7-methyl ether	$C_{16}H_{12}O_6$		
	4-Hydroxybenzoic acid	$C_7H_6O_3$		
	Genkwanin	$C_{16}H_{12}O_5$	Aerial parts, leaves	[2,15]
	Isoquercitrin	$C_{21}H_{20}O_{12}$	Aerial parts, leaves	
	Rutin	$C_{27}H_{30}O_{16}$	Aerial parts, leaves	
	Quercetin-3-O-α-L-rhamnopyranosyl-(1–>6)-β-D-galactopyranoside		Leaves	[15]
	Hyperin	$C_{21}H_{20}O_{12}$		
	3′-Hydroxy-genkwanin			
	Quercetin	$C_{15}H_{10}O_7$		
Bis-spirolabdane	Leosibirinone A	$C_{25}H_{38}O_8$	Aerial parts	[16]
	3α-Acetoxyleoheteronone C	$C_{25}H_{38}O_8$		
	Leosibirinone B	$C_{23}H_{36}O_7$		
	3α-Hydroxyleoheteronone A	$C_{23}H_{36}O_7$		
	3α-Acetoxyleoheteronone E	$C_{24}H_{36}O_8$		
	3α-Acetoxy-15-epileoheteronone E	$C_{24}H_{36}O_8$		
Labdane diterpenoids	Preleosibirone A	$C_{22}H_{32}O_6$	Leaves	[17]
	13-*epi*-Preleosibirone A	$C_{22}H_{32}O_6$		
	Isopreleosibirone A	$C_{22}H_{32}O_6$		
	Leosibirone A	$C_{22}H_{32}O_6$		
	Leosibirone B	$C_{22}H_{34}O_7$		
	15-*epi*-Leosibirone B	$C_{22}H_{34}O_7$		
Phenols	Chlorogenic acid		Aerial parts	[18]
	Quercetin-O-hexosylhexoside			
	Lavandulifolioside			
	Verbascoside			
	Lavandulifolioside-isomer			
	Leonoside A			
	Quercetin-O-deoxyhexosyl hexoside			
	Verbascoside-isomer			
	Leucosceptoside A			
	Leonoside A-isomer			
	Leonoside B			
	Ellagic acid		Root extracts	[19]
	p-Coumaric acid			
	Ferulic acid			
	Myricetin			
	Luteolin			
	Hesperidin			

7. Anti-diabetes activity

L. sibiricus is beneficial for the treatments of diabetes mellitus as a traditional medicine in many countries [4]. Many studies show the pharmacological prospects of bioactive compounds in controlling the type 2 diabetes mellitus [18]. The current study suggests that insulin released from INS-1E cells into the culture medium is significantly increased in presence of aqueous and methanol extract (500 mg/L) of *L. sibiricus* along with the expression of insulin receptor-α (Figure 1) [18].

8. Allelopathic activity of plants

The allelopathic effects of *L. sibiricus* demonstrate the use of its terpenoids and phenolic compounds in some orchard fields. Some phenolic compounds are identified from the root exudates

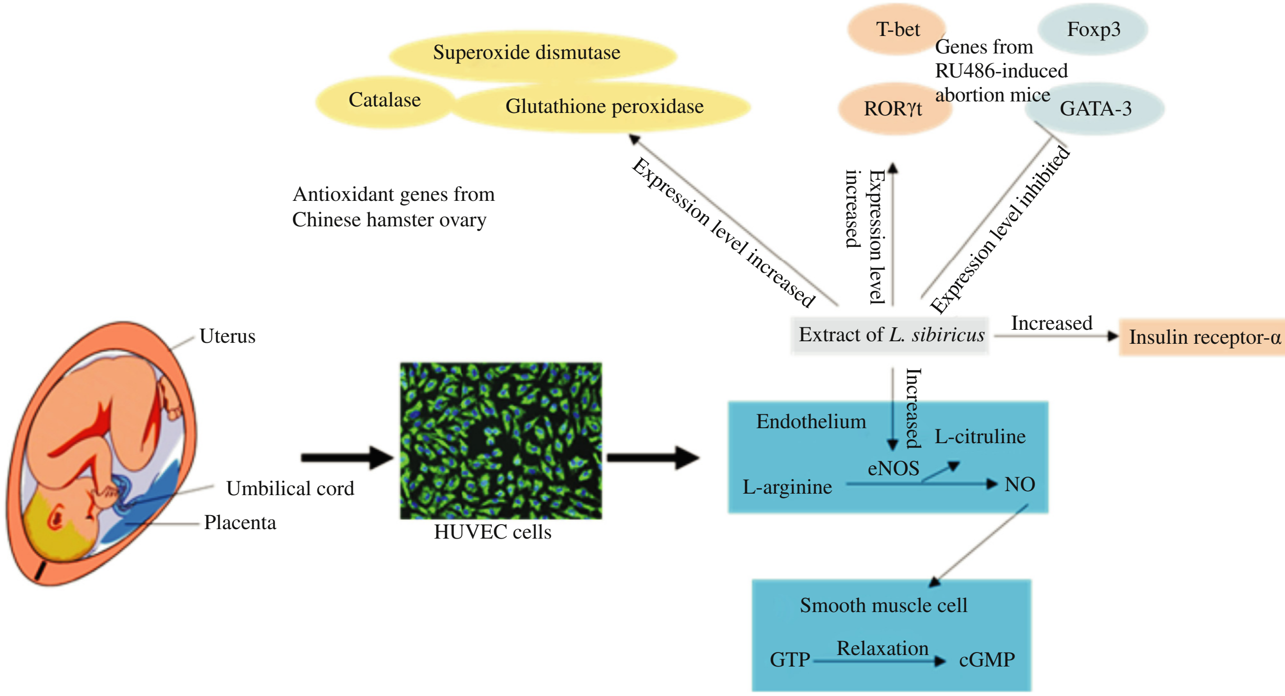

Figure 1. Schematic illustration of the possible mechanism conferring the effect of plant extract from *L. sibiricus* on different genes expression level.

specially caffeic acid. Root exudates show a concentration dependent stimulatory effect on rice, wheat and mustard [12]. The previous notion of *L. sibiricus* is thought to be harmful in orchards and coffee plantation. Aqueous extract of its leaves inhibits the germination of corn and tomato seedlings growth [39]. Generally, the flavonoid compounds show the protective activity in plants and can be extracted by methanol solvent system. The methanol extracted leaves of *L. sibiricus* suppress the germination of *Lactuca sativa* with no effects on the *Raphanus sativus* and *Lepidium sativum* germination processes [15]. Flavonoid compounds of 3′-OH-genkwanin and quercetin show the stronger antigerminative activity. In contrast, seedling growth reduced by rutin, isoquercitrin and 3′-OH-genkwanin is comparatively at higher concentration whereas stimulatory activity of seedling growth has found at lower concentration [15]. Aqueous, ethanol and acetone extracts significantly reduce the seed germination and seedlings growth of *Solanum melongena*, *Abelmoschus esculentus, Amaranthus tricolor* and *Cucumis sativus* [3]. In addition, the aqueous extracts of *L. sibiricus* show a concentration and time dependent activity on wheat seed germination and seedlings growth [40]. The methanol extract shows a concentration dependent sensitivity for the root growth than coleoptile of *Echinochloa crusgalli* [41]. The current investigations from extracts treatment show a significant inhibition of germination and root and shoot growth in Italian ryegrass, garden cress and lettuce [42].

9. Conclusion

The medicinal plants have been received attraction from past eras in the area of pharmacological study. Traditional medicinal plants practiced by the folk practitioners show the beneficial outcomes from ancient time without having known molecular basis of mode of actions. *L. sibiricus* is one of the potential medicinal plants used by folk practitioner in Bangladesh, China, India and some other countries. The published reports articulate it as a possible treatment of cancer, cardiovascular, diabetes and menstrual irregularities. Our review summarizes that *L. sibiricus* has potential pharmacological implications in agriculture especially for controlling the harmful weeds in the crop fields. It can be used for the formulation of bio-herbicide to control the weeds. Some chemicals have already been identified which have both stimulatory and inhibitory effects on seedlings growth. Bioactive chemicals have profound role in controlling diabetes, atherosclerosis and cancer with unknown molecular mechanisms. Interestingly, NO, a signaling molecule for vasodilation produced by the extract of *L. sibiricus* acts through the arginine dependent signaling pathway. Furthermore, *L. sibiricus* extract alters the genes expression profile which is directly and indirectly related to non-contagious diseases. There is no investigation of the effects of *L. sibiricus* on molecular mechanism in regulating the disease pathology. Our present review further suggests that *L. sibiricus* can be used as potential raw materials for the treatment of various diseases. The molecular mechanisms underlying pharmacological effects are poorly defined, hence, future studies are in prime concern.

Conflict of interest statement

We declare that we have no conflict of interest.

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