

## Review of the Pharmacological and Toxicological Effects of *Salvia leriifolia*

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### Abstract

*Salvia leriifolia* Benth. (vernacular names such as Nuruozak and Jobleh) is a perennial herbaceous plant that grows exclusively in south and tropical regions of Khorasan and Semnan provinces, I. R. Iran. Unlike other species of *Salvia* genus, the chemical constituents of *S. leriifolia* are not well recognized. The stem oil of the plant consisted mainly both monoterpenes and sesquiterpenes, while in leaf and flower oils monoterpenes predominated over sesquiterpenes. In recent years, the different properties of this plant such as the attenuation of morphine dependence, hypoglycemic, antinociceptive and antiinflammatory, antioxidant, anti-ischemia, anticonvulsant, antiulcer effects, antibacterial activities and antimutagenic effects were evaluated. These effects introduce this plant for more toxicological and clinical trials evaluations as a herbal medicine.

**Keywords:** *Salvia leriifolia*; Nuruozak, Lamiaceae, Herbal medicine

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## Introduction

Fifty-eight species of the genus *Salvia* (Lamiaceae) are found in I.R. Iran, of which 17 are endemic. *Salvia leriifolia* Benth. is a perennial herbaceous plant that grows exclusively in south and tropical regions of Khorasan and Semnan provinces, I. R. Iran (Figure 1). This plant was introduced in Florica Iranica in 1982 and has different vernacular names such as Nuruozak and Jobleh (1). In recent years, we investigated some pharmacological and toxicological effects of different parts of this plant and main of them are reviewed here.

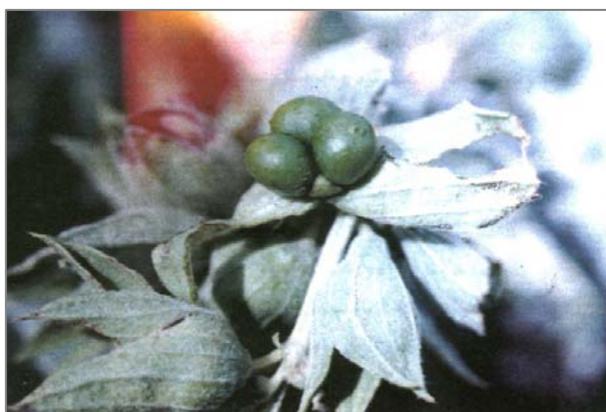


Figure 1. *Salvia leriifolia*

## Constituents

There are four main categories of chemical compounds in plants of genus *Salvia* including monoterpenes, diterpenes (tanshinones), phenolic acids and flavonoids, that tanshinones and phenolic acids are the most pharmacologically important. For example, more than 30 kinds of tanshinone compounds have so far been separated and identified from *S. miltiorrhizae* (2) and many pharmacological

effects have been attributed to these compounds. Regarding phenolic acids, the majority of these compounds in *Salvia* species is unique to *Salvia* (except for rosmarinic acid and lithospermic acid) and possesses a variety of biological activities including antioxidant, antiplatelet, antitumor and antiviral activities (3). Unlike other species of *Salvia* genus, the chemical constituents of *S. leriifolia* are not well recognized. The essential oils obtained by hydrodistillation of the stem, leaf and flower *S. leriifolia* Benth. were analyzed by GC and GC-MS. Thirty-four compounds representing 92.4 % of the stem oil of *S. leriifolia* were identified among them beta-pinene (19.0%), germacrene D (11.0 %) and delta-cadinene (10.5 %) were the major components. The leaf oil of the plant was characterized by higher amount of beta-pinene (31.5 %), 1, 8-cineole (24.7 %) and alpha-pinene (17.5 %) among the thirty components comprising 98.9 % of the total oil detected. Twenty-seven compounds representing 95.9 % of the flower oil of the plant were identified among them  $\gamma$ -terpinene (62.2 %) and p-cymene (11.1%) were the major ones. The stem oil of the plant consisted mainly both monoterpenes and sesquiterpenes, while in leaf and flower oils monoterpenes predominated over sesquiterpenes (4, 5). In addition to sesquiterpenes, diterpenes and flavonoids, which are also found in other species of this genus, the aerial parts of the plant also contained 5-hydroxy 4, 6, 7-trimethoxy flavon (I, a flavonoid) and a new labdane diterpene (II) (6).

Preliminary phytochemical tests have also showed that saponins and tannins are found in different parts of plant, especially in the plant leaf and root (7, 8). Alcoholic radix extract of *S. leriifolia* also contains a small amount of alkaloids, as recognized by Dragendorff reagent (8).

## Pharmacological properties

Recently, many studies have been conducted on the effects of *S. leriifolia* extract on various body systems *in vivo* and *in vitro* (Table 1). The following are a selection of these studies.

### *Effects on central nervous system*

Several studies have been performed in order to characterize the effects of *S. leriifolia* on the central nervous system. It was first shown that leaf and seed extracts of *S. leriifolia* significantly prolonged the survival time following hypoxic stress in mice (9). In this study, hypoxic stress was induced by putting mice individually in tight glass containers and the latencies for death were noted. This prolongation of survival time was comparable with those of sedative-hypnotic agents such as diazepam, chloral hydrate, phenytoin and 2-chloroadenosine. Interestingly, co-administration of theophylline (a non selective adenosine antagonist) reduced the survival time to control value not only for 2-chloroadenosine but also for leaf and seed extracts as well as chloral hydrate. The authors suggested that these effects, like *S. miltiorrhizae*, may be due to hypnotic, antioxidant or vasodilator agents, or release of ATP in brain tissue. It was also reported the anti-ischemic effect of aqueous extracts of *S. leriifolia* leaf and seed in rat hippocampus (7). The ischemic insult was induced using a four-vessel occlusion method and evaluated by light microscopy. The neural cell injury was reduced in all regions (CA1, CA2, and CA3-4) of the hippocampus following pretreatment of animals with aqueous seed extract but this reduction was not significant for the leaf extract. It seems that the seed extract contains more unsaturated fatty acids (antioxidant agents) than leaf extract, which may explain why seed extract was more active against ischemic damages. Several mechanisms such as antioxidant activity, reduction of NO production and reduction of glutamate release have been suggested for neuroprotective activity of other species of *Salvia* (10) but involvement of these mechanisms in protective effect of *S. leriifolia* against ischemia are still unclear. In a recent study, it was shown that the aqueous and the ethanolic extracts of *S. leriifolia* radix had protective effects against muscle ischemic injury and significantly decreased the lipid peroxide level in rat muscle following peripheral ischemia- reperfusion damages. This study showed *S. leriifolia*

extracts have a protective effect on ischemia reperfusion injury-induced oxidative stress in rat muscle that is at least partly due to antioxidant properties of *S. leriifolia* extract (11).

In another investigation, Hosseinzadeh *et al* showed that aqueous leaf extract of this plant exerts some muscle relaxant effect and prolongs the sleeping time induced by thiopental in mice. The hypnotic effect was dose-dependent and was seen at high doses (1.15 g/kg and 1.57 g/kg) but this effect was less than diazepam (3 mg/kg) (12). The potent muscle relaxant effect was seen only at a low dose of the extract (0.29 g/kg) which was unable to prolong thiopental-induced sleep significantly. This muscle relaxant effect was decreased by increasing dose. Moreover, the time-course study showed that unlike diazepam (1 mg/kg), the maximum relaxant effect of the extract was at 30 min after administration and decreased with time proceeding. *S. miltiorrhizae* has been used widely in China to treat neurasthenic insomnia, and miltirone, a diterpene quinine, has been isolated from the root of this plant which in radioligand studies inhibited the binding of [<sup>3</sup>H] flunitrazepam to central benzodiazepine. In contrast to diazepam (a full agonist), miltirone is a partial agonist and didn't produce muscle relaxation, sedation, dependence or withdrawal syndrome in mice at doses which are effective in the behavioral test (13). Comparing these effects with results obtained from *S. leriifolia*, it can be concluded that mechanisms other than partial agonism on benzodiazepine receptors are responsible for the sedative effects of *S. leriifolia*.

Hosseinzadeh *et al* also reported that intraperitoneal administration of aqueous and alcoholic extracts of *S. leriifolia* root significantly prolonged the survival time of mice subjected to hypoxic stress and decreased the neural loss in rat hippocampus following ischemic insult (8). The results of another investigation indicated that pretreatment with aqueous and alcoholic extracts of *S. leriifolia* root significantly reduced the elevated concentration of lipid peroxides in rat

hippocampus following ischemic-reperfusion injury (14).

The effects of aqueous and alcoholic extracts of *S. leriifolia* leaf and seed on convulsion induced by either pentylenetetrazole (PTZ) or maximal electroshock (MES) were investigated in mice. Only the aqueous leaf extract and alcoholic seed extract prolonged the onset of clonic convulsion induced by PTZ (90 mg/kg, ip) which was comparable to pentobarbital (20 mg/kg, ip) and none of the extracts showed protective effect against the MES test (15).

It has also been shown that the alcoholic extract of *S. leriifolia* leaf attenuates the withdrawal syndrome (naloxone-precipitated jumping) in morphine-dependent mice (16). The extract reduced the jumping episodes dose-dependently and the efficacy of the extract (500 mg/kg) to relief the withdrawal syndrome was comparable to diazepam (5 mg/kg). Moreover, co-administration of aminophylline (20 mg/kg, ip), a non selective antagonist of adenosine receptors, significantly blocked the inhibitory effect of the extract on the withdrawal syndrome. Again, the authors suggested that like other species of *Salvia*, especially *S. miltiorrhizae*, *S. leriifolia* might modulate ATP/Adenosine system or GABA<sub>A</sub>/benzodiazepine receptor complex (10, 16).

#### *Anti-inflammatory and analgesic actions*

Hosseinzadeh *et al*, using three anti-inflammatory tests in rats and mice (xylene-induced ear edema, increasing of vascular permeability by acetic acid and cotton pellet induced- granuloma), concluded that the aqueous extract of *S. leriifolia* is endowed with strong anti-inflammatory activity against acute and chronic inflammation, and the efficacy of the extract at the dose of 1.6 g/kg was comparable to the diclofenac (10 mg/kg) (17).

Recently, these authors have confirmed that the aqueous extract of *S. leriifolia* seed also has potent anti-inflammatory and antinociceptive effects in mice and rats. The mechanism of analgesia was examined by the use of the general opioid antagonist, naloxone. The extract showed significant and dose-

dependently antinociceptive activity over 7 hr, and this effect was abolished by naloxone pretreatment. The extract was also found to possess significant and dose-dependently activity against acute and chronic inflammation. These experiments suggest that *S. leriifolia* has supraspinal antinociceptive effects which may be mediated by opioids receptors (18).

#### *Antioxidant effect*

Using thin-layer chromatography (TLC), it has been shown that different fractions isolated from *S. leriifolia* leaf have appreciable antioxidant effects. Whole methanolic extract, precipitates of methanolic extract and most separated fractions showed more antioxidative activity than alpha-tocopherol. The fraction with the highest antioxidative activity showed 85.61% antioxidative activity of the synthetic antioxidant butylated hydroxyl toluene (BHT) based on a thiocyanate method (19). Moreover, Farhoosh *et al* investigated the heat stability or carry-through properties of major antioxidant fractions of *S. leriifolia* leaves in comparison with BHT and alpha-tocopherol using the Rancimat method at different temperatures and an active oxygen method (AOM). Descending order of antioxidant activity based on the methods of AOM and Rancimat at 90 °C were BHT, *Salvia* antioxidant then alpha-tocopherol and at 180 °C alpha-tocopherol, *Salvia* antioxidant then BHT (20).

Generation of free radicals may be, at least partially, the basis of many human diseases and conditions (such as inflammation and hypoxia-ischemia induced damages). Therefore, the antioxidant action of *S. leriifolia* may explain the claimed usefulness in hypoxia-ischemia or inflammation.

#### *Mutagenic and antimutagenic activity*

Fazly-Bazzaz and Isadyar, investigated the mutagenic and antimutagenic effects of 4 different fractions (water, dichloromethane, n-hexane and isobutanol) of ethanol extract of *S. leriifolia* aerial parts using three standard tester strains of *Salmonella typhimurium*

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(TA98, TA100 and TA102) (21). These results showed antimutagenic effects for aqueous and isobutanol fractions, while, none of the fractions being tested had mutagenicity effects using the Ames test (22). This is the first and only report that suggests *S. leriifolia* is endowed with antimutagenic properties, *in vitro*. On the other hand, it should be considered that some of the *Salvia* species (such as *S. officinalis*) that have antimutagenic effect in certain concentrations, are cytotoxic in higher concentrations (23).

### Antibacterial activity

Habibi *et al* determined the structure and antibacterial activity of a new labdane diterpenoid (8 (17), 12E, 14-Labdatrien-6, 19 olide) (compound I) isolated from aerial parts of *S. leriifolia* (24). The results showed that compound I was active against the Gram-positive bacterium *Staphylococcus aureus* at a concentration level of 0.4 mM but had only moderate inhibitory activity against the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. Antimicrobial studies conducted on other species of *Salvia* also have showed that these plants are more effective against Gram-positive bacteria and have almost no activity against Gram-negative bacteria (25). Using two different methods of hole plate and agar dilution, the antimicrobial activities of *S. leriifolia* methanol extract of root and seed were investigated. While no antimicrobial activity was detected from seed extract, the root extract showed antimicrobial activity comparable with the control on both Gram-positive (*Staph. aureus* and *Bacillus subtilis*) and Gram-negative, bacteria (*P. aeruginosa* and *E. coli*) and *Candida albicans*. The results were more pronounce with agar dilution than hole plate method (26).

### Antidiabetic action

The antihyperglycemic activity of leaf and seed extracts of *S. leriifolia* in normoglycemic, glucose-induced hyperglycemic and alloxan-induced diabetic mice was studied by Hosseinzadeh *et al* (27). The extracts had no effects on fasting blood glucose in normal mice. Following treatment of animals with a single oral dose (2 g/kg) of alcoholic seed

extract, a significant reduction in blood glucose level was seen only in glucose-induced hyperglycemic and not in alloxan-induced diabetic mice. Both oral and intraperitoneal administration of aqueous leaf extract (2 g/kg) showed a significant hypoglycemic activity in glucose-induced hyperglycemic and alloxan-induced diabetic mice. In another investigation, the hypoglycemic activity of the aqueous leaf extract of *S. leriifolia* was studied in sixty patients with non-insulin dependent diabetes mellitus, between 25 and 60 years old, using an open label crossover trial (28). The results indicated that treatment with the extract for one week did not reduce the elevated concentration of blood glucose significantly and also did not show any synergistic effects when administrated with glibenclamid. However, the authors reported that diabetic complications like neuropathy and polyphagia improved during treatment with the extract (27).

### Antihepatotoxic action

Using measurements of liver transaminases (serum glutamic pyruvic transaminase, SGPT and serum glutamic oxaloacetic transaminase, SGOT), Hosseinzadeh *et al* investigated the possible hepatoprotective effects of the alcoholic leaf extract of *S. leriifolia* in mice (29). The lower doses of the extract (50 mg/kg and 100 mg/kg) did not reduce the elevated activities of SGPT and SGOT significantly when administrated 1 hr after established hepatoxins, carbon tetrachloride and acetaminophen. *S. miltorrhizae* is effective in amelioration of CCl<sub>4</sub>-induced hepatotoxicity. It has been suggested that this effect is due to its ability to decrease the metabolic activation of CCl<sub>4</sub> by an increase in P450 2E1 protein content and its antioxidant activity associated with less increase in hepatic iNOS protein content (30).

### Antiulcer action

A single report in mice has suggested that the aqueous and alcoholic extracts of *S. leriifolia* leaves were effective in reducing the peptic ulcer index induced by HCl/ethanol, by about 71.60% and 75.11%, respectively. Moreover,

repetitive oral administration of the aqueous decoction and maceration extracts with intervals of 1, 12, 24, 36 and 48 hr before the necrotizing agent reduced the ulcer index by

85% and 86%, respectively which are comparable with sucralfate, a cytoprotective antiulcer agent (31).

Table 1. Pharmacological properties of *Salvia leriifolia*.

Effect	Part of plant	Method of study	Reference
Anti-hypoxic	leaf and seed	hypoxic stress	9
Cerebral anti-ischemic	seed	four-vessel occlusion	7
Cerebral anti-ischemic	root	four-vessel occlusion	8, 14
Anti-anxiety	leaf	elevated plus maze	32
Hypnotic	leaf	thiopental-induced sleep	12
Anticonvulsant	leaf and seed	pentylentetrazole or maximal electroshock	15
Attenuation of withdrawal morphine syndrome	leaf	naloxone-precipitated jumping	16
Anti-inflammatory and antinociceptive	seed	hot plate and tail flick, vascular permeability increased by acetic acid and xylene-induced ear oedema, cotton pellet	18
Anti-inflammatory	leaf		17
Muscle relaxation	leaf	behavioral test	13
Antiulcer	leaf	HCl/ethanol-induced mucosal membrane lesions	31
Antioxidant	leaf	thiocyanate method	19
Antimutagenic	aerial parts	Ames test	22
Antibacterial	labdane diterpenoid from aerial parts	disk method	25
Antibacterial	root	hole plate and agar dilution	26

### Toxicological properties

Table 2 summarizes the toxicological studies of *S. leriifolia*. The seed extract appears to have a low level of toxicity. The maximum tolerated (non-fetal) dose (MTD) of aqueous and alcoholic extracts of *S. leriifolia* seed were 10 g/kg and 4 g/kg (ip) in mice, respectively (15, 18). The LD<sub>50</sub> value of aqueous seed extract was found to be 19.5 g/kg (ip), in mice (18). The MTD of aqueous and alcoholic leaf extract has been reported to be about 2.9 g/kg and 1.5 g/kg in mice, respectively (12, 29). The MTD and LD<sub>50</sub> values (ip) of aqueous and alcoholic root extracts were 1 g/kg and 1.45 g/kg for aqueous extract and 1.125 g/kg and

1.55 g/kg for alcoholic extract in mice, respectively (8). Acute administration of high doses (0.2, 0.9, 1.2 and 1.5 mg/kg, ip) of alcoholic extract of *S. leriifolia* leaves to mice increased liver SGPT and SGOT activities (29).

The ethanolic and aqueous extracts of *S. leriifolia* leaf (28 and 84 mg/kg) caused significant decrease in weight gain of pregnant mice; length and weight of fetuses. Both extracts caused some abnormalities such as spina bifida, limb abnormalities, abdominal bleeding, and bone abnormalities. Thus, until further studies pregnant women should be careful in using this herb during pregnancy (33).

Table 2. Toxicological properties of *Salvia leriifolia* \*.

Part of plant	MTD (g/kg)	LD <sub>50</sub> (g/kg)	Effect	Reference
Seed, aqueous extract	10	19.5	-	15, 18
Seed, ethanolic extract	4	-	-	15, 18
Leaf, aqueous extract	2.9	-	-	12, 29
Seed, ethanolic extract	1.5	-	-	12, 29
Root, aqueous extract	1	1.45	-	8
Root, ethanolic extract	1.125	1.55	-	8
Leaf, Ethanolic extract	-	-	elevation of liver transaminase	29
Leaf, aqueous and ethanolic extracts	-	-	teratogenic effects such as spina bifida, limb abnormalities, abdominal bleeding, and bone abnormalities	33

\*In mice and intraperitoneal injection

### Conclusion

This review showed that *S. leriifolia* has different pharmacological activities such as anticonvulsant, anti-ischemia, anti-inflammatory and antinociceptive, antioxidant,

antibacterial, and antiulcer effects. These effects introduce this plant for more toxicological and clinical trials evaluations as an herbal medicine.

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