IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 9, Issue 8 Series. I (August 2019), PP. 12-21

Chemical Constituents and Pharmacological Effects of *Lithospermum officinale*

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Abstract: *Lithospermum officinale* was used traditionally as a remedy in diseases of the urogenital tract and as a spasmolytic, antidiarrhoeal, diuretic and lithotriptic, anti-gout, antitoxic, antiovulatory, febrifuge, for the stimulation of the digestion, for the elimination of foreign objects from the eyes and for the treatment of smallpox, measles and as antipruritic. *Lithospermum officinale* contained fatty acids, proteins, carbohydrates, pigments, minerals, shikonin, shikalkin, pyrrolizidine alkaloids, lavonoids and many other biologically active ingredients. The pharmacological studies revealed that it possessed endocrine, anticancer, burns healing, antimicrobial and antiparasitic, antioxidant, anti-inflammatory and protective effects. The current review discussed the traditional uses, chemical constituents and pharmacological and therapeutic effects of *Lithospermum officinale*.

Keywords: *Lithospermum officinale*, traditional uses, constituents, pharmacological effects, therapeutic effects

Date of Submission: 26-07-2019 Date of Acceptance: 12-08-2019

I. INTRODUCTION

In the last few decades there has been an exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of chemicals which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. Recent reviews revealed that the medicinal plants possessed central nervous, cardiovascular, antioxidant, reproductive, gastro-intestinal, respiratory, antidiabetic, galactagogu, antimicrobial, antiparasitic, dermatological, anticancer, anti-inflammatory, antipyretic and analgesic, immunological, hepato and reno-protective and many other pharmacological effects[1-35]. *Lithospermum officinale* was used traditionally as a remedy in diseases of the urogenital tract and as a spasmolytic, antidiarrhoeal, diuretic and lithotriptic, anti-gout, antitoxic, antiovulatory, febrifuge, for the stimulation of the digestion, for the elimination of foreign objects from the eyes and for the treatment of smallpox, measles and as antipruritic. *Lithospermum officinale* contained fatty acids, proteins, carbohydrates, pigments, minerals, shikonin, shikalkin, pyrrolizidine alkaloids, lavonoids and many other biologically active ingredients. The pharmacological studies revealed that it possessed endocrine, anticancer, burns healing, antimicrobial and antiparasitic, antioxidant, anti-inflammatory and protective effects. The current review discussed the traditional uses, chemical constituents and pharmacological and therapeutic effects of *Lithospermum officinale*.

Plant profile:
Synonyms:
Lithospermum officinale var. stewartii and *Margarospermum officinale*[(36)].
Taxonomic classifiation:
Kingdom: Plantae, **Subkingdom**: Viridiplantae, **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta; **Division**: Tracheophyta; **Subdivision**: Spermatophytina; **Class**: Magnoliopsida, **Superorder**: Asteranae; **Order**: Boraginales; **Family**: Boraginaceae; **Genus**: *Lithospermum*; **Species**: *Lithospermum officinale*[(37)].
Common names:
Arabic: Habb Alqalb, Shenjar Makhzani, Kaser El-Hajar; **Chinese**: xiao hua zi cao; **English**: common gromwell , gromwell, pearl gromwell; **French**: grémil officinal, millet d'amour, perlière; **German**: echter Steinsame; **Italian:** erba-perla maggiore; **Portuguese**: aljôfar; **Russian**: vorobejnik lekarstvennyj, **Spanish**: mijo de sol; **Swedish**: stenfrö[(38)].

Distribution:

It was distributed in **Asia** (Armenia, Azerbaijan, Georgia, Russian Federation- -Ciscaucasia, China, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Mongolia, Afghanistan, Iran, Lebanon, Syria, Bhutan, India, Nepal, Pakistan); and **Europe** (Belarus, Estonia, Latvia, Lithuania, Moldova, Russian Federation-European part, Ukraine, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Denmark, Ireland, Norway, Sweden, United Kingdom, Albania, Bulgaria, Croatia, Greece, Italy, Romania, Serbia, Slovenia, France, Portugal, Spain)[38].

Description:

Perennial up to 90 cm tall. Stem usually branched with both subappressed antrorse and patent hairs (up to 1.5 mm long) with swollen base. Leaves 60-70 x 10-16 mm, lanceolate or broadly so, antrorsely hairy; hairs c. 1.9 mm long, arising from a swollen base. Flowers racemose, bracteate, subsessile; bracts leafy but smaller. Pedicel pubescent, up to 4 mm long in fruit. Calyx 4-5 mm long, antrorsely hairy, slightly longer in fruit, lobes linear. Corolla white, tube ± 4 mm long; lobes ± spreading, ovate-obtuse, crenulate-wavy; limb 3.5-4 mm broad. Throat with 5 sac-like pubescent pouches. Anthers oblong, c. 1 mm long, situated below and alternating with pouches, subsessile, apiculate. Style 1.7 mm long, stigma sub-capitate. Nutlets 3-4 mm long, ovoid, pale white, smooth and shiny[39].

Traditional uses:

In former times, *Lithospermum officinale* was used as a remedy in diseases of the urogenital tract and as a spasmolytic drug. *Lithospermum ruderale* was used as an antidiarrhoeal drug by Indians in North America; a few tribes in Nevada used cold water extracts of the root as an oral contraceptive[40].

In India, leaves were used as sedative. Seeds were used as diuretic and lithotriptic. A decoction of roots and twigs was given in the form of syrup in eruptive diseases, such as smallpox and measles[41]. However, the aerial parts and the seeds of *Lithospermum officinale* were used internally as diuretic, anti-gout, antitoxic, antiovulatory, febrifuge, as anti-inflammatory in the urinary tract and for the stimulation of the digestion. The seeds were externally used for the elimination of foreign objects from the eyes. *Lithospermum officinale* roots were also used for the colouring of fibres and to obtain colours for make up[42]. The herbal tea made from the root and stem was used for the treatment of smallpox, measles and as antipruritic[43].

Parts used:

The whole plant, root, leaves, stem, seeds, fruits[43].

Chemical constituents:

The preliminary chemical analysis showed that *Lithospermum officinale* contained fatty acids, proteins, carbohydrates, pigments, minerals, silica (19.39%) and calcium carbonate (68.2%)[43].

Various constituents were identified from *Lithosperumum officinaIe* including phytoglucolipid, monophospho inositide, phosphatidyl ethanolamine, phosphatidy1 choline, cerebroside, and β-sitosterol. Various amino acids, cyanogenic glycoside, gallotannins and tannins of the catechin type, lithospermic acid and rosmarinic acid were also detected in the plant. The seeds contained 17-20% fatty oil, composed of neutral fats; 1.3% phosphatides and fatty acids, consisted of palmitic acid, stearic acid, hexadecadiene acid, octadecatriene acid, hydroxypentacosene acid, hydroxyeicosatriene acid, oleic acid, linolenic acid tetraenic acid, seeds also contained vitamin E and fructane. The seed ash (30%) was composed of CaO (59%), SiO_2 (27%), K_2O, MgO, P_2O_5, N_2O and Fe_2O_3[40, 44].

Lithospermum officinale produced shikonin, shikalkin, pyrrolizidine alkaloids, polyphenolic acids and 6,9,12,15,-n-octadecatetraenoic acid[45-48].

The shoots of *Lithospermum officinale* contained: allantoin 2.36 ± 0.88 mg/g dry matter, p-hydroxybenzoic acid 0.174 ± 0.003 mg/g dry matter, rutin 0.754 ± 0.303 mg/g dry matter, hydrocaffeic acid 0.215 ± 0.017 mg/g dry matter, rosmarinic acid 1.2 ± 0.1 mg/g dry matter, and chlorogenic acid 1.032 ± 0.06 mg/g dry matter; while the roots contained: allantoin 0.81 ± 0.36 mg/g dry matter, hydrocaffeic acid 0.131 ± 0.015 mg/g dry matter, rosmarinic acid 1.8 ± 0.31 mg/g dry matter and shikonin 0.079 ± 0.002 mg/g dry matter and acetyl-shikonin[41, 49]. Two pyrrolizidine alkaloids, O-7-3-hydroxy-3-methylbutanoyl-O-9-(-)-hydroxy viridifloryl retronecine and its acetyl derivative were also isolated from *Lithospermum officinale*[48].

Pharmacological effects:

Endocrine effects:

Water extracts from the above ground portion of *Lithospermum officinale* at doses of 50 mg/kg exhibited contraceptive effects in 27% of the rats. Water extracts from above ground parts of *Lithospermum officinale* depressed ovarian compensatory regeneration at a dose of 50 mg/kg bw. *Lithospermum officinale* also block the action and releasing of anterior pituitary hormones[50-56].

Saline extracts of the aerial parts and roots, administered to experimental animals by injection, inhibit oestrus and the functions of ovaries and testes; the activity of the thyroid gland was also reduced. The active principle was formed from phenolic precursors like caffeic, chlorogenic, rosmarinic acid as well as luteolin-7-beta-glucuronide by an oxidation[41].

In vitro, the effects of thyroid hormone was abolished by dry leaf extracts from *Lithospermum officinale*. *In vivo*, the same extracts in rats cause thyroid immobilization and suppression of oestrus[57].

The antithyrotropic activity of freeze-dried-extracts of *Lithospermum officinale* was investigated in the rat. When freeze-dried-extract was administered together with TSH, it blocked the TSH-induced increase in endocytotic activity of the thyroid glands followed by a strong decline of thyroid hormone levels. When the extract was injected alone, the endogenous TSH-levels, thyroidal secretion and thyroid hormone levels were declined. The efficacy of the extract in blocking thyroid secretion was compared to that of potassium iodide with faster onset and longer duration[58].

The antithyroid properties of *Lithospermum officinale* were investigated in the rat. The effect of *Lithospermum officinale* on serum levels of thyroxine and triiodothyronine and the secretion rate (endocytosis) were studied. *Lithospermum officinale* freeze dried extract decreased T4 and T3 level. However, *Lithospermum officinale* cold water freeze dried extracts significantly lowered thyroid hormone content in the serum whereas an inactivated extract exhibited a considerable loss of biological activity. The efficacy of different plant extracts greatly depended on the extraction procedure: extraction of powdered leaves with boiling water or ethanol yielded extracts without thyroid hormone-lowering capacity. The chemical oxidation of a hot-water (100°C) extract by KMnO4 served to reintroduce the antihormonal effectiveness. In goiter suppression test, the chronic administration of *Lithospermum officinale* freeze-dried-extract greatly suppressed TSH-levels and consequently goiter weight. The antithyrotropic and antithyroidal activity of a variety of plant extracts was accompanied by an additional FSH and prolactin diminution. *Lithospermum officinale* exhibited a strong antigonadotropic effectiveness and completely inhibited the PMS-stimulated growth of ovaries and uteri by as little as 100 µg of extract[59-60].

Aqueous extracts from *Lithospermum officinale*, inhibited both the extrathyroidal enzymic T4-5'-deiodination to T3. The specific inhibitory activity of the extracts was increased by extraction of freeze dried aqueous extracts and decreased by oxidation with KMnO4. The active principles were phenols or phenolcarboxylic acids [61].

The acute administration of *Lithospermum officinale* (Boraginaceae) freeze-dried extracts to euthyroid rats is associated with a decrease in serum thyroxine and triiodothyronine concentrations, suggesting a possible direct effect of the plant extract on circulating TSH (hypophyseal hormone blocking activity) and/or on TSH secretion[62-64].

The thyrotrophic, and to a lesser extent the gonadotrophic pituitary secretory systems were inhibited after the intraperitoneal treatment of rats for 17 days with 100 mg of *Lithospermum officinale* freeze-dried extract. The performic acid-alcianblue PAS method revealed morphologic changes in the thyrotrophic elements characterized by the presence of both hypergranulated and collapse cells, while the gonadotrophic cells in the periphery of the gland decreased in size as well as in number[65].

An indirect inhibitory effect on thyroid secretion by *Lithospermum officinale* has been reported for *Lithospermum officinale*, it act via the thyrotrophic (and also gonadotrophic) hormone of the pituitary gland[66].

The effects of *Lithospermum officinale* on thyroid glands were studied in euthyroid and hypothyroid rats. In the euthyroid rat, serum and pituitary TSH levels were greatly diminished by the plant extract. In hypothyroid rats circulating TSH was suppressed by *Lithospermum officinale* without any influence on the hypophyseal TSH stores. The chronic administration of *Lithospermum officinale* to hypothyroid rats suppressed TSH levels and correspondingly the goiter weight. These findings, that resemble the effect of low doses of thyroxine in euthyroid and hypothyroid rats, suggested that the antithyrotropic activity of plant extracts may be explained by 2 independent factors: a hypophyseal hormone blocking effect and a thyroid hormone-like activity at a hypophyseal site. At the same time prolactin serum levels and hypophyseal stores were reduced by the plant extract, this effect may be due to a thyroid hormone analog acting at a hypothalamical site initiating dopaminergic reactions responsible for the fall in prolactin and TSH concentrations[64].

The effects of the freeze-dried extracts of *Lithospermum officinale*, were studied on the binding and biological action of Graves'-IgG, the thyroid-stimulating immunoglobulin G (IgG), which found in the blood of patients with Graves' disease (Graves'-IgG) and which resemble TSH in their ability to bind to the thyroid plasma membrane, probably at the TSH receptor, and to activate the gland. The extract and their auto-oxidized constituents also inhibited the biological responses to Graves'-IgG[67].

Anticancer effects:

The anti-oxidative and anti-leukemic effects of methanol extract of *Lithospermum officinale* were studied in NB4 cell line. The methanol extract inhibited growth but not apoptosis in a time- and dose-dependent manner in NB4 cells. The methanol extract of *Lithospermum officinale* also inhibited oxidative stress induced by hydrogen peroxide in NB4 cells[68].

Wound burns healing effects:

The pharmacological effects of shikonin and acetylshikonin, pigments extracted by ether from *Lithospermum officinale* were studied in mice, rats, guinea pigs and rabbits. The pharmacological effect of Shikonin was similar to that of acetyl shikonin, systemic administration of these pigments showed the same effect as that of ether extract of *Lithospermum officinale*. They possessed no effect on blood coagulation, but inhibited the anticoagulant effect of heparin in rats. Topical application of both pigments (50 mg of 0.1% ointment) inhibited an increased vascular permeability and acute edema induced by histamine, anti-rat rabbit serum and heat. The activity was similar to that of 0.1% phenylbutazone ointment. The pigments increased proliferation of granuloma tissue in the cotton pellet method and promoted wound healing in rats. The results revealed that (shiunko), the main prescription of *Lithospermum officinale*, was an effective ointment for cutaneous injuries[69].

The effect of *Lithospermum officinale*, silver sulfadiazine and alpha ointments on healing of burn wounds was studied in rat. A hot plate was used for induction of a standard 3rd degree burn wound. Burn wounds were macroscopically and microscopically evaluated on days 7th, 14th and 21st after burn induction. A decrease in the number of inflammatory cells was noted when *Lithospermum officinale* was applied while the most inflammatory response was seen after administration of alpha ointment. The number of macrophages alone decreased after burn injury, while the frequency was the most when *Lithospermum officinale* and alpha ointment were applied. Histologically, the best results were observed for scoring of inflammation, re-epithelialization, angiogenesis, formation of granulation tissue and number of macrophage were recorded when *Lithospermum officinale* and alpha ointment were used after burn injury[70].

Antioxidant effects:

The pyrrolizidine alkaloids-free extract from the cell culture of *Lithospermum officinale* were tested for antioxidant capacity. The extract contained no toxic pyrrolizidine alkaloids while phenylpropanoid pathway was active toward phenolic acids formation not toward naphthoquinone derivatives. Rosmarinic acid was produced as the main constituent. Total phenolic content and antioxidant capacity of the proliferated cell extracts were similar to those of the extracts of the natural plant tissues, in particular from the root[71].

Pharmacology of shikonin:

Antimicrobial and antiparasitic activities:

Shikonin showed antibacterial activity against Staphylococcus aureus (including methicillin-resistant S. aureus), E. faecalis (including vancomycin-resistant E. faecium), Bacillus subtilis, Micrococcus luteus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella and Helicobacter pylori, it also inhibited biofilm formation by P. aeruginosa and Stenotrophomonas maltophilia[72-76].

Shikonin also possessed antifungal effects against Saccharomyces cerevisiae, Trichophyton rubrum, T. mentagrophytes, T. tonsulans var. sulfureum, Microsporum gypseum, Epidermophyton fluccosum, Candida albicans, Candida krusei and Candida glabrata[72, 78].

Shikonin possessed antiviral activity against HIV type 1, AdV3 and HCV[79-82].

Shikonin also showed antiparasitic activity against Culex pipiens and Aedes aegypti and exhibited the highest toxicity for intracellular persisting Leishmania major[83-84].

Anti-inflammatory and efficacy in autoimmune-mediated inflammatory diseases:

The anti-inflammatory effect of shikonin was confirmed in many animal models. Its anti-inflammatory effects were mediated by many mechanisms, these included: free radical scavenging effects, COX inhibition, inhibition of iNOS, inhibition of ERK, inhibition of the biosynthesis of leukotriene B4, inhibition of activity of the TNF-α promoter, blocking NF-κB nuclear translocation via inhibition of proteasome-mediated IκBα degradation and induced cell death by inhibiting the proteasome in macrophages, suppression of mast cell degranulation, inhibition of the respiratory burst in neutrophils, alteration of phosphatidylinositol-mediated signaling, and blockade of chemokine binding to the CCR-1[72, 85-93].

In addition, A poor activity was recorded for shikonin as a DPPH radical scavenger, with an IC_{50} value of 56.3 μg/ml, while, its IC_{50} values against ABTS and Fe^{2+}/ ascorbate/rat brain were 1.93 μg/ml and 6.3 μg/ml, respectively[88].

Shikonin was found to be active in a mouse model of collagen-induced arthritis. It also significantly improved the macroscopic appearance and decreased cartilage destruction, reducing the expression of the Th1 cytokines TNF-α and IL-12 in both the synovial tissue and the articular cartilage through a mechanism involving T-bet. It protected the cartilage in a murine model of rheumatoid arthritis and improved bone mineral density, bone mineral content, and joint histopathology, with a decrease in inflammation, joint destruction, and matrix metalloproteinase-1 production[(94-96)].

On the other hand, shikonin prevented the shortening of the colorectum and decreased weight loss by 5% while improving the appearance of feces and preventing bloody stools, in a mouse model of dextran sodium sulfate induced acute ulcerative colitis. MPO activity was reduced, with reduction of the expression of COX-2. Cytokine production (TNF-α, IL-1β, and IL-6) was also inhibited[(97-101)].

Furthermore, shikonin also inhibited histamine release mediated by anti-immunoglobulin E antibodies in basophils isolated from the blood of healthy volunteers. Shikonin was also able to inhibit the allergic reaction and airway hyperresponsiveness in asthmatic mice[(99-100)].

Protective effects:

Shikonin exhibited a neuroprotective effect against the damage caused by ischemia/reperfusion in mice, it decreased the neurological deficit scores, infarct size, and levels of malondialdehyde, carbonyl, and reactive oxygen species. The neuroprotective effect of shikonin could be mediated by its antioxidant effects. The neuroprotective activity of shikonin and its derivatives was also been described in microglial cells which were the prime effectors in immune and inflammatory responses of the central nervous. Two of shikonin's derivatives (isobutyryl- and isovaleryl shikonin) were more effective than shikonin in repressing microglial LPS-induced activation. Shikonin also protected dopaminergic neurons against 6-hydroxydopamine-induced neurotoxicity[(101-103)].

Anticancer effects:

Shikonin showed anticancer effects with many mechanisms of action, it inhibited tumor-specific pyruvate kinase-M2, caused cell cycle arrest, induced necroptosis, suppressed NF-κB-regulated gene products, inhibited proteasome activity and inhibited ROS generation[(104-111)].

It also inhibited Topo I/II activity, reversed NQO1 expression and produced anti-cancer effects as an anti-estrogen agent, and worked as a selective estrogen enzyme modulator by down regulation of the expression of steroid sulfatase, the important enzyme in the biosynthesis of estrogen[(112-114)].

II. CONCLUSION

This review discuss the chemical constituent, pharmacological and therapeutic effects of *Lithospermum officinale* as promising herbal drug because of its safety and effectiveness.

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IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 3365, Journal No-62875

Ali Esmail Al-Snafi. "Chemical Constituents and Pharmacological Effects of Lithospermum Officinale.". IOSR Journal of Pharmacy (IOSRPHR), vol. 9, no. 8, 2019, pp. 12-21.