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Original Research Article

Chemical constituents, and pharmacological and toxicological effects of Cynomorium songaricum: An overview

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Abstract

Purpose: *To review the chemical constituents, and the pharmacological and toxicological effects of Cynomorium songaricum (C. songaricum) and explore its potentials for further development as an alternative medicine.*
Methods: *A large number of research articles related to "Cynomorium songaricum" "pharmacological effects", "toxicological effects" and "chemical composition" in English and Chinese language were retrieved through an extensive literature review using various electronic databases including Medline (1966 - 2017) and EMBASE (1980 - 2017).*
Results: *Ethyl acetate and aqueous extracts of C. songaricum have promising pharmacological activities, due to the presence of various flavonoids, triterpenes and polysaccharides. In addition to promising effects against inflammation, aging, fatigue, viruses and cancer, C. songaricum has a protective effect on the nervous system and regulates hormones and immune functions. Oxidative regulation of hormone levels has a certain correlation with its pharmacological activities, e.g., cognitive functions, but its mechanism is not yet known, indicating the need for further research. Toxicity studies on C. songaricum have shown that it is not genotoxic to animals, but further toxicological studies are required to ascertain its safety in clinical use.*
Conclusion: *C. songaricum is a biologically important plant which has many proven bioactivities; however, it requires further studies to determine the mechanistic aspects of its pharmacological effects.*

Keywords: *Cynomorium, Chemical constituents, Inflammation, Aging, Fatigue, Virus, Tumor, Toxicological effect*

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INTRODUCTION

The medicinal importance of a large number of plants has been established; however, many plants including *Cynomorium songaricum* Rupr (*C. songaricum*) are still unrevealed for their medicinal features [1]. *C. songaricum* Rupr (Figure 1) is a holoparasitic parasitic plant that belong to *Cynomorium* genus and Cynomoriaceae family. Cynomorium plants are mainly distributed in Europe and Asia (especially in Gansu, Inner Mongolia and other northwestern areas of China). In traditional Chinese medication system, *C. songaricum* is widely used as a remedy for dysentery [2] and sexual

disorders, such as erectile dysfunction and menstrual problems [3].

C. songaricum contains anthocyanic glycosides, lignans, amino acids, fatty oils, tannins, cynoterpene, sterols, fatty acids and triterpenpoids. The main constituents of *C. songaricum* are gallic acid, cyanidin-3-O-glucoside, palmitic acid, oleic acid, proline, serine and aspartic acid [4]. *C. songaricum* has several pharmacological activities such as antioxidant, antiaging, neuroprotective, anti-stress, anti-fatigue, anti-virus and anticancer effects [2-15]. Additionally, this herb plays an important role in the regulation of hormone level, glucose metabolism, reproductive system and immune system. Moreover, *C. songaricum* contains some metals, such as copper, lead, cadmium, chromium, arsenic and mercury in an acceptable safe range [5].

With the passage of time, the chemical composition and pharmacological effects of *C. songaricum* are gradually being discovered. Thus, the chemical constituents and pharmacological and toxicological effects of *C. songaricum* have been summarized in this review article to provide a ground for future research on the medicinal properties of *C. songaricum*.

Cultivated plant Dried plant

Figure 1: The stems of *Cynomorium songaricum* in the cultivated and dried form

METHODS

A large number of research articles in English and Chinese language were retrieved through an extensive literature review, using various electronic databases including Medline (1966-2017) and EMBASE (1980-2017). We could not find any review article on this subject. Firstly, the articles related to "*Cynomorium songaricum*" were searched, and then an advance search was made using various keywords such as "*Cynomorium songaricum*" "pharmacological effects", "toxicological effects" and "chemical composition" altogether. This review article was constructed using the retrieved articles and the articles cited in those articles. An especial care to avoid duplication of articles was adopted.

RESULTS AND DISCUSSION

From prehistoric times, people are traditionally using various plants and herbs, which produce biologically active compounds. So far, more than twelve thousands active botanicals (also termed as herbal) have been discovered [2]. These compounds act on the living body in precisely the same way as pharmaceutical drugs, thus herbals could be advantageous as well as disadvantageous similar to conventional drugs [2]. Conversely, herbal therapy is a complex approach, since many phytochemicals including alkaloids, glycosides, polyphenols and terpenes are present in a single plant. Although phytotherapies are often used worldwide in traditional Chinese, Unani and Ayurvedic medicines, these medicines are not often systematically analyzed. In addition, phytotherapies can produce the undesired effects, whether by toxic compounds, by overdose, by adulterated species or by wrong prescription. Likewise, *C. songaricum* is widely used in traditional Chinese medicines [2], thus it has been widely tested for its chemical composition and biological effects.

Chemical composition

Numerous studies have been conducted to explore chemical composition of *C. songaricum*, revealing that it contains many bioactive compounds, as described in Figure 2.

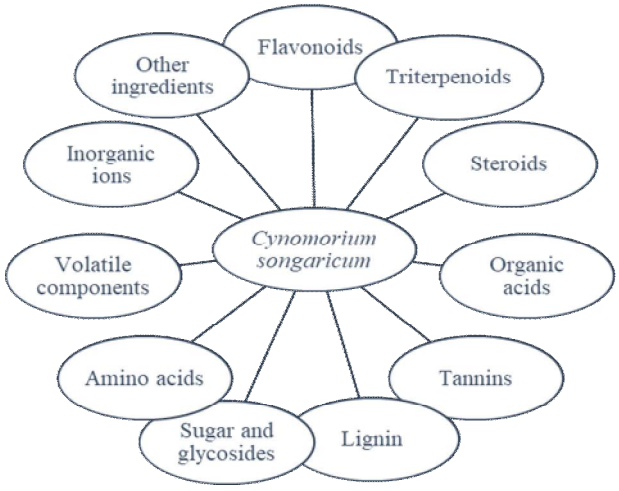

Figure 2: The reported chemical composition of *Cynomorium songaricum*

Flavonoids

Food and Drug Administration (FDA) has neither supported any health privilege for flavonoid nor accepted any flavonoid as pharmaceutical moiety. Even then, there is continuing research into the likely health advantages of flavonoids, which are known to have a number of biological functions such as antioxidant, antiinflammatory, anticancer, antibacterial, antifungal and antiviral activities. The main flavonoids in *C. songaricum* are (+)-catechin, citrusin-4-O-glucopyranoside, glycosides of citrinin [2], (-)-catechin [3], epicatechin [4], proanthocyanidins [5], epicatechin gallate [6] and epiphyllocoumarin [7]. In addition, Zhang *et al*. isolated (-)-epicatechin-3-O-gallate from *C. songaricum* [8].

Triterpenoids

Triterpenoids have a rich pharmacology due to the presence of pentacyclic moieties, especially against cancer. Ursolic acid [9], ursolic acid, ursonazole-12-ene-28-acid-3β malonic acid monoester [10], ursolic acid malonate [11], oleanolic acid, malonate [12] and triterpenoid saponins [10] have been separated from *C. songaricum*. These moieties could be drugs of future for treating cancer.

Steroids

Steroids are known to have two important bioactivities such as cell membrane constitution and cellular signaling. *C. songaricum* contains a number of steroids such as β-sitosterol, daucosterol [11], β-sitosterol palmitate [12], β-sitosterol-β-D-glucoside [13], 5α stigmasterol-9[11]-ene-3β-alcohol, 5α- stigmasterol 9[11]-ene-3β-alcohol-tetracosenoic triene ester [14], β-sitosterol oleate [11] and a series of 6'-O-fatty acids and daucosterol [15].

Organic acids

An organic acid, such as carboxylic acid, is an organic moiety having acidic features. Organic acids are famous for their application in nutrition and animal feed. The main organic acids in the fleshy stem of *C. songaricum* are gallic acid, protocatechuic acid [2], succinic acid [3], n-butyric acid [6], gentisic acid [6] and maslinic acid [16]. In addition, Wang *et al* [17] isolated vanillic acid from the whole plant.

Tannins

Tannins occur in several fruits and vegetables and are known to have astringent and nutritional value. The condensed tannins have also been identified in a concentration of 5 % in *C. songaricum* [18]. Lin *et al* [19] shows that tannin contents in the wild *C. songaricum* are higher than the cultivated *C. songaricum*. Tannin contents in *C. songaricum* at different stages of its growth are varied in a range of 3.42 - 6.64 % [20].

Lignin

Lignins are cross-linked phenolic compounds that fill the spaces in the cell wall. *C. songaricum* contains many lignins including lutein [7], isopropenyl-4-O-β-D-glucopyranoside and dehydrogenated cineol 9'-13-pyran glucoside [21].

Glycosides

Glycosides, the chemical entities comprising of a sugar molecule bound to another compound through glycosidic linkage, have many medicinal functions in the living body. Owing to this feature of glycosides, *C. songaricum* has gained excellent therapeutic importance because of having several glycosides. The investigators have got success in separating glucose [4], sucrose [10], ginger oil ketones glucoside [12], polysaccharides [22,23], heteropolysaccharide acidic heteropolysaccharide SYP-A and SYP-B [24], n-butyl-A-D fructofuranoside and n-butyl-β-D fructofuranoside [25] from *C. songaricum*. Sheng *et al* [26] worked on the natural *C. songaricum* and cultivated *C. songaricum* polysaccharide content determination and found that the cultivated *C. songaricum* polysaccharide content were greater than the natural *C. songaricum* by about 0.26 mg per 100 g.

Amino acids

Several crucial proteinogenic and non-proteinogenic amino acids, also termed as essential and non-essential amino acids, respectively not only play proteinaceous roles in the body, but also non-proteinaceous functions. For instance, GABA (gamma-amino-butyric acid) acts as an inhibitory neurotransmitter. Fubo *et al* [27] identified 17 amino acids in the aqueous extract of *C. songaricum*. The total amino acid content in the extract was 1.25%: out of which, aspartic acid and glutamic acid contents were the largest contents, especially aspartic acid that accounted for 61.61% of amino acid contents. Lin *et al* [19] showed that amino acid content in the cultivated *C. songaricum* and wild *C. songaricum* were almost equal to each other. The proline content of the cultivated variety was higher, while fraction of aspartic acid and glutamic acid were lower than that of wild one.

Volatile components

Volatile components have also been recovered from *C. songaricum*. Zhang *et al* [28,29] isolated 23 kinds of volatile components from the *C. songaricum* in a yield of 0.02 %. These volatile components accounted for 63 % of total volatile components. The content of volatile fatty acid and ester compounds was higher in *C. songaricum*, especially palmitic acid and oleic acid in a quantity of 22.69 % and 19.24 %, respectively. The distribution of pyrazine compounds in natural sources was small, but larger quantities of trimethyl-pyrazine, tetramethyl-pyrazine and 2,6-diethyl-3- methyl-pyrazine were isolated from *C. songaricum*.

Inorganic ions

It was determined that *C. songaricum* contains 33 kinds of trace elements as well as sulphate, phosphate, fluoride, chloride and nitrate. Besides, potassium, sodium, magnesium, calcium, iron, copper, zinc and manganese were also found in large quantities [28,30,31]. It is noteworthy that inorganic ions, in the form of electrolytes, play vital role in cellular activity, for instance, the osmosis maintenance, muscular activity and neuronal functioning.

Other ingredients

Others ingredients isolated from *C. songaricum* include octadecanoic acid α-monoglyceride [6], 4-methyl catechol [8], mannitol, phloroglucinol, 3,4-dihydroxyphenylethyl acetate [16], and vanilloid lactone (cis-5-deoxyglucoside-γ-lactone) [17].

Pharmacological activities

The pharmacological effects of *C. songaricum* include antioxidant, anti-aging, neuroprotective, anti-stress, anti-fatigue, anti-virus and anticancer activities. In addition, *C. songaricum* is also involved in the regulation of hormone level, glucose metabolism, reproductive system and immune system, as narrated in Figure 3.

Free radical scavenging activity

Lu *et al* [32] compared different extracts of *C. songaricum* for their *in vitro* antioxidant activity and their protective potential against hypoxanthine/xanthine oxidase-induced cell injury. The results showed that ethyl acetate and methanol extracts of *C. songaricum* significantly removed the free radicals as well as profoundly improved cell survival. Zhang *et al*. [33] found that polysaccharides collected from *C. songaricum* had a significant ability to remove superoxide anion radical, DPPH free radicals and hydroxyl radicals. In addition, Sharina [34] reported scavenging potential of methanolic extract of *C. songaricum* against superoxides. In short, these studies elaborate the promising antioxidant and antiaging potential of *C. songaricum.*

Neuroprotective activity

Flavonoids, triterpenes, glycosides, trace elements and other substances in *C. songaricum* can inhibit free radicals and their production leading to blockage of free radical-mediated damage to the chain reactions resulting in calcium level maintenance in neurons, thereby inhibiting brain neuronal cell apoptosis [35]. Tian *et al* [36] found that ethyl acetate extract of *C. songaricum* plays an estrogen-like role by enhancing the expression of GAP-43 protein and promoting the survival of hippocampal neurons and injury repairmen, and have a certain degree of protection of rat hippocampal neurons.

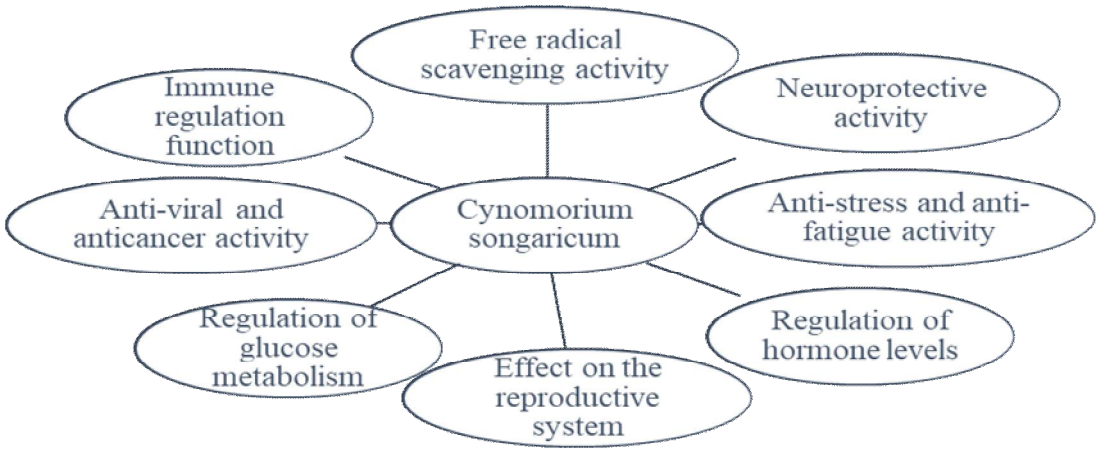

Figure 3: Pharmacological activities of *Cynomorium songaricum*

Anti-stress and anti-fatigue activities

Aqueous extract of *C. songaricum* can significantly prolong the survival time of hypoxic mice by reducing brain edema [37]. Xiong *et al* [38] found that polysaccharides obtained from *C. songaricum* can promote synthesis of exercise-related protein in rats, inhibit protein breakdown, promote glycogen storage in muscles, improve exercise related contents of hemoglobin and glycogen in rat, and prolong rat running and exhaustion time showing anti-fatigue effect of *C. songaricum*.

Yu *et al* [39,40] explored the effect and mechanism of *C. songaricum* in exercise tolerance in rats and measured the levels of monoamine oxidase (MAO) and glutathione peroxidase (GSH-Px). The level of MAO in *C. songaricum* treated group was significantly decreased, while GSH-Px was significantly increased. Thus, the flavonoids of *C. songaricum* increase the exercise endurance exerting the anti-fatigue effect on body.

Regulation of hormone levels

Liu *et al* [41] reported significantly increased levels of testosterone in male mice fed with oral solution *C. songaricum* for four weeks, while female mice showed significantly increased levels of progesterone and estradiol, indicating that *C. songaricum* promisingly ameliorates sex hormone levels in mice. In another study, polysaccharides obtained from *C. songaricum* was administered to the ovariectomized rats. The results showed an increased levels of rat serum estradiol (E2) and calcitonin (CT), improved bone mineral density and ameliorated osteoporosis symptoms [42]. Thus, the results indicate that *C. songaricum* plays an important role in the regulation of hormone levels.

Effect of the plant extract on the reproductive system

Aqueous extract of *C. songaricum* has promising effect against hydrocortisone-induced adrenal atrophy [43]. Yanga [44] reported the administration of *C. songaricum* extract to Wistar male rats for consecutively 56 days, resulting in the significant improvement in their sexual function. Moreover, *C. songaricum* decoction was used in testosterone propionate-induced prostate hyperplasia rat model. The results showed that wet weight of rat prostate and prostate index were significantly decreased [45]. It can thus be documented that *C. songaricum* has suppressive effect on benign prostatic hyperplasia.

Regulation of glucose metabolism

Oral water-soluble polysaccharides of *C. songaricum* (CSPA) can significantly reduce the streptozotocin-induced diabetic blood glucose levels, aspartate aminotransferase, alanine aminotransferase, serum urea nitrogen and creatinine activity. In addition, CSPA can effectively improve serum insulin levels and glycogen content in diabetic rats. The histopathological study showed that CSPA can promote islet cell recovery to near normal levels [43]. These findings reveal the regulation of glucose metabolism by using *C. songaricum.*

Anti-viral and anticancer activities

Ursolic acid, ursolic acid malonate, oleanolic acid malonate, acetylated ursolic acid and condensed tannin, extracted from *C. songaricum,* have inhibitory effect on HIV protease [11]. Cynomolgus triterpenes have anti-hepatitis C-protease role [42]. The inhibitory action of *C. songaricum* polysaccharides on human cervical cancer HeLa cells and human lung cancer A549 cells in a concentration-dependent manner has also been documented [8]. The inhibitory effect of *C. songaricum* polysaccharides on HeLa cells was stronger than that on A549 cells. Moreover, *C. songaricum* polysaccharides can significantly inhibit proliferation of human non-small cell carcinoma A549 cells [29].

Immune regulation function

Aqueous extract of *C. songaricum* can exert ameliorative effect on the immunosuppressive mice, previously treated with cyclophosphamide, showing that *C. songaricum* has a protective effect on immune imbalance [20]. Another study [31] narrated that phagocytic index, phagocytic cells and spleen lymphocyte transformations were significantly higher in aging rats treated with *C. songaricum* chewable medication than those without medication. It shows that *C. songaricum* chewable tablets can improve immune function of the aging animals. Liu *et al* [41] reported that *C. songaricum* as oral liquid can significantly increase the serum antibody level in rats, increase the rate of lymphocyte proliferation and enhance NK cell killing activity. It can be concluded that *C. songaricum* has a significant role in improving the immune function of rats.

Toxicological properties

Regardless of excellent pharmacological effects, several toxicological studies of *C. songaricum* have also been reported. In one of such studies, microwave digestion-high resolution continuous

light source atomic absorption spectrometry in *C. songaricum* was used for determining copper, lead, cadmium, chromium, arsenic and mercury content [32]. The results showed that these metal contents in *C. songaricum* extract were lower than MPPIGI (Medicinal Plant and Preparation of Imported Green Industry) standards and the National Standard for Food Safety. Another study [3] has reported the effect of *C. songaricum* in *Salmonella typhimurium*-treated mice by utilizing various tests such as mouse bone marrow polychromatic erythrocyte micronucleus test, sperm aberration test and genetic toxicity test. All three genotoxicity test results were negative, and *C. songaricum* showed no mutagenicity to the tested strains, mouse somatic cells and germ cells.

CONCLUDING REMARKS

In recent years, the determination of chemical composition of *C. songaricum* and its pharmacological and toxicological effects has gradually become a critical need for its further evolution. According to the reports in literature, flavonoids, triterpenes and polysaccharides of *C. songaricum* have promising pharmacological activities in the form of ethyl acetate and aqueous extracts. However, further studies are still needed to obtain its fingerprints. Oxidative regulation of hormone levels has a certain correlation between its roles, but its mechanism is not entirely clear, showing the need of further research for the development of new drugs. At present, *C. songaricum* toxicity studies have shown that it is not genotoxic to animals, but other aspects of toxicological evaluations are further warranted to assess.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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