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Biological Effects and Clinical Applications of Dwarf Elder (*Sambucus ebulus* L): A Review

Marzie Jabbari, MD, PhD[1], Babak Daneshfard, MD, PhDc[2,3], Majid Emtiazy, MD, PhD[1,4], Ali Khiveh, MD, PhDc[1], and Mohammad Hashem Hashempur, MD, PhD[5,6]

Abstract

Dwarf elder (*Sambucus ebulus* L) is one of the best known medicinal herbs since ancient times. In view of its benefits as a widely applicable phytomedicine, it is still used in folk medicine of different parts of the world. In addition to its nutritional values, dwarf elder contains different phytochemicals among which flavonoids and lectins are responsible for most of its therapeutic effects. Dwarf elder has been used for different ailments including: joint pains, cold, wounds, and infections. Nevertheless, recent evidence has revealed its potentials for making attempts at treating cancer and metabolic disorders. This review aimed to provide a comprehensive description of dwarf elder regarding its traditional uses and modern findings which may contribute to the development of novel natural-based therapeutic agents.

Keywords

Sambucus ebulus, dwarf elder, medicinal plants, phytotherapy, traditional Persian medicine

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Medicinal herbs have been the inseparable part of almost all of traditional and nontraditional schools of medicine since at least 5000 years ago.[1,2] During the long history of herbal therapy, a great endeavor has been made to evaluate and collect the effects and clinical applications of medicinal herbs in various nations and in different historical eras, among which "Islamic Middle Era" is a brilliant period.[3-5] Nowadays, phytotherapy is pursued as a popular branch of complementary and alternative medicine, capable of being helpful in variety of ailments.[6,7]

Sambucus ebulus L is one of the ancient plants, commonly known as dwarf elder or danewort. An early description of its therapeutic use in humans could be found in *Naturalis Historia* by Pliny the Elder (AD 23-79). Dioscorides (AD 40-90), the famous Greek physician, has called this herb *Akte* in his encyclopedia *De Materia Medica* and mentioned its multiple therapeutic effects.[8] The genus *S ebulus* was originally classified into the Caprifoliaceae family. Nonetheless, it was later moved—alongside Viburnums—to Adoxaceae family.[9]

Adoxaceae is a family of flowering plants in the order of Dipsacales, Magnoliopsida class, to be the subclass of Asteridae. It comprises around 30 species, the best known of which include *Sambucus nigra*, *Sambucus racemosa*, *Sambucus palmensis*, *Sambucus Canadensis*, and *Sambucus ebulus*.[10]

Sambucus ebulus is a perennial plant with an underground stem rhizome from which unbranched erect stems grow in large groups near each other to a height of 1 to 2 m. The leaves have 5 to 9 leaflets 15 to 30 cm long, with fetid smell, pinnate, and opposite to each other. The stems end in a corymb, 10 to 15 cm in diameter, with white (occasionally pink) flat-topped flowers (Figure 1). Its fruit is dark blue to

[1] Department of Traditional Medicine, Faculty of Iranian Traditional Medicine, Shahid Sadoughi University of Medical Sciences, Ardakan, Yazd, Iran
[2] Essence of Parsiyan Wisdom Institute, Phytopharmaceutical Technology and Traditional Medicine Incubator, Shiraz University of Medical Sciences, Shiraz, Iran
[3] Department of Traditional Persian Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Research Center of Iranian Traditional Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5] Noncommunicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran
[6] Department of Traditional Medicine, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran

Corresponding Author:
Mohammad Hashem Hashempur, MD, PhD, Department of Traditional Medicine, School of Medicine, Fasa University of Medical Sciences, Fasa, Iran.
Email: hashempur@gmail.com

Figure 1. A photograph of *Sambucus ebulus* from an uncultivated site in Fouman (Gilan province), North of Iran (photo by Marzie Jabbari).

violet in color. *S ebulus* is native to Southern and Central Europe, Northwest Africa, and Southwest Asia (especially Northern Iran).[11]

This review aimed at summarizing the previous traditional and modern findings regarding efficacy and clinical applications of *S ebulus* to uncover novel therapeutic potentials of this herb and pave the way for further studies.

Bioactive Constituents of *Sambucus ebulus*

Phytochemical compounds of *S ebulus* have been reported in several studies. It is revealed that elderberries have considerable nutritional value due to their accumulation of sugars, fibers, vitamins, and minerals.[12] Moreover, Sambucus plants store numerous secondary metabolites such as: anthocyanins, phytosterols, flavonoids, phenols, triterpenes, tannins, iridoid glycosides, cardiac glycosides, derivatives of caffeic acid (like volatile substances), chlorogenic acid, ursolic acid, and lectins.[8,13-18]

Lectins are considered to be amongst the most studied bioactive compounds of Sambucus.[19] Ebulins, which are protein-synthesis-inhibitory lectins, have been separated from different parts of *S ebulus* such as leaves (ebulin l), fruits (ebulin f), and rhizomes (ebulins r1 and r2).[20,21] SELld in leaves, SELlm in shoots, and SELfd in fruits are B-B type lectins with D-galactose-specific activity that are also found in *S ebulus*.[22] Other ingredients of *S ebulus* seeds are α-linolenic, linoleic acid, oleic acid, and palmitic acid as essential polyunsaturated fatty acids (PUFAs).[23]

Traditional and Folk Use of *Sambacus ebulus*

As an ancient plant, berries from *S ebulus* have been used as food or medicine since 5000 years in Italy and France.[24,25] Traditionally, various parts of *S ebulus* have been used to treat different ailments such as rheumatoid arthritis, fever, infections, bites, and sore throat.[26,27]

It has been known as *Khaman* and *Palem* in traditional Persian medicine and recommended as an analgesic for different painful conditions and various bone and joint disorders such as: joint pain, fracture, and dislocation. *S ebulus* is also suggested for uterine diseases, burns, gout, dental ailments, dropsy, fistula, and bite.[28-30] Furthermore, in Iran's folklore medicine, *S ebulus* is used for several therapeutic purposes such as arthritis, sore throat, and bee bites. It has also been recommended as a diuretic and purgative agent.[31,32]

In addition to Iran, Sambucus plants play an important role in folk medicine of other countries from Western Europe to Middle East.[12] In Turkish settlements—due to its wide range of applications—it is called *hekimana* in Anatolia, which means "mother physician." These applications comprise external use of *S ebulus* leaves for rheumatic pain, abscess, wound, sunstroke, snakebite, edema, common cold, eczema, high fever, and against piles on foot. In addition, the leaves are used internally as a purgative, diuretic and/or diaphoretic as well as against hemorrhoids and stomachache as the folk medicine of this area.[13] In Turkey, before fruit maturation of *S ebulus*, fresh leaves are collected and cooked with milk for 20 minutes. Then, its poultice is used externally for rapid recovery of wounds.[33]

In Bulgarian folk medicine, the berries, rhizomes, and less commonly: the flowers of *S ebulus* are used as diuretic, antiseptic, tonic, and purgative agents.[34] Also in Romania, *S ebulus* is used for rheumatic pains and cold.[35] Moreover, it is known as a bacteriostatic and diuretic agent in Romanian folk medicine.[36]

Sambucus ebulus in Biomedical Researches

Preclinical Studies

Antioxidant Activity. Phenolic and polyphenolic compounds as natural antioxidants are attributed to the therapeutic effects of most of medicinal herbs.[37] The main role of such compounds is protection against oxidative stress caused by reactive oxygen species which are known to be involved in disorders like cancer and hypertension. Hydroalcoholic extract of *S ebulus*, which contains considerable amounts of flavonoids and phenol, has shown an effective protection against lung toxicity induced by gamma irradiation, posing its lipid peroxidation effect.[38] This antioxidant activity has also been observed in methanol extracts of *S ebulus* fruit, which have shown hydrogen peroxide scavenging and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging effects.[39] As a rich-in-anthocyanin plant, *S ebulus* possesses considerable total polyphenol content and total antioxidant capacity. In comparison to the others, *S ebulus* has the highest level of total antioxidant capacity and total polyphenol content in anthocyanin-containing plants.[40,41] Its free radical scavenging effect, as a confirming evidence for its antioxidant activity, has been proved in an in vitro study.[42] Moreover, antioxidant activity of *S ebulus* makes it a protective agent against teratogenicity of albendazole. In an animal study, coadministration of *S ebulus* extract with albendazole decreased the rate of skeletal malformations in Wistar rats.[43]

Anti-Inflammatory Effect. *Sambucus ebulus* extract has been used traditionally to treat inflammatory conditions such as sore throat, joint pains, and rheumatic pains. Its anti-inflammatory

potential has been proved where extract of its flowers and leaves effectively suppressed the biosynthesis of tumor necrosis factor–α (TNF-α), interleukin 1-α (IL1-α), and interleukin 1-β (IL1-β).[44] Additionally, TNF-stimulated expression of vascular cell adhesion molecule 1 (VCAM-1)—an associated molecule with chronic inflammatory disorders—in human umbilical vein endothelial cells, could be inhibited by leave extract of *S ebulus*.[8] This inhibitory effect is attributed to ursolic acid, which plays an anti-inflammatory role by interaction with COX-2 pathway.[45] *S ebulus* fruit extract has also exhibited a significant nitric oxide—an indicator of inflammation—scavenging activity.[46] This property, which is correlated with its total flavonoid content, could be another explanation for its anti-inflammatory effect.[47,48] An animal study in rats revealed that methanol and *n*-hexane extract of *S ebulus* have a considerable inhibitory effect on carrageenan-induced paw edema in comparison with diclofenac.[48]

Analgesic Effect. There has, of course, been conducted yet another study indicating the significant antinociceptive effect of *S ebulus* in rats. Such analgesic activity, which is not linked to opioid system, may be related either to interfacing with serotonergic system, tachykinin pathway, and α-2 adrenoceptor, or endogenous glucocorticoid release.[18]

Antimicrobial Activity. There is an increasing concern toward antimicrobial resistance as a global health care issue.[49] This would naturally push us to find out new solutions for this terrible growing problem. As a natural antimicrobial agent, *S ebulus* methanol extract has emanated antibacterial effect on methicillin-resistant *Staphylococcus aureus*.[50] Its acceptable minimum inhibitory concentration against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Klebsiella pneumonia*, and *Bacillus subtilis* (which is attributed to the flavonoid content of the extract) proves good antimicrobial potential of *S ebulus*.[51] *S ebulus* chloroform extract is also effective on eradicating helicobacter pylori which is manifested as a pathogenic factor for peptic ulcer disease.[52,53] This anti H. pylori effect of S. ebulus is due to the potent urease inhibitory activity of its flavonoids.[54,55] Another study shows antibacterial activity of S. ebulus fruit extract on *Pseudomonas fluorescens* and *Enterococcus faecalis* which makes S. ebulus a good candidate for production of new natural-based drug besides its being an antifungal agent.[35]

Anticancer. It is known that tumor cells release proangiogenic factors to induce a vascular network for oxygen and nutrient supply of tumor mass.[56,57] Based on this mechanism of tumor development, application of immunotoxins and immunoconjugates for antivascular therapy against tumor neovasculature, is deemed an anticancer approach.[56] Such immunotoxins have been constructed by ribosome-inactivating proteins (ebulin) of *S ebulus*.[21,58] In addition, *S ebulus* ethyl acetate extract—as an effective anticancer agent—has demonstrated high toxicity against human hepatocarcinoma and human colon carcinoma cancer cell lines.[59]

Wound Healing Activity. One percent concentration of *S ebulus* methanol extract has shown a considerable wound healing activity in both linear and circular excisions in animal model. This property, which is related to "quercetin 3-O-glucoside" as a flavonoid derivative, is supported by histopathological examination of wound models.[33]

Antidepressant. Attempts to control the depression is an ongoing process; depression is expected to be in the second rank of global disease burden by 2020. In an animal study, fruit extract of *S ebulus* evinced a significant antidepressant effect in both tail suspension tests and forced swimming test in mice.[60] This property is supposed to be the effect of polyphenolic ingredients like flavonoids.[61,62]

Antigiardial Activity. Beside excellent in vitro antigiardial activity of *S ebulus*, its methanol extract has had an extremely significant antigiardial activity on *Giardia lamblia* cysts.[63]

Scolicidal Activity. Most of scolicidal agents used to treat hydatid cysts are not safe enough because of their possible side effects. In an in vivo study, *S ebulus* fruit methanol extract demonstrated a significant scolicidal activity in different concentrations ($P < .0001$). Therefore, it could potentially be used as an effective scolicidal drug in hydatid cyst surgery.[64]

Neuroprotective Effect. Neuroprotective effect of *S ebulus* has been established where its methanol extract exhibited a prominent antiemetic activity. This effect is attributed to free radicals scavenging, plasma antioxidants increasing, and protein modification inhibitory effects of *S ebulus*.[65]

Clinical Studies

Paederus Dermatitis. Anti-inflammatory effect of *S ebulus* fruit extract has been found to be effective in treating paederus dermatitis. This irritant contact dermatitis has significantly responded to anti-inflammatory, wound healing, and analgesic effect of palemolin (5% fruit extract of *S ebulus* in ethanol 70%) in a randomized double-blind placebo-controlled trial.[66]

Metabolic Disorders. *Sambucus ebulus* fruit infusion has been found effective on metabolic disorders related to impaired lipid profile and oxidative stress. A study, in which 21 healthy participants consumed 200 mL *S ebulus* fruit infusion daily for 1 month, brought out a significant potential for decreasing total cholesterol (15.04%), triglycerides (14.92%), and low-density lipoprotein (24.67%) besides increasing high-density lipoprotein/low-density lipoprotein ratio (42.77%). It improves total thiol levels and serum antioxidant capacity.[41] This anti-inflammatory and antioxidative activity could potentially be preventive for oxidative stress-related disorders, such as type 2 diabetes and metabolic syndrome.[67]

Knee Osteoarthritis. *Sambucus ebulus gel* (10% aqueous extract) showed significant effect on treatment of knee osteoarthritis. In

a recent study, 79 patients with knee osteoarthritis were allocated in 2 parallel groups of a randomized double-blind active-controlled clinical trial. Topical *S ebulus* gel or 1% diclofenac gel were prescribed for the patients, 3 times a day for a period of 4 weeks. The patients were assessed by visual analogue scale for pain and Western Ontario and McMaster Universities Osteoarthritis Index questionnaire. At the end of intervention period, visual analogue scale score, total and pain Western Ontario and McMaster Universities Osteoarthritis Index scores were significantly lower in the *S ebulus* group when compared with diclofenac group.[68] Therefore, it seems that *S ebulus gel* could be introduced as an effective alternative topical treatment for patients with knee osteoarthritis.

Toxicity and Side Effects

Sambucus ebulus raw berries are considered to be poisonous while excess consumption of the other parts might well lead to toxicity. For instance, high-dose consumption of *S ebulus* fruits may induce vomitory toxicity, especially in children.[33] Some genuses of Sambucus have poisonous leaves and stems in a way that contact dermatitis may be caused by their leaves. Stomach upset also could happen by the fruit of these species. Yet, this toxicity is at such a low level that could be prevented by cooking.[69] It has proven that short-term heating could eliminate potential risks of toxic lectins of *S ebulus* without any significant reduction in polyphenol and antioxidant contents.[70]

Nephrotoxicity and hepatotoxicity have also been observed to be induced by *S ebulus* ethyl acetate extract in mice model.[71,72] Still, no state of being venomous has been reported after 2 mg/kg intraperitoneal injection in this model.[48] Lethal dose 50% (LD_{50}) of its rhizome methanol extract is 600 mg/kg.[18]

Conclusions

As an ancient herb, *S ebulus* has a long history of nutritional and medicinal applications and is still used in different countries in our modern time. Its high potential for therapeutic applications due to multiple bioactive phytochemicals would naturally foreshadow a brilliant future for this medicinal herb. *S ebulus* is supposed to be a protective agent against cancer and cardiovascular events. Although any material—including medicinal herbs—could potentially be harmful, *S ebulus* is relatively safe when used in the proper manner. Of course, there is an obvious need for further rigorous preclinical and clinical investigations to evaluate its safety and efficacy in order to provide promising evidence for its wide range of therapeutic effects.

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The work presented in this article was carried out through collaboration between all authors. MJ and MHH made the initial hypothesis. MHH and MJ defined the research theme. MJ, ME, AKH, and BD contributed toward data gathering. MJ, MHH, and BD drafted the manuscript. All authors revised and approved the final version of the manuscript.

Declaration of Conflicting Interests

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ORCID iD

Babak Daneshfard, MD, PhDc http://orcid.org/0000-0001-6729-9113

Ethical Approval

Ethical approval is not required for this study as no human subjects were involved.

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