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Therapeutic potential of *Zataria multiflora*: A narrative review of current evidence

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ABSTRACT

Zataria multiflora Boiss is a perennial plant with a wide spectrum of biological and pharmacological activities including antidiabetic, anti-nociceptive, anti-asthmatic, anti-fever, anti-spastic, anti-oxidative, anti-inflammatory, and antimicrobial properties. This paper reviews the therapeutic effects of *Zataria multiflora* based on recent reports. The relevant reports were extracted by checking the electronic databases including PubMed, Scopus, Web of Science, and Google Scholar from the beginning of 2010 until the end of May 2023. The neuroprotective effects of *Zataria multiflora* can be attributed to inhibition of acetylcholinesterase, enhancement of brain-derived neurotrophic factor, and alleviation of brain oxidative damage. *Zataria multiflora* also exerts its protective effects on the respiratory system, liver, and kidney by reducing the level of inflammatory cytokines, scavenging the free radicals, and augmenting the antioxidant enzymes. Additionally, *Zataria multiflora* accelerates wound healing *via* upregulating transforming growth factor-β, insulin-like growth factor 1, fibroblast growth factor 2, and vascular endothelial growth factor, and inducing angiogenesis and collagen biosynthesis. Overall, the protective impacts of *Zataria multiflora* on different organs are mainly attributed to its antioxidant and anti-inflammatory properties.

KEYWORDS: *Zataria multiflora*; Anti-inflammmatory; Anti-oxidative; Neuroprotective; Organs

1. Introduction

Zataria multiflora (*Z. multiflora*) Boiss is a perennial plant from Laminaceae family with limited geographic distribution in the world. It mainly grows in Iran, Afghanistan, and Pakistan[1]. Among the people of Iran, it is known as Avishan-e-Shirazi. *Z. multiflora* is an herbaceous plant with 60-90 cm in height. This aromatic plant possesses small and egg-shaped leaves and white flowers. The presence of compounds including carvacrol, thymol, alkanes, fatty acids, phytosterols, hydroxycinnamic acids, flavonoids, tannins, saponins, and resins has been confirmed in the extract and essential oil of *Z. multiflora*[2]. These compounds especially carvacrol and thymol have been demonstrated to be responsible for biological and pharmacological activities of *Z. multiflora*[3,4].

Z. multiflora often is used as a flavoring component in food. In traditional medicine, *Z. multiflora* has been suggested to have properties such as diuretic[2], anti-cough[5], anti-bronchitis, anti-asthmatic[6], anti-spasmodic[7], anti-fever and analgesic[8] activities. In the gastrointestinal tract, *Z. multiflora* can relieve bloating and irritable bowel syndrome (IBS)[9]. Attenuation of headache and migraine symptoms[10] and treatment of vomiting[11] also are attributed to *Z. multiflora*. Previously, it has been recognized that *Z. multiflora* extract and carvacrol derived from it could inhibit muscarinic[12] and histamine receptors[13] and stimulate

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β-adrenoceptors[14]. The researchers reported that *Z. multiflora* improves cognition deficits by inhibiting acetylcholinesterase (AchE) activity and the injurious effects of amyloid β[15]. The ability of *Z. multiflora* to reduce blood glucose in diabetic rats has been also documented[16]. Besides all these effects, the scientific evidence shows that *Z. multiflora* possesses anti-inflammatory, anti-oxidative[17], antimicrobial[18], and anti-septic activities[19]. This paper aimed to review the therapeutic potential of *Z. multiflora* on different organs based on recent reports.

2. Method

In this paper, all known electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were used for data extraction. The reports were collected from the beginning of 2010 until the end of May 2023 using the terms "*Zataria multiflora*" and "neuroprotective" or "lung" or "renoprotective' or "hepatoprotective" "gastroprotective" or "cardioprotective" or "antidiabetic" or "anticancer" and "antimicrobial".

3. Neuroprotective effects

Alzheimer's disease (AD) is a progressive neurological disorder associated with loss of neurons and memory impairment[20]. The hippocampus is a principal brain area involved in learning and memory processes which are mainly affected by AD[21]. Accumulation of intracellular neurofibrillary tangles and amyloid β protein (Aβ) in the brain tissue is the most important characteristic of AD[22]. It has been also demonstrated that the inhibition of AchE[23] and use of natural antioxidant agents[24] can attenuate the symptoms of AD. In a rat model of AD, oral administration of 100 μL/kg of essential oil of *Z. multiflora* improved spatial memory. The neuroprotective effect of *Z. multiflora* was associated with the decrease of AchE activity and increase of brain-derived neurotrophic factor level in the hippocampus tissue of rats[25]. Majlessi *et al*. also examined the effect of 50, 100, and 200 μL/kg of essential oil of *Z. multiflora* on memory deficits in a rat model of AD. They concluded that the doses of 100 and 200 μL/kg modulated spatial memory dysfunction in rats[26]. Ahmadi *et al*. reported that 100 μL/kg of essential oil of *Z. multiflora* can ameliorate cognitive deficits and reduce hippocampal tau protein and tumor necrosis factor-alpha (TNF-α) level[27]. Scopolamine is an anti-muscarinic medication that can inhibit acetylcholine (Ach) effects in the nervous system[28]. Additionally, anticholinergic drugs such as scopolamine are also used to induce amnesia and memory impairment in animal studies[29]. In amnesic rats induced by scopolamine, 100, 200, and 400 mg/kg of *Z. multiflora* extract exerted anti-amnesic impacts and ameliorated memory disturbances. These effects of *Z. multiflora* extract were linked to its anticholinesterase properties[30]. Taheri *et al*. also revealed that treatment with 200 mg/kg of methanolic extract of *Z. multiflora* had memory-enhancing effects against lead-caused memory damage in rats *via* exerting anticholinesterase and antioxidant effects[31]. Moreover, 80 and 200 mg/kg of hydroalcoholic extract of *Z. multiflora* reinforced learning and memory and improved inhaled paraquat-induced inflammation and oxidative stress in lung tissue[32].

In experimental studies, lipopolysaccharide (LPS) as a powerful bacterial toxin is employed to induce memory impairment and to evoke anxiety and depression-like behaviors[33]. It has been demonstrated that the pernicious effects of LPS mainly are mediated by evoking inflammatory reactions and oxidative stress[34]. The scientific findings show that intraperitoneal injection of 50, 100, and 200 mg/kg of hydro-ethanolic extract of *Z. multiflora* attenuated LPS-caused anxiety and depression-like behaviors in rats, which is related to its anti-inflammatory properties[35]. In a study achieved by Arab *et al*., the beneficial effect of 50, 100, and 200 mg/kg of *Z. multiflora* extract against LPS-induced memory impairment has also been confirmed. According to the biochemical results

Table 1. The neuroprotective effects of *Zataria multiflora* (*Z. multiflora*).

Type of study	Dose	Route of administration	Effects	Reference
Rat	100 μL/kg	Oral	Improvement of spatial memory by decreasing AchE activity and increasing BDNF level in hippocampus tissue	[25]
Rat	50, 100 and 200 μL/kg	Intraperitoneal	Modulation of spatial memory dysfunction	[26]
Rat	100 μL/kg	Oral	Amelioration of cognitive deficits and reduction of hippocampal tau protein and TNF-α level	[27]
Rat	100, 200 and 400 mg/kg	Intraperitoneal	Amelioration of memory disturbances *via* the inhibition of cholinesterase	[30]
Rat	200 mg/kg	Intraperitoneal	Improvement of memory dysfunction by preventing the cholinesterase activity and oxidative damage	[31]
Rat	200 and 80 mg/kg	Oral	Reinforcement of learning and memory	[32]
Rat	50, 100 and 200 mg/kg	Intraperitoneal	Modulation of anxiety and depression-like behaviors through suppressing the inflammatory reactions	[35]
Rat	50, 100 and 200 mg/kg	Intraperitoneal	Improvement of memory retention through reducing the IL-6, MDA, and NO concentration and augmenting the total thiol content and CAT and SOD activity	[36]
Mice	300 and 600 mg/kg	Intraperitoneal	Alleviation of PTZ administration-induced seizure attacks	[38]

AchE: acetylcholinesterase, BDNF: brain-derived neurotrophic factor, TNF-α: tumor necrosis factor-alpha, IL-6: interleukin-6, MDA: malondialdehyde, NO: nitric oxide, CAT: catalase, SOD: superoxide dismutase, PTZ: pentylenetetrazole.

of this study, the memory-enhancing impacts of *Z. multiflora* were accompanied by a significant decline in interleukin (IL)-6, malondialdehyde (MDA), and nitric oxide (NO) concentration and a remarkable augmentation in total thiol content and catalase (CAT) and superoxide dismutase (SOD) activity in rats' brain[36]. Pentylenetetrazole is a gamma-aminobutyric acid (GABA) receptor antagonist causing seizure attacks when injected in high doses. Therefore, it is widely used for stimulating the seizure attracts and understanding the antiepileptic effects of drugs in animal models[37]. Shamsizadeh *et al*. found that 300 and 600 mg/kg of hydroalcoholic extract of *Z. multiflora* alleviated pentylenetetrazole-induced seizure attacks in mice[38]. The neuroprotective effects of *Z. multiflora* are summarized in Table 1.

4. Protective effects on the respiratory system

Asthma and chronic obstructive pulmonary disease (COPD) are two respiratory diseases resulting from inflammation and obstruction of the airways[39]. The symptoms of these disorders include coughing, shortness of breath, and wheezing[40]. It has been found that anti-inflammatory and antioxidant compounds exert positive impacts on asthma and COPD[41,42].

Therapeutic effects of 0.4, 0.8, and 1.6 mg/kg of the hydro-ethanolic extract of *Z. multiflora* and 60, 120, and 240 µg/mL of carvacrol on inflammatory, oxidative stress and blood parameters in the lung tissue of guinea pig exposed to cigarette smoke were evaluated. Based on the results, *Z. multiflora* and carvacrol significantly decreased IL-8, eosinophil, and neutrophil levels and increased the thiol content[43]. In the study of Habibi *et al*, pretreatment with 50, 100, 200, and 400 mg/kg of the ethanolic extract of *Z. multiflora* protected the mice from cyclophosphamide-caused lung toxicity *via* inhibiting lipid peroxidation and improving oxidative stress[44]. In a human study, 5 and 10 mg/kg of *Z. multiflora* extract improved clinical symptoms and pulmonary function tests in asthmatic patients by modulating oxidative stress and decreasing the level of inflammatory cytokines[45]. Administration of 20 mg/kg of the hydro-ethanolic extract of *Z. multiflora* induced a bronchodilatory effect comparable to theophylline in asthmatic patients[46]. In patients with COPD, use of 3 and 6 mg/kg/day of *Z. multiflora* extract for two months remarkably reduced the serum level of inflammatory cytokines such as IL-6 and TNF-α and enhanced forced vital capacity and forced expiratory volume in 1 s (FEV1)[47]. In another human research, treatment with 3 and 6 mg/kg/day for two months of *Z. multiflora* extract lessened the level of MDA, NO, and C-reactive protein, increased the thiol content and SOD and CAT activity, improved FEV1, and finally relived the symptoms of COPD[48].

Khazdair *et al*. reported that 5 and 10 mg/kg of *Z. multiflora* extract ameliorated respiratory symptoms including coughing, and wheezing, enhanced FEV1 and mitigated the serum level of TNF-α and vascular endothelial growth factor (VEGF) in veterans exposed to sulfur mustard. Treatment with 10 mg/kg of *Z. multiflora* also considerably lowered the serum level of monocyte chemotactic protein-1 and epidermal growth factor[49]. The therapeutic effects of *Z. multiflora* on the respiratory system are depicted in Table 2.

5. Hepato– and reno–protective effects

The liver is a digestive organ that participates in multiple biological functions including protein synthesis[50], carbohydrates and lipids metabolism[51], and detoxification[52]. Liver tissue can be threatened by drugs and toxins[53,54]. One of the drugs causing hepatotoxicity in high doses is acetaminophen[55] In the liver, acetaminophen is converted into *N*-acetyl-*p*-benzoquinone imine (NAPQI) by cytochrome P450 enzymes. Acetaminophen-induced hepatotoxicity happens through generation of NAPQI in response to oxidative stress, glutathione (GSH) depletion, and mitochondrial dysfunction[56]. It has been documented that oral administration of 200 mg/kg of *Z. multiflora* extract and 20 mg/kg of carvacrol could prevent the noxious effects of acetaminophen on the liver of rats *via* decrementing the lipid peroxidation and enhancing the thiol, CAT, and SOD level[57]. Adriamycin (doxorubicin) is a drug employed against cancer cells[58]. In experimental studies, adriamycin is used

Table 2. The therapeutic effects of *Z. multiflora* on the respiratory system.

Type of study	Dose	Route of administration	Effects	Reference
Guinea pig	0.4, 0.8 and 1.6 mg/kg	Oral	Decreases IL-8, eosinophils, and neutrophils, and increases the thiol content	[43]
Mice	50, 100, 200 and 400 mg/kg	Intraperitoneal	Protection of lung tissue *via* inhibiting lipid peroxidation and improving oxidative stress	[44]
Human	5 and 10 mg/kg	Oral	Improves asthma symptoms by modulating oxidative stress and decreasing the level of inflammatory cytokines	[45]
Human	20 mg/kg	Oral	Dilation of airways and amelioration of asthma symptoms	[46]
Human	3 and 6 mg/kg	Oral	Reduces serum level of inflammatory cytokines and enhances FVC and FEV1	[47]
Human	3 and 6 mg/kg	Oral	Decreases the level of MDA, NO, and C-reactive protein, increases thiol content and SOD and CAT activity, and improves FEV1	[48]
Human	5 and 10 mg/kg	Oral	Enhancement of FEV1 and mitigation of the serum level of TNF-α and VEGF	[49]

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, IL-8: interleukin 8, VEGF: vascular endothelial growth factor.

to induce hepatotoxicity[59], nephrotoxicity[60] and cardiotoxicity[61]. The detrimental impacts of adriamycin mainly are mediated by inducing inflammatory responses and releasing free radicals[62]. In a rat model with adriamycin-induced hepatotoxicity, 200 mg/kg of hydroalcoholic extract of *Z. multiflora* and 20 mg/kg of carvacrol lowered the MDA concentration and elevated the thiol, SOD, and CAT content in the liver tissue and improved the liver function[63]. Cyclophosphamide is an immunosuppressive medication for the treatment of various types of cancers such as lymphoma[64], leukemia[65], multiple myeloma[66], and breast cancer[67]. In the study accomplished by Shokrzadeh *et al*., pretreatment with 50, 100, 200, and 400 mg/kg of the ethanolic extract of *Z. multiflora* had a noticeable hepatoprotective effect against cyclophosphamide in mice by reinforcement of antioxidant defense[68]. Cisplatin is another anticancer medication that is used to induce liver toxicity[69]. It has been confirmed that 50, 100, 200, and 400 mg/kg of metabolic extract of *Z. multiflora* reversed the harmful effects of cisplatin on the liver of rats by elevating the antioxidant indicators such as SOD, CAT and glutathione peroxidase and suppressing the lipid peroxidation[70]. In addition, the clinical and experimental results demonstrated that cisplatin induces nephrotoxicity[71]. Karimi *et al*. reported that oral administration of 200 mg/kg of *Z. multiflora* lightened the toxic impacts of cisplatin on the kidneys by mitigating the MDA content and enhancing the GSH level[72]. Panahi Kokhdan *et al*. revealed 500 mg/kg of *Z. multiflora* displayed the nephroprotective impact against cisplatin *via* scavenging the free radicals[73]. Additionally, adding 0.8 mg/mL of *Z. multiflora* extract to drinking water of rats alleviated the toxic effects of gentamicin on the kidney tissue by inhibiting the lipid peroxidation and reducing the free radicals[74].

Sodium nitrite ($NaNO_2$) is a compound used as a flavoring in food industries[75]. Over-intake of $NaNO_2$ can result in body organ damage *via* the induction of inflammation, DNA oxidation, and cancer[76]. Ahmadi *et al*. examined the effect of 200 mg/kg of the hydroalcoholic extract of *Z. multiflora* on $NaNO_2$-stimulated liver toxicity in rats and found that *Z. multiflora* extract modulated oxidative stress of liver tissue and finally reversed $NaNO_2$-caused hepatic dysfunction[77]. Liver fibrosis is a disorder characterized by the accumulation of extracellular matrix proteins such as collagen that can happen in various hepatic diseases[78]. Stimulation of hepatocytes by oxidative agents is considered a crucial step in occurrence and development of liver fibrosis[79]. Treatment with 500 μL/kg of *Z. multiflora* essential oil overturned the CCl_4-induced liver fibrosis in rats by preventing oxidative stress[80]. It has been also confirmed that 100, 200, and 400 mg/kg of methanolic extract of *Z. multiflora* decremented the lipid peroxidation and protein carboxylation, incremented the activity of antioxidant enzymes and GSH levels, and consequently alleviated paracetamol-caused liver dysfunction in rats[81]. In a study carried out by Arab *et al*., 50, 100, and 200 mg/kg of hydroalcoholic extract of *Z. multiflora* attenuated LPS-evoked hepatic dysfunction in rats *via* reducing MDA, NO metabolites, and IL-6 levels and elevating thiol concentration and the activity of SOD and CAT[82]. Moreover, in another study, 1 000 mg/kg of the hydroalcoholic extract of *Z. multiflora* prevented liver damage in diabetic rats by modulating oxidative stress and improving the blood level of TNF-α and glucose[83].

Cystic echinococcosis (CE) or hydatid is a health-threatening disease that mostly affects liver and lung tissues. CE is induced by infection with *Echinococcus granulosus sensu lato* larvae[84]. Albendazole is a drug selected for the treatment of CE that can cure only a third of infections in patients[85]. Therefore, treatment with natural compounds is recommended. In a nonrandomized clinical trial, 60 mg/day of essential oil of *Z. multiflora* reduced the volume of the hydatid cysts and the serum level of liver enzymes in CE patients compared to those treated with albendazole[86]. The hepato- and reno-protective effects of *Z. multiflora* are demonstrated in Table 3.

Table 3. The hepato- and reno-protective effects of *Z. multiflora*.

Type of study	Dose	Route of administration	Effects	Reference
Rat	200 mg/kg	Oral	Decrement of lipid peroxidation and enhancement of thiol, CAT, and SOD level	[57]
Rat	200 mg/kg	Oral	Reduction of MDA and elevation of thiol, SOD, and CAT	[63]
Mice	50, 100, 200 and 400 mg/kg	Oral	Reinforcement of antioxidant defense	[68]
Rat	50, 100, 200 and 400 mg/kg	Oral	Elevation of antioxidant indicators such as SOD, CAT, and GPx and suppression of lipid peroxidation	[70]
Rat	200 mg/kg	Oral	Mitigation of MDA content and enhancement of GSH level	[72]
Rat	500 mg/kg	Oral	Neutralization of free radicals	[73]
Rat	0.8 mg/mL	Oral	Inhibition of lipid peroxidation and reduction of free radicals	[74]
Rat	200 mg/kg	Intraperitoneal	Modulation of oxidative stress	[77]
Rat	500 μL/kg	Intraperitoneal	Suppression of oxidative stress	[80]
Rat	100, 200 and 400 mg/kg	Oral	Decrement of lipid peroxidation and protein carboxylation and increment of the activity of antioxidant enzymes and GSH level	[81]
Rat	50, 100 and 200 mg/kg	Intraperitoneal	Reduction of MDA, NO metabolites, and IL-6 and elevation of thiol concentration and the activity of SOD and CAT	[82]
Rat	1 000 mg/kg	Oral	Modulation of oxidative stress and adjustment of blood level of TNF-α and glucose	[83]
Human	60 mg/day	Oral	Reduction of volume of the hydatid cysts and the serum level of liver enzymes	[86]

GPx: glutathione peroxidase, GSH: glutathione.

6. Other effects

Besides the therapeutic effects presented above, other pharmacological properties of *Z. multiflora* include cardioprotective, gastroprotective, antimicrobial, antidiabetic, and anticancer activities. Sepsis is a serious condition in which the body's immune system has an improper response to an infection[87]. Intensive inflammation caused by sepsis can result in tissue injury, organ failure, and lastly death[88]. Bacterial toxins such as LPS have been suggested for uncontrolled release of inflammatory mediators and induction of sepsis[89]. Meanwhile, one of the organs severely affected by sepsis is the heart[90]. Hosseini *et al*. found that oral injections of 50, 100, and 200 mg/kg of *Z. multiflora* and 25, 50, and 100 mg/kg of carvacrol had cardio-protective effects against LPS-induced sepsis in rats. The protective effect of *Z. multiflora* and carvacrol was mediated *via* a decrease in oxidant agents such as MDA and NO and an increase in antioxidant factors including SOD, CAT, and thiol in the heart and aorta tissue[91].

IBS is a gastrointestinal ailment associated with annoying abdominal pain and disturbance in bowel movements. Although the etiology of IBS has been not fully understood, environmental and genetic factors are listed as the main causes[92]. Based on the report of Bordbar *et al*., two soft gel capsules containing 180 mg of essential oils of *Z. multiflora* exerted a positive effect on IBS symptoms[93]. It has been demonstrated that oral drops of *Z. multiflora* essential oil (2%) could apply analgesic, anti-spastic, anti-ulcer, and anti-inflammatory impacts and lastly alleviate IBS symptoms[94]. Minaiyan *et al*. also reported that 100, 200, and 400 mg/kg of *Z. multiflora* hydroalcoholic extract lessened the myeloperoxidase activity and ameliorated the indomethacin-stimulated gastric ulcer in rats[95].

The skin is an important organ that prevents the penetration of harmful fungi and bacteria. *Staphylococcus aureus*[96] and *Pseudomonas aeruginosa*[97] are bacteria that induce infected wounds. The level of inflammatory cytokines including IL-1β and TNF-α increased in inflammation phase of wound healing process[98]. In proliferative phase, insulin-like growth factor 1 (IGF-1) promotes re-epithelialization of the wound site[99]. VEGF, fibroblast growth factor-2 (FGF-2), and IL-10 also exert positive effects on the wound[100]. Farahpour *et al*. showed the therapeutic effect of ointments containing 2% and 4% of *Z. multiflora* essential oil on wounds infected with *Staphylococcus aureus* and *Pseudomonas aeruginosa* in mice. This antibacterial property was accompanied by the mitigation of the wound size, total bacteria count and IL-1β and TNF-α expression, upregulation of IL-10, transforming growth factor-β (TGF-β), IGF-1, FGF-2, and VEGF and enhancement of angiogenesis and collagen biosynthesis[101]. Furthermore, 20 and 40 μL/kg of *Z. multiflora* essential oil decreased replication of H9N2 influenza virus in challenged broiler chicks[102].

Diabetes mellitus is a metabolic disorder that is characterized by a high content of blood glucose and a low level of insulin. Uncontrolled diabetes can lead to cardiovascular dysfunction, liver and kidney damage, and blindness[103,104]. Use of antioxidants has been suggested as a strategy for the treatment of diabetes[105]. In an animal model of streptozotocin-induced diabetes, oral administration of 50 μL/kg of essential oil of *Z. multiflora* attenuated the diabetic injuries by removing the oxygen and nitrogen radicals[106].

Cancer is one of the main causes of death in the world. Breast cancer and melanoma are prevalent forms of cancer[107]. It has been documented that essential oil of *Z. multiflora* dose-dependently inhibited the proliferation of breast cancer and melanoma cell lines[108]. Based on the results of the study of Aghamohammadi *et al*., 25, 50, 100, 150, and 200 μg/mL of *Z. multiflora* enhanced radiation-caused apoptosis in human glioblastoma cells[109]. Ahani *et al*. also demonstrated that essential oil of *Z. multiflora* suppressed cell proliferation and stimulated apoptosis in human colon cancer cell lines in a time- and dose-dependent manner[110].

7. Conclusion

The scientific findings demonstrate that *Z. multiflora* has a wide spectrum of therapeutic properties including neuroprotective, anti-asthmatic, hepatoprotective, renoprotective, cardioprotective, gastroprotective, antimicrobial, antidiabetic, and anticancer activities. Mechanisms such as suppression of inflammatory responses and attenuation of oxidative stress have a principal contribution to the therapeutic effects of *Z. multiflora* on different organs. It has been found that the neuroprotective effects of *Z. multiflora* may be mediated *via* a decreased level of AchE activity. In addition, the wound-healing activity of *Z. multiflora* can be attributed to upregulation of TGF-β, IGF-1, FGF-2, and VEGF and induction of angiogenesis and collagen biosynthesis.

Even though *Z. multiflora* has good protective effects against the injuries of various body systems in experimental studies, its effects in clinical studies are not fully known. Therefore, clinical tests are necessary to verify the safety and efficacy of this plant.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

RN contributed in supervision and revision of the manuscript. FA contributed in data collection and revised the amuscript. AA designed the work, collected the data, prepared and revised the manuscript.

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