

## Potential Therapeutic Effects of *Falcaria vulgaris* Bernh: A Systematic Review

### Abstract

**Introduction:** *Falcaria vulgaris* Bernh (FV) is a plant of the Apiaceae (Umbelliferae) family, which is known as Ghaziaghi in the Iranian Azeri language and Paghaza in the west of Iran. This plant is usually consumed in spring as a local vegetable and food. FV is recommended by traditional medicine resources for the treatment of skin diseases, gastrointestinal complaints, liver disease, blood purification, and increasing breast milk. The presence of tannins and saponins and the absence of flavonoids and terpenoids have been shown in FV. As various significant properties and special characteristics of FV have been expressed in numerous studies, this study aimed to collect documents and summarize and classify the properties of this plant through a systematic review method. **Materials and Methods:** We extracted 304 articles by searching electronic databases using the following keywords: “Paghazeh,” “Ghaziaghi,” “*Falcaria vulgaris* Bernh,” and “qazayagi.” Then, after eliminating duplicates and unrelated studies, finally, 19 studies were entered into a systematic review. **Results:** Significant therapeutic effects have been reported for FV through studies investigating the medicinal properties of the plant, including antioxidant, antimicrobial and antidiabetic effects, healing properties of skin and stomach ulcers, and protection of the liver and kidney. Most of these effects are related to antioxidant content and the presence of tannins and saponins in the plant. **Conclusion:** FV has significant effects on treatment of various diseases in animal studies and can be concluded in human clinical trials.

**Keywords:** *Falcaria vulgaris* Bernh, ghaziaghi, paghazeh, qazayagi

### Introduction

The use of plants for treating disease is older than human history.<sup>[1]</sup> Medicinal herbs and their products have been effectively used from ancient time. They have many therapeutic properties and are recommended in various ailments by great Persian intellectuals. They are used as such or in the form of various medicinal preparations or formulations. Therapeutic effects of medicinal plants are due to the presence of bioactive chemical constituents such as alkaloids, terpenoids, tannins, and phenolic compounds. Herbal medicines either have little or no side effects compared to chemical medicines. Also, due to the fact that the raw materials of many drugs are imported and the pharmaceutical industry needs these materials, so the use of native medicinal plants that have long been popular in the area is one way to reduce this need.<sup>[2]</sup> *Falcaria vulgaris* Bernh (FV) is one of the most important medicinal plants which is widely used in Persian medicine to prevent control and

treat various diseases. In some parts of Iran, people use FV as food, where FV can be an integral part of the diet as a low-cost food.<sup>[3]</sup> FV is recommended in traditional medicine textbooks for the treatment of skin diseases (including pigmentation disorders and injuries), gastrointestinal complaints, liver disease, blood purification, and increasing breast milk.<sup>[4-6]</sup> Studies have shown the anti-inflammatory, antibacterial, antiviral, and antifungal effects of FV extract and it is also effective in the treatment of gastric ulcers and diabetes.<sup>[7,8]</sup> Some phytochemical studies have shown the presence of tannins and saponins and the absence of flavonoids and terpenoids in FV, whereas other publications have reported the presence of these phytochemicals; these results show that several factors such as local, climatic, seasonal and experimental conditions can influence the composition of essential oil of medicinal plants (reference added). It has also been shown to contain vitamin C, phytosterols, protein, and starches.<sup>[9]</sup> Alphapinene is the main component of flowers, leaves, and stem oils of FV. Also, large amounts of  $\beta$ -caryophyllene,

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l, 8-cineole, alpha-terpinyl acetate, and limonene were recorded in FV extract.<sup>[10]</sup> The antioxidant and antimicrobial compounds of FV contain the highest concentrations of spathulenol, carvacrol oil, and fumaric acid.<sup>[11]</sup> Spathulenol and carvacrol have antimicrobial activity.<sup>[10]</sup> The protective effect of FV extract on ethanol-induced gastric ulcer has also been reported.<sup>[7,8]</sup> tannins and saponins have the property of lowering blood glucose.<sup>[12,13]</sup>

Given that the mass body of studies emphasized the various properties and characteristics of FV plant and the ability to prevent and treat various diseases, so this study aimed to collect documents, summarize and classify the properties of FV through a systematic review.

## Materials and Methods

In this study, the published studies on the effects of FV were searched by systematic review method. For this purpose, all Persian and English articles published in PubMed, Ovid, Scopus, ISI (Web of Science), Proquest, SID, Science direct, and Magiran electronic databases until March 2020 were searched using the following keywords: Paghazeh, Ghaziaghi, *Falcaria vulgaris* Bernh, and qazayagi in the title and abstract of the articles. Finally, clinical trial, case-control and cross-sectional studies that had examined the effect of FV plant on the structure of various tissues including heart, kidney, brain, and skin were included in this systematic review.

While reviewing the databases, a total of 304 related studies were identified, 75 studies were deleted due to duplication; the title and abstract of the remaining 229 studies were reviewed. A total of 163 articles were deleted based on inclusion and exclusion criteria, and the full text of 66 studies was reviewed; of which 47 were unrelated. Finally, 19 studies were included in the systematic review [Figure 1].

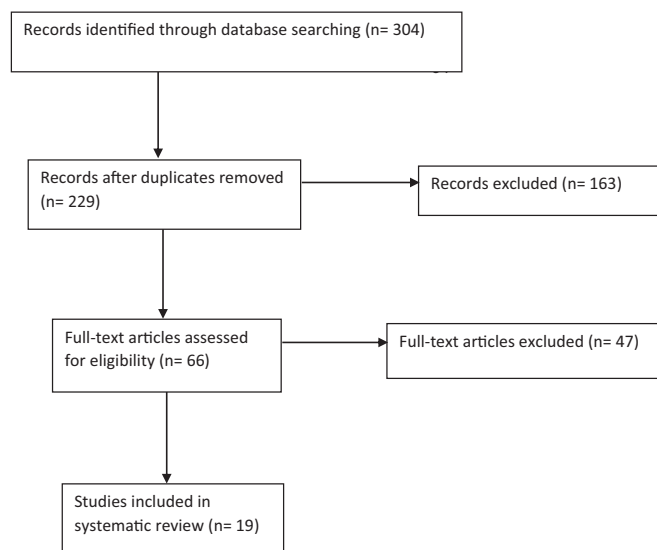


Figure 1: Flowchart of the study selection

## Results

The results of 19 evaluated related articles are shown in Table 1. In this study, studies on the effects of FV on various diseases have been reviewed; the results were categorized based on the type of the effect on disease treatment or the effects on specific organs.

### *Falcaria vulgaris* Bernh impact on diabetic rats

#### *Effects of Falcaria vulgaris Bernh on serum glucose and insulin levels*

In one study, treatment of streptozotocin (STZ)-induced diabetic rats with different doses of FV, similar to the glibenclamide-treated group, significantly reduced ( $P < 0.05$ ) glucose concentrations on days 16 and 20.<sup>[3]</sup> In another study, blood glucose levels in STZ-induced diabetic rats were significantly reduced after treatment with FV extract at doses of 100 and 150 mg/kg ( $P < 0.001$ ). Also, in diabetic groups treated with FV extract at a dose of 150 mg/kg, serum insulin levels increased significantly ( $P < 0.001$ ).<sup>[11]</sup>

#### *Effect of Falcaria vulgaris Bernh on pancreatic tissue and serum levels of insulin, glucose, and nitric oxide*

In a study by Rafiey *et al.*,<sup>[11]</sup> the effect of different doses of FV on histological changes in the islets of Langerhans as well as serum levels of insulin, glucose, and nitric oxide in STZ-induced diabetic rats was measured. The results showed that treatment with 100 and 150 mg/kg doses of FV extract reduced serum glucose levels ( $P < 0.01$ ) and increased islet Langerhans diameter ( $P < 0.05$ ). In addition, at a dose of 150 mg/kg, increase in serum insulin levels ( $P < 0.01$ ), weight gain ( $P < 0.01$ ), and increase in the number of islets and beta cells ( $P < 0.05$ ) as well as decrease nitric oxide ( $P < 0.01$ ) were reported.

#### *Effects of Falcaria vulgaris Bernh on hematological parameters in diabetic rats*

In one study, blood parameters in STZ-diabetic rats showed a significant increase in the number of white blood cells, platelets, and the percentage of eosinophils and basophil ( $P < 0.05$ ), as well as a decrease in the percentage of lymphocytes and monocytes, hemoglobin concentration, MCV, MCH, MCHC, PCV, and erythrocytes ( $P < 0.05$ ). The samples were then treated in different groups with glibenclamide and different doses of FV (200, 600, or 1800  $\mu\text{g}/\text{kg}$  orally) and re-examined for blood parameters. Treatment with FV at all doses (especially FV 1800) similar to glibenclamide significantly improved the blood parameters compared to untreated diabetic rats ( $P \leq 0.05$ ).<sup>[3]</sup>

#### *Effects of Falcaria vulgaris Bernh on biochemical parameters of kidneys*

In a study by Zangeneh *et al.*,<sup>[3]</sup> the concentrations of urea and creatinine in STZ-induced diabetic mice were significantly increased compared with the control group ( $P \leq 0.05$ ). Treatment with different doses of FV (200, 600, or 1800  $\mu\text{g}/\text{kg}$  orally) significantly improved ( $P < 0.05$ ) urea and

**Table 1: Therapeutic effects of *Falcaria vulgaris* Bernh: Literature review**

S. no.	First author	Ref. no	year	Animal type	Sample size	Applied combination/dosage	Factors examined	results summary
1	Jalili C	<sup>[14]</sup>	2019	Wistar male rats	48	3 doses of 50, 100, 150 mg/kg of FV extract Hydro alcoholic extract	Ethanol-induced kidney damage	FV reduces ethanol-induced kidney damage by reducing oxidative stress and lipid peroxidation.
2	Salahshoor MR	<sup>[15]</sup>	2019	Wistar male rats	64	100 g of powder with 70% ethanol. 3 doses of FV hydro alcoholic extract [50, 100, 150 mg/kg]	Oxidative liver damage in diabetic rats	FV Improves liver damage in diabetic rats
3	Jalili C	<sup>[16]</sup>	2019	Wistar male rats	64	100 g of powder with 70% ethanol. 3 doses of FV hydro alcoholic extract [50, 100, 150 mg/kg]	Kidney damage caused by diabetes	FV Reduces diabetes-induced kidney damage in rats.
4	Salahshoor MR	<sup>[17]</sup>	2019	Wistar male rats	64	FV Hydro alcoholic extract	Effects of FV against the toxic effects of ethanol on rat liver	FV Protects against ethanol-induced oxidative stress in the liver.
5	Roshankhah Sh	<sup>[18]</sup>	2019	Wistar male rats	64	100 g of the powder was added to 70% ethanol. FV Hydro alcoholic extract	Therapeutic effects of FV on nicotine-induced injury in the DG region of the rat hippocampus	FV administration improves DG damage due to nicotine.
6	Zangeneh MM	<sup>[3]</sup>	2018	Male BALB/c mice	60	150 g of the obtained powder was extracted with 450 mL distilled water aqueous FV extract	Antidiabetic, hepatoprotective, and renal protection effects of FV aqueous extract	FV has antidiabetic properties, protects the liver, and protects against diabetic nephropathy.
7	Goorani S	<sup>[19]</sup>	2018	Wistar male rats	60	Aqueous FV extract [ointment 3%]	Antioxidant effects and healing of skin wounds	Aqueous FV extract ointment can heal skin wounds.
8	Zangeneh MM	<sup>[20]</sup>	2018	male mice	60	20, 40, 80 and 160 mg/kg FV aqueous extract	Protective effects against CCl <sub>4</sub> -induced liver damage	FV aqueous extract can protect liver tissue and regulate liver enzymes in CCl <sub>4</sub> -induced liver poisoning.
9	Goorani S	<sup>[21]</sup>	2018	Wistar male rats	60	300 g of powder dissolved in 3000 cc of distilled water [aqueous extract]	Blood parameters Antianemic property	Aqueous extract of FV showed beneficial antianemia properties.
10	Jalili C	<sup>[22]</sup>	2018	Wistar male rats	64	50, 100, and 150 mg/kg of FV extract Hydro alcoholic extract	Sperm parameters in diabetic rats	The number and quality [motility, morphology, and viability] of sperm increased
11	Salahshoor MR	<sup>[23]</sup>	2018	adult female Wistar rats	32	20, 50, 100 mg/kg of FV Hydro alcoholic extract	Milk production parameters in the mammary glands of female rats	FV had positive effects on milk production parameters in mammary glands.
12	Rafiey Z	<sup>[11]</sup>	2017	Wistar male rats	64	50, 100, and 150 mg/kg of FV extract Hydroalcoholic extract	Pancreatic tissue in diabetic rats	FV extract lowers blood glucose in diabetic rats.

Table 1: Continued

S. no.	First author	Ref. no	year	Animal type	Sample size	Applied combination/dosage	Factors examined	results summary
13	Yadegari M	[24]	2015	Young male rats	35	100 g of the powder was added to 70% ethanol. FV Hydro alcoholic extract	Aspirin-induced stomach ulcers	FV decreased ulcer index and increased collagen fiber formation compared to aspirin and omeprazole groups
14	Yadegari M	[25]	2010	Female unborn NMRI rats	24	150 mg/kg of FV Hydroalcoholic extract	Antifertility properties	FV has antifertility effects in rats
15	Shakibaei D	[26]	2009	Adult male NMRI rats	23	FV extract by soaking in 70% ethanol FV Hydroalcoholic extract	Coronary artery dilator in an isolated heart of rat	FV caused a significant increase in coronary flow in the isolated heart of rats.
16	Shakibaei D	[27]	2009	Adult male NMRI rats	11	Aqueous-alcoholic FV extract by soaking and concentrating in amounts of 7.5, 15, 22.5, and 30 mg	activity of isolated heart of rats	FV had a direct vasodilator effect on the isolated heart of rats.
17	Shakibaei D	[28]	2006	Adult male NMRI rats	31	Dried leaves of the plant, 5% and 10% alcoholic extract of FV	Time to heal deep skin cuts and skin elasticity in rats	FV had positive effects in healing deep skin wounds.
18	Yadegari M	[24]	2006	Young NMRI rats	24	150 mg/kg of FV Hydroalcoholic extract	Aspirin-induced gastric ulcer in rats	FV had a significant protective effect on aspirin-induced gastric ulcer.
19	Khazaei M	[8]	2006	Male albino rats	30	100 g of FV powder with 70% ethanol using density Three doses of 50, 100, 150 mg/kg of Hydroalcoholic extract of FV	Ethanol-induced gastric ulcer in rats	FV had a protective effect on ethanol-induced ulcer in rats.

creatinine, but there was no significant difference in urea and creatinine concentrations ( $P < 0.05$ ) between groups treated with FV 200, FV 600 and glibenclamide. In another study, intraperitoneal injection of FV extract at concentrations of 50, 100, and 150 mg/kg in STZ diabetic rats at all concentrations significantly reduced malondialdehyde (MDA) levels as the last product of lipid peroxidation in the kidney tissue, blood urea nitrogen (BUN), and creatinine and nitrite oxide (NO), compared to the diabetic control group. In addition, histopathological evaluation showed that FV significantly decreased diameter and increased glomerular count in diabetic rats ( $P > 0.05$ ), increased tissue Ferric reducing antioxidant power (FRAP) levels, and reduced diabetes-induced renal damage.<sup>[16]</sup>

#### *Effects of Falcaria vulgaris Bernh on sperm parameters in diabetic rats*

A study was performed to evaluate the effect of FV extract on sperm parameters in diabetic male rats by SZT injection. The results showed that sperm count, motility, viability, and normal morphology in the diabetic groups showed a significant decrease compared to the normal control group

( $P < 0.05$ ). The diabetic sample treated with different doses of FV (intraperitoneal 50, 100, or 150 mg/kg) were evaluated for sperm parameters. All parameters including sperm count, motility, and normal morphology in all groups treated with FV in comparison with the diabetic control group showed a significant increase.<sup>[22]</sup>

#### *Effect of Falcaria vulgaris Bernh on liver damage in diabetic rats*

In an animal study performed by Salahshoor *et al.*,<sup>[15]</sup> STZ injection increased levels of hepatic MDA, NO, mean of vein diameter in central hepatic and hepatocytes, as well as hepatic enzymes, as well as liver weight loss in the diabetic control group compared with the normal control group. After injection of different doses of FV (50, 100, or 150 mg/kg through oral gavage), a significant increase in liver weight, and tissue FRAP level, and decrease in liver enzymes, hepatic NO, MDA, mean of vein diameter in central hepatic and hepatocytes was reported at all doses ( $P < 0.05$ ). After STZ administration in the diabetic control group, the liver showed obvious changes and damage. These abnormalities include increased white blood cells (inflammation), increased irregularities, sinus dilation,



and hepatocyte depletion (necrosis). Treatment with FV + STZ at each dose reduced liver damage due to STZ toxicity.

### **Falcaria vulgaris Bernh infertility effects**

In the study by Yadegari *et al.*,<sup>[25]</sup> intraperitoneal injection of 150 mg/kg of FV extract, in all three experimental groups including single dose immediately before pregnancy, five doses during the pre-implantation period (days 1 to 5 of pregnancy), and three doses during the implantation phase (days 5 to 7 of pregnancy), significantly ( $P < 0.05$ ) reduced the number of neonates and the number of implantation sites compared to the control group. In this study, FV extract showed obvious antifertility effects in the form of reducing the number of implantation sites and not giving birth in fertilized female mice, but did not affect neonatal weight and appearance abnormalities.

### **Protective effects of Falcaria vulgaris Bernh against liver damage caused by carbon tetrachloride**

Administration of CCl<sub>4</sub> causes liver damage in rats, which is manifested by increasing the level of ALP, AST, ALT, cholesterol, and LDL parameters in serum. Injecting different doses (20, 40, 80, 160 mg/kg) of aqueous FV extract through gavage, significantly ( $P < 0.05$ ), increased levels of ALP, AST, ALT, cholesterol, LDL, WBC, and PLT decreased and HDL, superoxide dismutase (SOD), Catalase (CAT), and red blood cells compared to the untreated group. Other results of the study showed that the liver of mice affected by CCl<sub>4</sub> experienced significant hypertrophy, which led to an increase in weight, and volume, and length of liver structures. These changes were significantly reduced at all FV doses (especially 160 mg/kg).<sup>[20]</sup>

### **The effect of Falcaria vulgaris Bernh on ethanol-induced liver damage**

Ethanol significantly increases total antioxidant capacity, NO level, mean diameter of Central Hepatic Vein (CHV) and hepatocytes, as well as the level of liver enzymes, and reduces liver weight compared to the normal control group. In an animal study, administration of different doses (50, 100, and 150 mg/kg) of FV hydro alcoholic extract by gavage for 28 days in all doses reduced the mean diameter of liver cells and CHV, liver enzymes, and NO levels, and increased liver weight compared to the ethanol control group. FV appears to protect the liver against ethanol-induced oxidative stress, and this effect may be due to the plant's potential antioxidant properties.<sup>[17]</sup>

### **The effect of Falcaria vulgaris Bernh on hematological parameters**

In a study in male Wistar rats, after induction of anemia following intravenous administration of phenyl hydrazine, the samples were treated with different concentrations (25, 50, 100, and 200 mg/kg) of aqueous FV extract. WBC, platelet and RBC count, neutrophil percentage, and levels of Hb, PCV, MCV, MCH, and MCHC were significantly decreased ( $P < 0.05$ ) in the untreated group. Treatment with FV aqueous

extract significantly ( $P < 0.05$ ) increased the above parameters. No significant changes in the percentage of lymphocytes, neutrophils, monocytes, eosinophils, and basophils were observed among the groups treated with different doses of FV and the control group. In terms of lymphocyte, monocyte, eosinophil, and basophil percentage ( $P < 0.05$ ) no significant change was observed among all groups.

Toxicity induced by phenyl hydrazine significantly increased iron, ferritin, erythropoietin, ALP, AST, ALT, GGT, urea, and creatinine ( $P \leq 0.05$ ) compared to the control group. All doses of aqueous FV extract were significantly ( $P < 0.05$ ) improved the above parameters compared to the untreated group, but no significant changes were observed in all FV and control groups in GGT and creatinine levels. Also, no significant change was observed between FV 200 and the control group in terms of urea concentration. Also, no significant change was observed between FV 200 and the control group in urea concentration. On the contrary, oral treatment with FV aqueous extract in all concentrations caused a significant increase in the weight of the samples compared to the untreated group. Except for the best results in the FV 200 group, no significant difference was observed between the groups treated with other doses.<sup>[21]</sup>

### **Effect of Falcaria vulgaris Bernh on the heart**

In one study, different concentrations (7.5, 15, and 22.5 mg/mL) of FV were used to measure the effect of aqueous-alcoholic extract of FV on cardiac parameters including diastolic left ventricular development (DLVP), heart rate (HR), and coronary solution flow (CF). These extracts were prepared and administered to isolated hearts of adult male rats at 10-min intervals. The above parameters were measured in the follow-up period, that is, before receiving the extract, and at intervals of 5 and 10 min after receiving the extract.

After administration of 7.5, 15, and 22.5 mg/mL doses of FV hydroalcoholic extract, the amount of CF increased significantly in the fifth minute compared to the control group. These changes were also observed at a dose of 30 mg but were not statistically significant. The HR was almost constant during consecutive stages. Left ventricular pressure under the influence of the first dose of the extract showed a relative increase but was not significantly different from the control group. The Rate Pressure Product (RPP); the product of left ventricular pressure multiplied by the number of heartbeats per minute under the influence of pressure changes, showed a relative increase in the first stage of extract receiving, the difference with the control stage was not statistically significant. Overall, changes in left ventricular pressure, HR, and ventricular diastolic pressure did not change significantly. As in the study, the increase in coronary flow occurred without a significant change in cardiac activity, it can be said that the increase in CF did not occur secondary to tissue metabolism, but was a direct effect of FV extract on the heart.<sup>[27]</sup>

Shackebaei and Godini<sup>[26]</sup> conducted a study to investigate the mechanism of the effect of FV on vasodilation and to assess

the possible cell damage following FV administration and the role of nitric oxide as one of the most important mechanisms of vascular dilation. The results showed that infusion of 1, 0.2, and 5 µg/mL of FV alcoholic extract significantly ( $P < 0.001$ ) increased coronary fluid flow in the third to fifth minutes after infusion. Also, the amount of fluid flow from the coronary arteries after injecting bolus doses of 15 and 22.5 mg was measured and had a significant. This increase was also significant in the presence of N ( $\omega$ )-nitro-L-arginine methyl ester (L-NAME) and suggests that the mechanism of nitric oxide did not play a role in this regard. On the contrary, due to the lack of significant differences between the levels of LDH released after injection of 15 and 22.5 mg with control doses, it can be said that FV has no toxic effect on heart cells.

#### Effect of *Falcaria vulgaris* Bernh on the brain

In an animal study performed by Roshankhah *et al.*,<sup>[18]</sup> prescribing different doses (50, 100, and 150 mg/kg) of FV alcoholic extract improved the nicotine-induced damage in the DG area of the hippocampus. In this study, a significant increase in the number of neurons and dendritic spines was observed following FV injection. Also, after FV administration, serum levels of nitrite oxide decreased and total antioxidant capacity increased significantly.

#### Effect of *Falcaria vulgaris* Bernh on wound healing

The use of 3% ointment prepared from FV aqueous extract or tetracycline on the skin wound of the tested samples, led to a significant reduction ( $P < 0.05$ ) in the area of the wound, the total number of cells, lymphocytes, neutrophils, and macrophages and significant increase ( $P < 0.05$ ) in wound contraction, and levels of hydroxyproline, hexosamine, fibrocyte, fibroblast, and fibrocyte to fibroblast rate in the treated groups compared with the control groups and the groups treated with Eucerin [lanolin alcohol] ointment. FV ointment significantly improved wound surface and wound contraction compared to tetracycline ointment and increased levels of hydroxyproline and hexosamine. Also, inhibition of free radicals of DPPH (2, 2-diphenyl-1-picrylhydrazyl) in the presence of FV extract indicates the effective inhibitory role of this plant compared to butylated hydroxytoluene (BHT) as a control. The rate of inhibition of free radicals by FV depends on dose increasing.<sup>[19]</sup>

In one study, to evaluate the effect of FV in the forms of dried leaves, 5% alcoholic extract, and 10% alcoholic extract, the mean differences between wound surface and skin tensile strength were measured on the third, sixth, and sixteenth days. The results showed that the mean differences between the treated and control wound surface in each sample in all three forms of the plant (dried leaves, 5% and 10% alcoholic extract) were statistically significant, but an increase in skin tensile strength was observed only in the group treated with 5% alcohol extract.<sup>[28]</sup>

#### The effect of *Falcaria vulgaris* Bernh on milk increase

In one study, after injecting different intraperitoneal doses of FV (20, 50, 100 mg/kg), the mean blood prolactin levels in

FV-treated mice in all treatment groups improved significantly compared with the control group. Also, the effect of FV on the expression of prolactin receptor gene (PRLR) in breast tissue was significantly improved in all doses compared to the control group.

FV resulted in a significant increase in the average diameter and numbers of alveoli in the group treated at all doses compared with the control group and also the breast tissue of the FV-treated group showed an increase in lobule size and alveolar volume.<sup>[23]</sup>

#### The effect of *Falcaria vulgaris* Bernh on aspirin-induced gastric ulcer

In one study, administration of three doses of aspirin 200 mg/kg/day in 1% Carboxymethyl cellulose solution resulted in obvious mucosal and submucosal lesions (ulcer formation, mucosal discontinuity, extensive edema, and leukocyte penetration into the gastric mucosa). On macroscopic examination, multiple bleeding lesions with different sizes were observed in the gastric gland. After the injection of FV alcoholic extract at a dose of 150 mg/kg/day, the ulcer index in animals was significantly reduced compared to the control groups of distilled water and omeprazole. Ulcer healing percentage also increased compared to a negative control (distilled water) and positive control (omeprazole) groups. In the mentioned study, the FV alcoholic extract had a significant healing effect on aspirin-induced gastric ulcer compared to the omeprazole.<sup>[24]</sup>

A histological study showed a normal amount of collagen sediment in the submucosal layer in the tissue of the control group. Animals treated with aspirin showed more inflammatory cells, and irregular or less collagen. Tissue from the FV extract-treated group showed a lower number of inflammatory cells and increased collagen production compared to the aspirin group. Omeprazole also increased collagen formation, but lesser than the extract group.<sup>[29]</sup>

#### The effect of *Falcaria vulgaris* Bernh on ethanol-induced gastric ulcer

One study showed that the FV hydro-alcoholic extract significantly protected the stomach against ethanol-induced mucosal damage. Microscopic examination of the samples, following the administration of 50% ethanol, showed mucosal bleeding, mucosal necrosis of part of the gastric epithelium, edema, and extensive penetration of leukocytes under the mucosa. Samples treated with FV either had very mild lesions with interstitial bleeding or no lesions. Ulcer index in FV-treated animals significantly reduced compared with rats treated with distilled water and ranitidine. It should be noted that different doses of FV (50, 100, and 150 mg/kg) had more protection against ethanol (50 mg/kg) than ranitidine.<sup>[8]</sup>

#### The effect of *Falcaria vulgaris* Bernh on kidney damage caused by ethanol

In a study by Jalili *et al.*,<sup>[14]</sup> ethanol injection significantly increased Bowman's space, histopathological quality indices,

renal MDA, BUN, creatinine, and nitrite oxide levels, and significantly reduced total antioxidant (TAC) levels and the diameter and number of corpuscles of the kidney. Dose-dependent FV treatment significantly reduced Bowman's space, histopathological quality indices, renal MDA, BUN, creatinine, and nitrite oxide levels, and also significantly reduced TAC level, diameter, and several renal corpuscles.

## Discussion

Considerable use of medicinal herbs in recent years has led researchers to discover the effective and active ingredients, the mechanism of action and possible side effects through detailed and extensive studies.

FV has a high content of volatile essential oils and a variety of proteins, starches, and resins. The essential oils contain such constituents as asparagines, small amounts of alkaloids and a large amount of sugar. The plant resin contains phytosterols, phytosterolins, a mixture of fatty acids (including palmitic, stearic, and oleic and linoleic acids) and vitamin C.<sup>[10]</sup> The presence of tannins, saponins, and monoterpenes was also shown in a phytochemical study.<sup>[30]</sup> The main constituents of the FV leaf oil were shown as  $\alpha$ -pinene (31.5%), spathulenol (27.1%), carvacrol (20.9%), and limonene (14.4%) in a study; the related effects are displayed in Figure 2. (Ref added/ no 2)

Diabetes is the most common endocrine disorder affecting more than 285 million people worldwide and is projected to reach 438 million or 8.7% of the world's adult population by 2030.<sup>[31]</sup> Some plants contain large amounts of alkaloids, flavonoids, naphthoquinones, saponins, tannins, and triterpenes and can slow the progression of diabetes.<sup>[32,33]</sup> Glibenclamide, which is a drug in the sulfonylurea family, lowers blood sugar mainly by stimulating insulin secretion from pancreatic  $\beta$  cells. It can be assumed that FV extract, similar to glibenclamide has hypoglycemic and antidiabetic effects by increasing insulin secretion or insulin-like effects. High doses of FV extract

reduce blood glucose in diabetic laboratory samples and also improve serum insulin levels.<sup>[11]</sup> Decreased blood glucose can be attributed to the presence of tannins, saponins, carvacrol, and other compounds in FV extract.<sup>[34,35]</sup> Studies have shown that tannins have significant biological effects, such as antioxidant properties and eliminating free radicals. Its properties such as inhibiting lipid peroxidation, lipoxygenase, and antidiabetic have also been proven.<sup>[36]</sup>

Diabetes causes a variety of sexual disorders, so that 90% of diabetics experience decreased libido and productivity.<sup>[37]</sup> Hyperglycemia alters sperm parameters and destroys DNA integrity by increasing the production of free radicals and oxidative stress.<sup>[38]</sup> Most herbs that are rich in antioxidants increase sperm motility and morphological ability. Antioxidants protect sperm from free radical damage and improve sperm quality.<sup>[39]</sup> Saponin is one of the main components of FV that improves sexual function in animal models. Saponins can also increase testosterone levels and play a vital role in improving sperm quality.<sup>[40]</sup> Therefore, it seems that treatment with FV as an antioxidant by reducing oxidative stress reduces diabetes-related disorders on sperm parameters.

FV as an herb is rich in anti-inflammatory and antioxidant compounds such as spatollenol, carvacrol, alpha-pinene, and limonene. Studies have shown that it can increase the levels of HDL, SOD, and CAT by improving liver function following CC14-induced damage, and this hepatoprotective effect of FV may be due in part to its anti-inflammatory and antioxidant properties.<sup>[7,30,41]</sup>

In a laboratory study, FV extract led to a significant increase in coronary flow. On the contrary, the amount of lactate dehydrogenase released from the heart following the use of the extract was not significant and cardiac parameters did not decrease even in the longer period and wider range use of the extract. Therefore, it can be concluded that the FV extract does

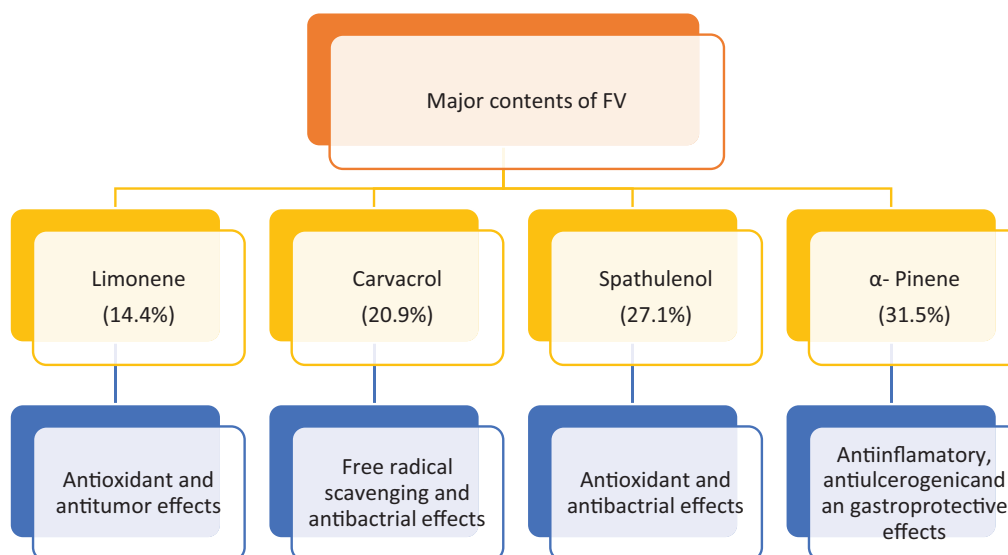


Figure 2: Major constituents of the FV oil and related pharmacological effects



not lead to myocardial damage and its clinical applicability is emphasized. Also, as this flow increase was repeated without/ and with NO inhibitors in a relatively similar pattern, it is clear that the mechanism of this effect was not through the mechanism of nitric oxide.<sup>[26]</sup>

Due to the presence of antioxidant compounds in the FV, its effects in various tissues have been studied. It seems that FV can have protective effects against nicotine-induced oxidative stress in the Dentate Gyrus (DG). Nicotine is rapidly delivered to brain tissue within 10–20 s and connects to nicotinic acetylcholine receptors (nAChRs).<sup>[42]</sup> The hippocampus is part of the limbic system that is essential for the formation of different types of learning and memory.<sup>[43]</sup> It appears that nicotine can destroy dendritic spines by inactivating  $\beta$ 2-nAChRs in postsynaptic cells in the hippocampal region.<sup>[44]</sup> Nicotine by affecting the central and peripheral nervous system can develop many outcomes and side effects.<sup>[45,46]</sup> Consumption of FV extract has been shown to improve DG tissue and prevent the adverse effects of nicotine on total antioxidant capacity, nitric oxide, numbers of nerve cells, and dendritic spines, and such FV ability may be due to its potential antioxidant properties.<sup>[18]</sup>

Also, the potential effects of FV, especially its antioxidant effects against the toxic effects of ethanol have been shown in various studies, and FV hydroalcoholic extract has been able to reduce some liver damage due to the toxic effects of ethanol in laboratory samples.<sup>[17]</sup> Excessive alcohol consumption is one of the most important causes of liver cirrhosis.<sup>[47]</sup> Alcohol can cause acute and chronic esophageal and gastric dysfunction, changes in liver fat, hepatitis, pancreatitis, suppression of the immune system, and functional disorders of the reproductive system.<sup>[48]</sup>

Ethanol is excreted in various ways, for example, partly through exhalation and partly through urine.<sup>[49]</sup> Ethanol pathogenicity in the kidneys is directly related to the increase of free radicals and oxidative stress, which leads to structural and functional disorders in the kidneys.<sup>[50]</sup> Ethanol has adverse effects on kidney tissue and functional parameters, causing oxidant-antioxidant imbalances and increasing nitrite oxide levels. Laboratory findings have shown that FV reduces the various effects of ethanol on the kidney. FV is also able to reduce lipid peroxidation, lower MDA levels, and increase the antioxidant capacity (TAC) of kidney tissue, thus reducing oxidative stress and improving kidney function.<sup>[14]</sup>

For a long time, dried powder of the FV plant, especially in the western and southwestern regions of Iran, has been traditionally used to accelerate wound healing. Currently, disinfectants such as Betadine, acetic acid, saline solution, and antibiotic and hydrocortisone ointments are used for wound healing. Each of these drugs has its limitations and shortcomings. Recent studies have shown that many disinfectants such as Betadine, acetic acid, iodophore, and hydrogen peroxide are toxic to fibroblasts, lymphocytes, and cells required for wound healing.<sup>[51-57]</sup> Therefore, a lot of research has been designed and conducted to achieve natural, efficient, and safe compounds. In

one study, there was a significant difference in wound surface between the two groups treated with FV extract or powder compared to the control sample, and FV accelerated wound healing and deep skin wound healing.<sup>[28]</sup>

In addition to medicinal uses, FV is used as food in some areas. Because in studies, administration of its extract in laboratory samples has led to increased expression of PRLR gene, increased serum prolactin levels, and positive changes in BRST gland tissue such as increased milk,<sup>[26]</sup> It can be recommended to improve and enhance breast milk production. Researches on milk-enhancing chemicals drugs have shown that these drugs are not widely used due to their side effects,<sup>[58]</sup> and it seems that it is safer to modify nutrition or use herbal medicines.

This also applies to other diseases, for example, treatment of gastric ulcer with chemical drugs such as metronidazole, ranitidine, and omeprazole is expensive, with side effects and problems such as autoimmune phenomenon and the possibility of recurrence of ulcers after stopping treatment with.<sup>[59]</sup> In the studies, FV extract significantly reduced aspirin-induced gastric mucosal damage, and collagen fiber deposition in the submucosal layer was significantly increased in the FV extract-treated group compared with the other groups. Therefore, FV extract reduces the microscopic ulcer index and increases the therapeutic ratio or percentage of protection.<sup>[28]</sup>

## Conclusion

In this systematic review, the effects of FV on various tissues including liver, kidney, heart, brain, pancreas, breast, stomach, and skin were examined by considering histopathological and biochemical indicators. Finally, in laboratory studies, favorable and significant effects of this plant were reported and no significant side effects were observed. On the contrary, as this plant has been a native food used by humans for many years, it can be considered as an effective and recommended herb in the human population. However, more extensive studies are suggested to produce standard, safe and effective medicinal products from this plant.

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## Conflicts of interest

There are no conflicts of interest.

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