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Constituents and Pharmacology of *Fumaria Officinalis*- A Review

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Abstract: *Fumaria officinalis* contained alkaloids, carbohydrates, phenolic compounds, flavonoids, glycosides, terpenoids, phytosterols, proteins, amino acids, saponins, fixed oils, steroids, tannins and many other chemical constituents. The previous pharmacological studies showed that *Fumaria officinalis* possessed neural, analgesic, antioxidant, anticancer, antibacterial, antidiabetic, aphrodisiac effect and beneficial effect in biliary disorders and irritable bowel syndrome. This review highlighted the chemical constituents and pharmacological effects of *Fumaria officinalis*.
Keywords: chemical constituents, pharmacology, Fumaria officinalis

I. INTRODUCTION:

As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals [(1)]. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[(2-35)]. Phytochemical analysis showed that *Fumaria officinalis* contained alkaloids, carbohydrates, phenolic compounds, flavonoids, glycosides, terpenoids, phytosterols, proteins, amino acids, saponins, fixed oils, steroids, tannins and many other chemical constituents. The previous pharmacological studies showed that *Fumaria officinalis* possessed neural, analgesic, antioxidant, anticancer, antibacterial, antidiabetic, aphrodisiac effect and beneficial effect in biliary disorders and irritable bowel syndrome. This review will highlight the chemical constituents and pharmacological effects of *Fumaria officinalis*.

Plant profile:
Synonyms:
Fumaria angustifolia, *Fumaria cirrhata*, *Fumaria diffusa*, *Fumaria disjuncta*, *Fumaria gasparinii*, *Fumaria major* *Fumaria media*, *Fumaria muraliformis*, Fumaria *muralis* *Fumaria officinalis* var. elegans, *Fumaria officinalis* subsp. officinalis, *Fumaria officinarum*, *Fumaria petteri* and *Fumaria pulchella*[(38)].

Taxonomic classification:
Kingdom: Plantae; **Subkingdom**: Viridiplantae; **Infrakingdom**: Streptophyta; **Superdivision**: Embryophyta; **Division**: Tracheophyta; **Subdivision**: Spermatophytina; **Class**: Magnoliopsida; **Superorder**: Ranunculanae; **Order**: Ranunculales; **Family**: Papaveraceae, **Genus**:Fumaria; **Species**: *Fumaria officinalis*[(39)].

Common names:
English: fumitory, common fumitory, wax-dolls; **French**: fumeterre officinal; **Portuguese**: erva-molarinha, erva-moleirinha, fel-da-terra, fumária; **Swedish:** jordrök[(40)]

Distribution:
The plant was distributed in **Africa** (Algeria, Egypt, Libya, Morocco, Tunisia); Asia (Russian Federation, Iraq, Palestine , Lebanon, Syria, Turkey, China, Taiwan); **Europe**: (Belarus; Estonia; Latvia; Lithuania, Austria, Belgium, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Denmark, Ireland, Norway, Sweden, United Kingdom, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Montenegro, Romania, Serbia, Slovenia, France, Portugal, Spain); **Northern America:** United states, Argentina; **Australasia** (New Zealand)[(40)].

Description:

Mature plant: Semi-erect to sprawling with a climbing habit, slender, herbaceous, freely branching and between 30-70cm tall. Stems: Unevenly five-angled, green, smooth, succulent and weak. Fumitory has a strong tap root. Cotyledons: Spear shaped with a pointed apex and hairless. Leaves: Triangular and deeply lobed, soft, hairless, green or blue-green in colour, arranged alternately. Flowers: Occur in clusters of 10 to 40 flowers, 6-12mm long, white, pink or red depending on the species[41-42].

Traditional uses:

Fumitory has been used in many countries for the treatment of skin diseases, rheumatism, hypertension or infections. in northern Portugal, it was used against hepatic and gallbladder diseases as tea. In Italy, the plant was used as cholagogue, hypertensive, antispasmodic, respiratory stimulant, and anti-arteriosclerosis. The plant was used in hypertension, constipation, as liver detoxification, and spasmolytic in Cyprus. The plant was also used for the treatment of hypertension and cardiac disease in Morocco. The plant was part of the constituents of many pharmaceutical phyto- preparations used for the treatment of colicky pains of gastrointestinal tract and biliary system[43-47].

Juice or syrup or seed were used in cutaneous eruptions such as eczema and psoriasis, in scabies, syphilis,leprosy, tatters, and itches. In Iranian folk medicine the plant also used in skin diseases, scabies, anti-scorbite, anti-bronchite[48-50].

The extracts of *F. officinalis* L. also used in traditional medicine for varied purposes treatment of digestive problems, certain metabolic diseases, liver disorders and to purify blood[51].

Physico-chemical characteristics:

The physico-chemical characteristics the entire dried *Fumaria officinalis*: ash values: (total ash (w/w) 10.46, acid Insoluble ash (w/w) 2.82, water soluble ash (w/w) 7.72, sulphated ash 15.25); moisture content (v/w) 5.92; solubility (alcoholic soluble matter (w/w) 2.18, water soluble matter (w/w) 5.38); successive extractives (petroleum ether (60-800C) 4.52, di-ethyl ether 2.55, chloroform 1.11, absolute alcohol 14.66, distilled water 24.10); bulk density 0.37; loss in weight on drying at 1050C (%) 12.35; pH- values (1% aqueous solution 6.74, 10% aqueous solution 6.92); and total Alkaloid Content (%) 0.13[52].

Chemical constituents:

The preliminary phytochemical analysis showed that the entire dried *Fumaria officinalis* contained alkaloids, carbohydrates, phenolic compounds, flavonoids, glycosides, terpenoids, phytosterols, proteins, amino acids, saponins, fixed oils, steroids and tannins[52-55].

The phytochemical investigations of different extracts of leaves of *Fumaria officinalis* showed that petroleum ether extract contained phytosterols, saponins and fixed oils. The chloroform extract contained proteins. The ethanolic extract contained carbohydrates, saponins, flavonoids, phytosterols, tannins and phenolic compounds[56].

The plant contained alkaloids isoquinoline-type. Protopines including protopine. (fumarine) as the major alkaloid and cryptopine, protoberberines including aurotensine, stylopine, sinactine and N-methylsinactine, spirobenzylisoquinolines including fumaritine, fumaricine and fumariline, benzophenanthridines including sanguinarine, and indenobenzazepines including fumaritridine and fumaritrine. It also contained acids: Chlorogenic, caffeic and fumaric acids and Other constituents: Bitter principles, flavonoids, mucilage and resin[57-58].

Two new isoquinoline alkaloids, fumaranine and fumarostrejdine, along with 18 known alkaloids were isolated from aerial parts of Fumaria officinalis[59].

Total alkaloids mg/ 100g dry weight of the aerial parts of plants was 540, alkaloids isolated from *F. officinalis* were included (mg/100g dry weight): protopine (protopine: 42, cryptopine: 11), tetrahydroprotoberine (sinactine: 6), (adlumine: 2) and spirobenzyl isoquinoline (parfumine: 2, fumariline: 3, fumarophycine: 3, fumaritine: < 2)[60].

The weight of protopine alone could be reach 230 mg/ 100 g of *F. officinalis* dry weight[61].

GC-MS analysis of chemical composition of polar fractions of five Bulgarian Fumaria *officinalis* aerial parts (leaves, stems and flowers) revealed the presence of (% of total relative content of identified primary metabolites of polar fractions): carbohydrates 59.6, monosaccharides : 36.1, disaccharides : 23.5 and organic acids : 39.6. The analysis revealed the presence of ten carbohydrates of which seven saccharides (% of total ion current of all identified compounds in polar fractions): ribose: trace , fructose I: 11.2 , fructose II : 8.2, galactose I: not detected, mannose: not detected, glucose I : 13.3, galactose II : 2.4, trehalose: trace, myoinositol : 1.0. The plant also contained six organic acids: succinic: trace, glyceric: trace, malic: 6.5, threonic: trace, citric 30.3, and *iso*-citric acids: 2.6. The analysis of polar fractions showed the presence of nine amino acids: L-valine: 0.1, L-isoleucine: 0.1, L-proline: 0.4, L-glycine: trace, L-serine: 0.1, L-threonine: 0.1, L-phenylalanie:

trace, L-asparagine: trace and L-tyrosine: trace. The results of analysis of apolar lipid revealed the presence of (% of total ion current of all identified compounds in polar fractions): palmitic acid (C16:0) : 20.3, stearic acid (C18:0): 2.4, oleic acid (C18:1): 1.0, linolenic acid (C18:3): 1.6, 1-palmitoyl-glycerol: 0.5, 1-stearoyl-glycerol: 73.7 and octacosanol: 0.5[62].

The total phenolic content of methanolic extract of aerial parts of *Fumaria officinalis* was 10.50 mgGAE/g dry weight[63].

The polyphenols isolated from ethanol extracts of *F.officinalis* were included (mg/g dry weight): flavonols (myricetin: 0.25 ± 0.01, kaempferol 0.08 ± 0.01 and quercetin 0.49 ± 0.03); quercetin glycoside (rutin: 6.47 ± 0.13 and hyperoside: 6.51 ± 0.12); flavanone glycoside (hesperidin: undetected); flavone (apigenin: 0.12 ± 0.02); phenolic acids (*p*-coumaric acid: 1.10 ± 0.03, ferulic acid: 2.35 ± 0.04 and sinapic acid: 0.68 ± 0.02)[64].

Pharmacological effects:

Neural effects:

The neuropharmacological activities of ethanolic extract of *Fumaria officinalis* were studied in experimental animal models. *Fumaria officinalis* at 100, 200 and 500 mg/kg bw, ip was evaluated for muscle relaxants activity using Rota rod, Traction test and fall off time. The results of the present study revealed significant (P< 0.001) and dose dependent muscle relaxant and sedative potentiating effects of *Fumaria officinalis*[56].

Isoquinoline alkaloids isolated from aerial parts of Fumaria officinalis were evaluated for their acetylcholinesterase, butyrylcholinesterase, prolyl oligopeptidase (POP), and glycogen synthase kinase-3β inhibitory activities. Parfumidine and sinactine exhibited potent POP inhibition activities (IC_{50} 99±5 and 53±2 μM, respectively)[59].

F. officinalis appeared the most potent AChE acetylcholinesterase inhibitors among many *Fumaria* species, on a plant dry weight basis (IC_{50} = 4.7 ±0.2 mg dry weight/ml), acetylcholinesterase inhibitory effects were correlated to the amount of protopine contained in 1 g of complex alkaloid islated from the species[65].

The muscle relaxant and sedative activities of ethanolic extract of *Fumaria officinalis* were evaluated in experimental animal models. *Fumaria officinalis* (*FO)* (at 100,200 and 500 mg/kg body weight, ip) was evaluated for muscle relaxants activity by using Rota rod, Traction test and fall off time. The results revealed significant (*p*< 0.001) and dose dependent muscle relaxant and sedative potentiating effects of ethanolic extract of *Fumaria officinalis*, it demonstrated its depressant action on the central nervous system[56].

Analgesic effect:

The analgesic effects of ethanol extract of arial parts of *Fumaria officinalis* were investigated using different models. The result of the effect of *Fumaria officinalis* extract on hot plate induced pain in mice showed that the extract 200 and 500 mg/kg significantly ($p < 0.001$, $p < 0.0001$ respectively) increased the post drug PRT. The tail withdrawal response or tail flick time was significantly ($p < 0.0001$) increased from 3.583±0.2386 seconds in the control group (10ml/ kg normal saline) to 13.75±0.2141seconds in the diclofenac sodium 10 mg/ kg and 12.42±0.2386 seconds in the highest dose of the extract (500 mg/kg). The percentage inhibition of writhing was also dose dependently increased from zero in the control group (normal saline) to 33% in the group that received 500mg/ kg of the extract. In acetic acid induced writhing method, there was significant analgesic effects produced by were given 200mg/ kg and those treated with the reference drug diclofenac 500 mg/ kg of extract[53].

Antioxidant effects:

Antioxidant activity of methanolic extract of aerial parts of *Fumaria officinalis* was determined by measuring the inhibition of the volatile organic compounds and the conjugated diene hydroperoxides arising from linoleic acid oxidation. Extracts showed high antioxidant capacity (78.93%)[63].

The antioxidant capacity of the methanolic extract from Fumaria officinalis leaves was measured by various assays including ferric reducing antioxidant power assay, cupric reducing antioxidant capacity assay, DPPH radical scavenging, ß-caroten-linoleic acid assay and metal chelating capacity. Total phenolic and flavonoid content of the extract were measured as gallic acid and quercetin equivalent. The methanolic extract showed higher antioxidant activity related to high phenolic content 250 mg GAE and falvonoid content 200 mg QE/g dry weight[66].

The antioxidant activity of *F. officinalis* extracts was evaluated by four popular spectro-photometric methods, the results revealed that antioxidant activity of *F. officinalis* was, DPPH: 160.05 ± 3.27 mM TE/g dry weight, (EC50, mg dry weight/ml): 2.39 ± 0.04 mM TE/g dry weight; ABTS: 131.14 ± 6.08 mM TE/g dry weight; reduce ferric ion (FRAP): 161.48 ± 2.67 mM TE/g dry weight; reduce cupric ions (CUPRAC): 625.67 ± 7.44 mM TE/g dry weight[64].

Effects on biliary disorders:

The plant was used traditionally in Austeralia in dyskinesia of the biliary duct, pain in case of cholelithiasis when surgery is not possible, pain in case of cholecystitis and cholangitis, postcholecystecomia syndrome and posthepatic syndrome with cholestasis[67].

The amphocholeretic activity of fumitory has been demonstrated in animals, it has no effect on normal choleresis but modified bile flow which was artificially increased or decreased , slowing down artificially increased flow and increasing reduced flow. Fumitory extract also inhibited the formation of gall bladder calculi in animals[68-70]

However, in a comprehensive study of patients with cholecystopathies, the extract had an improvement in 70% of the treatment group, and further over 80% Improvement of the symptoms of concomitant biliary dyskinesia[68, 71-72].

A double blind placebo clinical trial was performed in a group of 30 patients (20 women, 10 men of 26-57 years old) with different biliary disorders (dyskinesia, cholocystitis, hepatopathy, chololithiasis, post-operation cholocystectomy syndrome). Patients were taking 3 tablets of (Fumaria-Nebulisat) (water extract 4-6:1) 250 mg daily (two before meals and the third before sleep), for 28 days. The results were successful, especially against the symptoms of fullness and flatulence. The tratment was tolerated and safe[73].

Antibacterial effects:

Bactericidal activity against the Gram-positive organisms Bacillus anthracis and Staphylococcus have been recorded[74].

The antimicrobial activity of aqueous and methanolic extract of aerial parts of *Fumaria officinalis* was carried out by disc diffusion test against *Acinetobacter lwoffi, Alcaligenes feacalis Bacillus cereus, Bacillus subtilis* ATCC 6633, *Enterobacter cloacae, Escherichia coli* 1328, *Escherichia coli* 1402, *Klebsiella pneumonia* subsp. *ozanae* 5713, *Klebsiella pneumonia* subsp. *pneumonia* 2124, *Listeria monocytogenes* 8353, *Proteus mirabilis* 3242, *Proteus vulgaris* KÜKEM, *Providencia alcaliaciens, Pseudomonas aeruginosa* ATCC 9027, *Pseudomonas aeruginosa* 3428, *Pseudomonas fluorescens* 7324, *Pseudomonas pseudoalcaligenes* 3445, *Pseudomonas putida* 1617, *Salmonella typmiruim* RSSK 95091, *Staphylococcus aureus* 7231 , *Staphylococcus hominis* 3221, *Streptococcus pyogenes* ATCC 176, *Candida albicans* ATCC 1223, *Saccharomyces boulardii 6128, Saccharomyces cereviciae* 6541, *Aspergillus niger* BC 102 , *Cladosporium herbarum, Paecilomyces variotii* 108, *Penicillium brevicompactum, Penicillium roquefortii* BC 111, *Penicillium roquefortii* BC 113 and *Trichothecium roseum*. The methanolic extract showed activity against *Staphylococcus aureus* 7231(15mm), *Cladosporium herbarum* (14mm), *Pseudomonas aeruginosa* 3428 (10mm), *Saccharomyces boulardii* 6128 and *Paecilomyces variotii* 108 (7 mm) and moderate activity against *Saccharomyces cereviciae* 6541, *Pseudomonas aeruginosa* ATCC 9027 and *Bacillus cereus* 6230[75].

Antidiabetic effect:

The antidiabetic effects of *Fumaria officinalis* was studied in an animal model of DM2. Diabetes was induced in male Wistar rats by feeding 21% fructose in drinking water for 8 weeks. They were treated with aqueous extracts (10%) of the plant for 8 weeks. *Fumaria officinalis* treated group did not show any significant changes in the blood glucose, plasma insulin, urine glucose and urine volume between the 8th and the 16th week[76].

Hepatoprotective effect:

Hepatoprotective activity of ethanolic extract of *Fumaria officinalis* was in carbon tetrachloride (CCl_4) induced liver damage in rats. The ethanolic extract at a dose of 200 and 500 mg/ kg orally induced significant ($p<0.001$) hepatoprotective effect by reducing the serum marker enzymes like SGPT, SGOT, ALP. Extract also reduced the elevated levels of serum total and direct bilirubin, cholesterol, triglycerides. Ascorbic acid in rat's urine and histophathological studies further conform the hepatoprotective activity of *Fumaria officinalis* when compared to the CCl_4 treated control groups[77].

Effect in irritable bowel syndrome:

The efficacy of two herbal remedies used in the treatment of irritable bowel syndrome was assessed clinically using a randomized, double-blind, placebo-controlled trial, IBS patients were randomly assigned to one of three treatment groups: *Curcuma xanthorriza* 60 mg daily (curcuma group), *Fumaria officinalis* 1500 mg daily (fumitory group) and placebo. The study treatment was applied three times a day for 18 weeks. IBS-related pain was decreased by −0.9±11.5 (mm±SD) in the fumitory group,IBS-related distension was increased by 0.3±9.3 in the fumitory group. Additionally, the global assessment of changes in IBS symptoms and psychological stress due to IBS did not differ significantly among the three treatment groups[78].

Aphrodisiac effect:

The aphrodisiac activities of *Fumaria officinolis* fruit aqueous/ ethanol extract 500mg/kg were studied in rats. *Fumaria officinolis* increase ($p<0.05$) in mounting behaviour when compared with the control within the first and the third hour respectively. However, the it induced no significant difference in mounting behavoiur within the first and third hour[(54)].

Cytotoxicity:

Cytotoxicity of air-dried n-hexane, ethyl acetate, ethanol, methanol and water extracts of *Fumaria officinalis* was evaluated by the brine shrimp lethality bioassay. The n-hexane extract of F. officinalis showed cytotoxic activity against the brine shrimp (LC_{50}: 901.24 µg/ml). Protopine, the most important alkaloid of *Fumaria officinalis*, which was previously found to be cytotoxic, could be responsible for the observed brine shrimps lethality activities[(51)].

Toxicity and side effects:

In the acute toxicity study ethanolic extract of leaves *Fumaria officinalis* showed that LD_{50} cut off value of ethanolic extract was 2000 mg/kg body weight[(56)].

No reported side-effects or documented toxicity studies were located, although possible adverse effects include raised intraocular pressure and oedema[(79)].

One case of acute hepatitis has been reported with parallel use of Fumaria and *Vitis vinifera* plant therapy products[(80)].

Monomethyl fumarate was found to be non-hepatotoxic in doses up to 1 mg/ml in vitro and up to 50 mg/kg in in vivo studies in albino rats[(81)]

Another side of this matter showed that alkaloids found in other members of the *Fumariaceae* family have caused trembling, seizures and death when taken in great quantities[(82)].

The effects of *F. officinalis* hydroalcoholic extract on the Blood Urea Nitrogen (BUN) and serum creatinine concentrations as indicators of kidney function were investigated in rabbits (200 and 400 mg/kg of *F. officinalis* extract for 28 days). In day 28, blood samples were taken and (BUN) and creatinine concentrations were assayed by enzymatic methods with spectrophotometerThe results showed that *F. officinalis* hydroalcoholic extract administration increased BUN and serum creatinine concentrations significantly in low doses, but BUN decreased and serum creatinine increased significantly in high doses ($P<0.05$)[(83)].

The haematological effects of *F. officinalis* hydroalcoholic extract (200 and 400 mg/kg bw, orally)were studied in rabbits. The results showed that *F. officinalis* hydroalcoholic extract produces a non-dose-dependent significant ($P < 0.05$) decrease in PCV, Hb, MCV, RBC, total WBC and neutrophil percentage, compared with the control group. However, it increased lymphocyte, eosinophil and monocyte percentages[(84)].

Hypotensive actions have been documented in animal studies. The safety of fumitory during pregnancy and lactation has not been established. In view of lack of pharmacological and toxicity data, the use of fumitory during pregnancy and lactation should be avoided[(57)].

Dose:

Herb 2-4 g or by infusion three times daily. Liquid extract 2-4 ml (1 : 1 in 25% alcohol) three times daily. Tincture 1-4ml (1 :5 in 45% alcohol) three times daily[(57)].

The ethanol-induced immunosupression and antioxidant activity of alcoholic extract of Fumaria officinalis were investigated in rats. The ethanol-treated (2 g/kg, 20% w/v, po, daily for four weeks) rats concurrently received either alcoholic extract of Fumaria officinalis or a combination of vitamin E and C (each 100 mg/kg, po) daily for the same period. Phagocytosis, total leukocyte count (TLC), humoral and cell-mediated immune responses, lipid peroxidation (LPO), reduced glutathione (GSH) content, superoxide dismutase (SOD) and catalase (CAT) activities were assessed. It was found that the chronic administration of ethanol decreased the humoral and cell-mediated immune response, phagocytosis, phagocytosis index, TLC, GSH, CAT and SOD activities and increased the LPO. These influences of ethanol were prevented by concurrent daily administration of alcoholic extract of Fumaria officinalis and the effect was comparable with that of the combination of vitamin E and C[(85)].

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