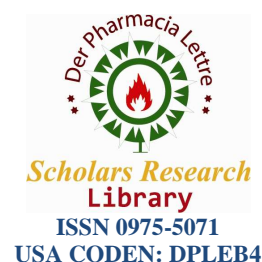




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## A review of chemical components and pharmacological effects of *Kelussia odoratissima* Mozaff

Sepide Miraj<sup>1</sup>, Nahid Jivad<sup>2</sup> and Sara Kiani<sup>3\*</sup>

<sup>1</sup>Clinical Biochemistry Research Center Resident of Obstetrics and Gynecology, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>2</sup>Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

<sup>3</sup>Molecular and cellular research center, Shahrekord University of Medical Sciences, Shahrekord, Iran

### ABSTRACT

*Kelussia odoratissima* Mozaff. is a perennial aromatic herb, which grows up to 120 to 200 cm high. The flowers are 1 to 2 mm in diameter, all hermaphrodites and petals are yellow and produced in compound umbels. While this plant has lots of properties, the aim of this study is to overview its therapeutic, nutritive and industrial effects. This review article was carried out by searching studies in PubMed, Web of Science, and Iran Medex databases up to 2015. The search terms were “*Kelussia odoratissima* Mozaff.”, “therapeutic”, “pharmacological”, “keluss”, “karafs e koohi”, “wild celery” or their combinations. Totally, of 100 found articles, 47 articles (42 in vitro and 5 in vivo) were included. Various studies have shown that *Kelussia odoratissima* Mozaff. has antioxidant, antibacterial and anti-fungi, larvicidal and insecticidal, anti-cancer, antimicrobial, sedative, anxiolytic, analgesic, anti-spasm, anti-inflammatory, anti-hyperlipidemic, anti- hypercholesterolemic, antigenotoxic and fibrinolytic properties. *Kelussia odoratissima* Mozaff. is widely used for therapeutic and purposes that trigger its significant value. Various combinations and numerous medicinal properties of its extract, essential oils, its stems and leaves demand further and more scientific studies about the effective compounds this plant and their mechanism actions.

**Keywords:** Wild celery, Phytochemicals, Therapeutic effects, Pharmacognosy, Alternative and complementary medicine.

### INTRODUCTION

Medicinal plants have been shown to have various therapeutic and nutritional and industrial uses [1-6]. The available drugs have been predominantly prepared from herbal medicines. Medicinal plants are generally safer than synthetic drugs and researcher are trying to prepare more effective drugs [7-14]. In this regard, a lot of medicinal plants have shown promising results in the prevention and treatment of various diseases including cancer [15-19], infection diseases [20-26], central nerves disorders [27-34], cardiovascular diseases [35-41], degenerative diseases [42-45], liver diseases [46], hyperlipidemia [47], diabetes [48-58], and other diseases [59-74].

*Kelussia odoratissima* Mozaff. , known as Keluss or Karafs-e- Bakhtiari in Persian is one of these plants which is found merely in central Zagros Mountains [75]. It is a sweet-smelling, self-growing plant belonging to Apiaceae family and is a wild rebus, erect, glabrous, perennial aromatic herb growing up to 120 to 200 cm high. *Kelussia odoratissima* is an endemic and endangered ethnomedicinal plant from Iran. Stem of this plant is short and covered by basal leaves. Generally, this plant is located and grown in snowy parts of central Zagros. Chilling has very significant effect on seed germination of *Kelussia odoratissima* and soaking treatment increases the germination percentage [76]. *Kelussia odoratissima* was reported to have a mainly symmetrical, isopolar, prolate, operculate and tricolporate morphology and prolate in shape, are operculate and tricolporate structurally and the surface is regulate [77].

It possesses tremendous uses as food, spice and medicinal herb. It bears a unique flavorful smell; Pickles of this plant that are common in Chaharmahal Bakhtiari province are vastly used as spice especially in yogurt or used as food additives in traditional preparations such as pickles [77]. It has various therapeutic uses [78, 79]. The leaves of this plant can be used as an edible, wild vegetable, flavoring and it is traditionally consumed as a medicinal plant to treat hypertension, inflammation, ulcer and cardiovascular diseases [75]. This species traditionally have anti -ache, anti -inflation and anti - cough effects. Seed and root of this plant are boiled and used to cure the common cold and intense coughs and its organs are used to treat the stomachache, rheumatism and blood refining. The flavonoid compounds as a main part of this plant has anti-inflammatory anti-inflammation, anti-viral, anti-diabetic, anti-cancer and anti-toxin, anti-stress effects [80, 81]. It also has antioxidant and antihyperlipidemic, ulcerative, sedative, antibacterial, larvicidal, antibacterial, anti-tumor, insecticidal, anti-spasmodic, antihelminthic, antidiabetic, antilipidemic and anti-allergic effects and improves spatial memory [82-87]. Phthalides constitute 70% of the *Kelussia odoratissima* essence with several effects: liver protection, prostaglandin F<sub>2</sub> $\alpha$  inhibition, prevention of cancer, tumors, treatment of epilepsy and liver disorders and reduction in blood viscosity [88,89]. It can be said that the *Kelussia odoratissima* could be used as natural preservative agents in foodstuff [90]. The essential oils from aerial parts of *Kelussia odoratissima* have a potential to be used as a new source in drug and food industries [91]. Phthalides constitutes 70% of the plant essence with the effect of liver protection, prostaglandin F<sub>2</sub> $\alpha$  inhibition, cancer tumors prevention, epilepsy and liver disorders treatment and blood viscosity reduction [92,93]. The ligustilid extracted from *Kelussia odoratissima* leads to relax rat's vessels [4]. This plant is also used to cure some rheumatism disorders, common cold, cough, blood pressure, blood lipid and stomachache [94]. Results of a study showed that the major composition of essential oil of aerial parts of the three ecotypes [Koohrang, Bazoft and Samsami] of *Kelussia odoratissima* is Phthalides [such as Z-ligustilid] that have therapeutic potential in treating vascular dementia and cerebrovascular insufficiency [95]. While this plant has lots of properties, the aim of this study is to overview its therapeutic effects than its nutritive and industrial effects.

## MATERIALS AND METHODS

This review article was carried out by searching studies in PubMed, Web of Science, and Iran Medex databases up to 2015. The search terms were “*Kelussia odoratissima* Mozaff.”, “therapeutic”, “pharmacological”, “keluss”, “karafs e koochi”, “wild celery” or their combinations. Totally, of 100 found articles, 47 articles [42 in vitro and 5 in vivo] were included.

### Chemical composition

Forty-nine constituents were identified in the oil of this plant that are as Z-ligustilide (77.73%), 2-octen-1-ol acetate (6.27%), E-ligustilide (2.27%) and butylidene phthalide (1.97%) [95, 96]. Major components of the stem were identified as being borneol (36.9 %), bornyl acetate (14.0 %) and 1,8-cineol (13.6 %) and in the flower were found to be 1,8-cineol (22.0 %), camphor (20.1 %),  $\alpha$ -pinene (19.0 %) and camphene (12.0 %). In the leaf oil of the plant  $\beta$ -terpinene (23.0 %) was the predominant compounds [97].  $\alpha$  Caryophyllene (22.60%),  $\alpha$  Humulene (20.00 %), Tetracyclononan-3-one (CAS) Triasteranone (16.04%) and Cyclopropane (11.54%) were the major compounds [90]. Its essential oil are largely consisted of Neophyadiene, 3 n butyl phthalide, E3- tetradeceneylacetate, Butylidene phthalide .Hexadecanoic, 6-butyl-1.4- cycloheptadin. Their percentage are reported as phthalides, 3-butylidene-4, 5-dihydrophthalide (z-Ligustilide) (85.9%), cis-3butylidene phthalide (0.4%) and 3n butyl phthalide (0.3%) , Unknown-A (4.47%), (E)-Ligustilide (2.57%), (Z)-Butylidene phthalide (2.37%), 5-pentyl cyclohexa-1,3-diene (1.57%) and kessane (0.77%) [97]. 1,8-cineol was the main component found in essential oils from aerial parts (27.95%) of *Kelussia odoratissima* in flowering stage [91]. content of the essential oil of this plant was more in fruit, root , stalk , leaf , inflorescence respectively. The total number of compounds identified and quantified was thirty-two in roots, thirty-one in stalks, twenty-one in leaves, twenty-one in inflorescences and six in fruits. The major compounds exciting in its all organs were phthalide (Z)-ligustilide and (2E)-decen-1-ol [98]. Fatty acids extracted from its oil were: Linoleic acid (25.46%),  $\alpha$ -linolenic acid (16.66%), palmitic acid (11.92%), oleic acid (9.33%), stearic acid (4.72%), petroselinic acid (2.53%), arachidonic acid (2.51%) and erucic acid (1.76%) [97].

### Mechanism of action

Phthalides as the main phytochemical element of *Kelussia odoratissima* have important molecular and cellular effects consisting of the inhibition of DNA methyltransferases via resulting in DNA hypermethylation, stimulation of glutathione transferase activity, antiproliferative effects on colon cancer cells, potential anti-fibrotic effects for the treatment and prevention of hepatic fibrosis and protective effects on focal cerebral ischemia in rats. z-Ligustilide (3-butylidene-4,5-dihydrophthalide, LIG) possess different biological activities including relaxation of smooth muscle, improved microcirculation, antiasthma and Sedative effects, antiproliferative properties on smooth muscle cells and significant neuroprotective effects by antioxidant and antiapoptotic mechanisms [99].

**Antioxidant activity**

Antioxidant activity of methanol extracts [ME] of *K. odoratissima* Mozaff. and *Echinophoraplalyloba* DC. and *Heracleumlasio petalum* Boiss plants was examined and it was concluded that the level of their antioxidant activity in these plants varied in a great extent and it was suggested that flavonoids compounds is the highest in extract of *E. platyloba* and the lowest in *K. odoratissima* Mozaff [77]. In an *in vitro* study, antioxidant activity of Hydro-distilled essential oils of *K. odoratissima* Mozaff. was studied which indicated that its essential oil possessed high antioxidant activity and could be utilized as an potential preservative instead of artificial ones in food industry [100]. In addition, the antioxidant activity of the methanolic extract of this plant was evaluated and it was found that it was generally less effective than that of ascorbic acid, but comparing to the activities of  $\alpha$ -tocopherol and BHT, it is more effective. The methanolic extract inhibited the oxidation of sunflower oil at  $60 \pm 3$  °C more efficiently than did BHT. It may be concluded that BHT and extract have synergistic effects at low concentration [101].

**Antibacterial and anti-fungi properties**

The antibacterial activities of this EO was investigated against Food born pathogenic bacteria (*Salmonellathyphimurium*, *Escherichia coli*, *Listeria monocytogenes* and *Staphylococcus aureus*) and probiotic bacteria (*Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus plantarum* and *Lactobacillus ramnus*) by standard Microplate serial dilution method. Most of the probiotic bacteria showed a relatively high resistance. Among the pathogenic bacteria, *S. aureus* was the most sensitive bacteria followed by *L. monocytogenes*. Among the probiotic bacteria tested, the *L. ramnus* was the susceptible and *L. casei* and *L. plantarum* were the resistant [90]. The antibacterial effects of the essential oil of *K. odoratissima* Mozaff was tested by agar disc diffusion and it was found that antibacterial activity of Essential oils of Lamiaceae family is higher than that of Apieacea species [102]. The antibacterial activity of ethanol extracts of *Kelussia odoratissima* and some other plants was examined against *Streptococcus* spp. by disc diffusion and serial dilution assays. Most of the extracts and essential oils showed a relatively high antibacterial activity against *Streptococcus iniae* [103].

In a comparative study, antibacterial activity of ethanol extract and essential oil of *K. odoratissima* Mozaff. And those of some other plants were evaluated against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiellapneumoniae*. Most of the extracts and essential oils showed relatively high antibacterial activity against all the tested bacteria with the diameter of inhibition zone ranging between 8 and 23 mm. The MIC values for active extract and essential oil ranging between 0.039 and 10 mg/ml [83].

Evaluation of antibacterial effect of aqueous and ethanolic extracts of *Kelussia odoratissima* leaves showed all concentrations of these extracts did not have inhibitory effect on *Salmonella typhimurium* ATCC 14028. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) were also studied and it was found that the increase in the concentration of the aqueous and ethanolic of *Kelussia odoratissima* leaves trigger increase in the inhibition zone [104]. In an *in vitro* study, antifungal activity of *Kelussia odoratissima* and some other plants were investigated against *Candida albicans*. Most of the extracts showed relatively high anti-*Candida* activity against the tested fungi with the diameter of inhibition zone ranging between 8 and 17 mm [99].

**Larvicidal activity and insecticidal properties**

The larvicidal activity of essential oil of *Kelussia odoratissima* was examined against two mosquito species, *Anopheles stephensi* and *Culex pipiens* and it was shown that *Kelussia odoratissima* oil is a potential for larvicidal compounds for mosquito larval control and it was found that lower dose of this plant causes high mortality for these insects [84]. The five organs of *K. odoratissima* were studied and was demonstrated that they are valuable source of phthalides being well-known for their insecticidal activities [94].

**Antileishmanial effect**

In an *in vitro* study, the effects of *K. odoratissima* essential on the promastigot form of *Leishmania major* was studied and it was suggested that the effect of essential oil of *K. odoratissima* was different with the ones of negative and positive controls and was dependent on the concentration i.e. the higher the concentrations, the stronger the effect on promastigots [105].

**Anti-tumor and anti-cancer effects**

The hydro-distilled essential oils obtained from the different organs [roots, leaves, stalks, inflorescences and fruits] of *Kelussia odoratissima* were assayed and it was proposed that five studied organs of *K. odoratissima* were rich in phthalides, being famous for their anti-tumor [94]. The flower, leave and seed extracts of *K. odoratissima* grown in Fereydonshahr showed potent cytotoxic effect on the MCF7 cells but not its crude methanol extracts of different organs of *K. odoratissima*. the results demonstrated that different extracts *K. odoratissima* grown in fereydonshahr could be evaluated as an anticancer agent [106].

**Antimicrobial activity**

All concentrations of ethanolic extract of this plant were shown to have inhibitory effect against *Bacillus subtilis* and *Staphylococcus aureus*. The results showed that the extract of *Kelussia odoratissima* had a satisfactory antimicrobial activity and the ethanolic extract of *Kelussia odoratissima* leaves had greater inhibitory effects on the strains studied compared to aqueous extract *in vitro*. A significant correlation was also observed between zone of inhibition and concentration of extracts [83]. Antimicrobial activity of *Kelussia odoratissima* and some other plants was examined against strains of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli* O157:H7, *Yersinia enterocolitica*, *Bacillus cereus*, *Listeria monocytogenes*, *Campylobacter coli*, *Campylobacter jejuni* and *Candida albicans* and it was found that this plant has a relatively high antimicrobial activity against all the tested bacteria and fungi [107]. Antimicrobial activities of extract of *Kelussia odoratissima* and those of some other herbs were investigated against strains of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli* O157:H7, *Yersinia enterocolitica*, *Bacillus cereus*, *Listeria monocytogenes*, *Campylobacter coli*, *Campylobacter jejuni* and *Candida albicans* and it was found that Some of these herbal medicines have rather high antimicrobial activity against all the tested bacteria and fungi [85].

**Sedative, anxiolytic, and analgesic effect**

The sedative properties of *K. odoratissima* was confirmed which it is likely to be affected by the bioactive phthalides existed in this plant, but there were no profound anxiolytic effects [99].

**Anti-spasm effect**

In an animal study carried out on 48 Wistar rats, anti-spasm effect of *K. odoratissima* extract was evaluated and it could be concluded that *Kelussia* alcoholic extracts inhibited ileum contractions of rat through the effect on voltage dependent and beta adrenergic receptors and it might be used to relieve intestinal spasms [78]

**Anti-Inflammatory Effect**

The effect of this herbal extract on a model of acute ulcerative colitis was evaluated and it was found that both lower doses of extract were effective to reduce all the symptoms of colitis. It is concluded that *Kelussia odoratissima* has anti-inflammatory action in rat model of colitis but further detailed studies are recommended to identify the mechanisms are involved and the active constituents are responsible for these findings [80]. The hydro-distilled essential oils obtained from the different organs [roots, leaves, stalks, inflorescences and fruits] of *Kelussia odoratissima* and it was indicated that the five studied organs of *K. odoratissima* have large volume of phthalides being known for their anti-inflammatory [94].

**Anti hyperlipidemic and Anti- hypercholesterolemic effect**

Anti-hyperlipidemic effect of *Kelussia odoratissima* was studied in a study upon mice and it was shown that the levels of all serum lipids including cholesterol, HDL, VLDL, LDL, triglyceride and FBS had a significant decrease two weeks after the beginning of the study. Thus, it was concluded that *Kelussia odoratissima* may enjoy a desirable effect on serum lipid profile and possess a potential hyperlipidemic effect [82]. The anti-atherosclerotic effects of this plant on the development and progression of fatty streaks was examined on Male rabbits and it is found that there is a significant difference between the groups supplemented with herbal medicine and others ( $p < 0.05$ ). Thus, *Amirkabiria odoratissima* Mozaffarian was shown to have anti-atherosclerotic effects but its mechanisms of action is not obvious [81].

**Antigenotoxic Effects**

The protective effects of methanolic and aqueous extracts of *K. odoratissima* was evaluated on DNA damage induced by methyl methanesulfonate [MMS] and it was suggested that some Concentrations of aqueous extracts and methanolic extracts of *K. odoratissima* remarkably reduced MMS-induced damage to DNA of HepG2 cells, so, the antigenotoxic or genoprotective effect of aqueous and methanolic extracts of *K. odoratissima* against DNA damage caused by MMS was confirmed [108].

**Fibrinolytic activity**

In an animal study, the effect of the plant extract on the secretion rate of acid and pepsin in the stomach of the rats studied and it was shown that the administration of this plant decreases gastric acid secretion and would be helpful in gastro intestinal disorders [109]

**Safety and Side effects**

In a review study, the efficacy and safety of effective herbal medicines in the management of hyperlipidemia in human was assayed in Fifty three relevant clinical trials including *Kelussia odoratissima* Mozaff. and no significant adverse effect or mortality were reported about this plant [110].

## CONCLUSION

Kelussia odoratissima Mozaff. has lots of medical, nutritional and industrial properties. Various studies have shown that Kelussia odoratissima Mozaff. has antioxidant, antibacterial and anti-fungi, larvicidal and insecticidal, anti-cancer, antimicrobial, sedative, anxiolytic, analgesic, anti-spasm, anti-inflammatory, anti-hyperlipidemic, anti-hypercholesterolemic, antigenotoxic and fibrinolytic properties. Kelussia odoratissima Mozaff. is widely used for therapeutic and purposes that trigger its significant value. Various combinations and numerous medicinal properties of its extract, essential oils, its stems and leaves demand further scientific studies about the effective compounds of this plant and their mechanism actions. Most of pharmacologic activities of this plant have been attributed to present of phenolic compounds and antioxidant activity, however, there are a lot of other plants [111-124] possessing these compounds. Hence, if this is true these plants should have these effects.

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