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# Potential health benefits of the plant *Levisticum officinale* (lovage) in relation to its polyphenolic content

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**Abstract:** *The purpose of the present study was to gather information about the effects of the herb Levisticum officinale (lovage) and of its phenolic ingredients and to elucidate the potential health benefits of the plant in relation to its polyphenolic content. The study was performed by searching different internet-based databases (Google Scholar, ScienceDirect, PubMed, etc.).*

*Levisticum officinale (lovage) is a perennial aromatic plant from the Apiaceae family. This herb is rich in essential oil and is widely used as a seasoning for culinary purposes. Lovage contains up to 860 mg GAE/100 g fresh weight phenolic substances as well. Polyphenols in L. officinale belong to the classes of flavonoids (quercetin, rutin, kaempferol and anthocyanins) and phenolic acids (chlorogenic, neochlorogenic, ferulic, gallic, ellagic). They contribute to potent antioxidant properties of the plant. Anti-inflammatory, anticancer, neuroprotective, antidiabetic, antibacterial, hepatoprotective and other properties of L. officinale extracts have also been demonstrated. Phenolic substances abundant in lovage have shown to be protective in models of osteoporosis and different cardiovascular diseases as well.*

*The information confirms our assumption that Levisticum officinale is not only an useful and pleasant-tasting Mediterranean-cuisine seasoning but also a herb that can contribute to the healthy lifestyle.*

**Keywords:** *Levisticum officinale*, polyphenols, flavonoids, phenolic acids



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## Introduction

*Levisticum officinale* W.J.D. Koch (lovage) is a perennial herbaceous aromatic plant from *Apiaceae* (*Umbelliferae*) family, widespread in Asia, Europe and even North America [1]. It is defined by some authors as endangered in wild conditions [2]. Many other culinary and medicinal plants such as *Anethum graveolens* (dill), *Petroselinum crispum* (parsley), *Apium graveolens* (celery), *Coriandrum sativum* (coriander), *Carum carvi* (caraway), *Cuminum cyminum* (cumin), *Foeniculum vulgare* (fennel), *Pimpinella anisum* (anise), *Daucus carota* (carrot) and *Pastinaca sativa* (parsnip) also belong to the same family. The potential health benefits of *Levisticum offcinale* have once been popular among the native people, since the Bulgarian name of the plant means 'nine powers'. In the Bulgarian folk medicine, a decoction of lovage roots has been used to increase diuresis and to stimulate appetite [3]. The leaves are also used as a seasoning, especially in seafood recipes from the Mediterranean region and in meat dishes from the cuisine of the Middle East. The most commonly investigated parts of lovage are leaves, roots and seeds.

*Levisticum officinale* is rich in essential oil with important applications in food, beverage and other industries, and many authors investigate the composition of this oil [4]. The edible parts contain also polyunsaturated fatty acids (mainly alpha-linolenic), organic acids (mainly oxalic) and vitamin E [5].

Phenolic substances are abundant in lovage. The data about total polyphenolic content highly vary according to the method used for determination. Some authors report up to 860 mg GAE (gallic acid equivalents) per 100 g fresh herb weight [6]. It is worth mentioning that the herbs for that exact experiment were gathered in the Dobrudzha region (in Romania), which is just north of the border with Bulgaria, and thus can be regarded as representative for the lovage grown in our country as well. The main polyphenols in *Levisticum officinale* belong to the classes of flavonoids and phenolic acids. The flavonoids in lovage are several flavonols (quercetin, rutin, kaempferol) and anthocyanins. The detected phenolic acids were gallic, ellagic, chlorogenic, neochlorogenic and ferulic [6-10]. The concentration of phenolic substances remains stable even after several months of storage [11].

## Review results

### *Antioxidant activity*

*Levisticum officinale* herb extracts were found to possess strong radical-scavenging properties when assessed by FRAP (ferric reducing/antioxidant power) and DPPH (2,2-diphenyl-1-picrylhydrazyl) radical assays [12, 13]. The antioxidant capacity of lovage strongly correlates with the high concentration of phenolic substances [12], especially caffeic acid derivatives [14]. Antioxidant activity of *Levisticum officinale* essential oil has also been demonstrated [15].

Phenolic substances from lovage also possess radical-scavenging properties [5]. Potent antioxidant activity of the flavonoids present in *Levisticum officinale* was revealed using different assays [16-18].



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Hydroxybenzoic (gallic, ellagic) and hydroxycinnamic (chlorogenic, ferulic) acids exert high radical-scavenging activity *in vitro* and *in vivo*, performed by versatile mechanisms [19]. Gallic acid appears to be an effective antioxidant in human trials as well [20].

***Anti-inflammatory and anti-nociceptive effects***

Phenolic substances isolated from *Levisticum officinale* leaves possess anti-inflammatory activity. The probable mechanisms are inhibition of the pro-inflammatory enzymes cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) [9, 21].

Quercetin counteracts inflammation and pain [22]. Its anti-inflammatory properties are due to suppression of the production of TNF-α, pro-inflammatory interleukins and the enzymes COX and LOX, as well as to modulation of various intracellular pathways. These effects were found *in vitro* and proven in animal studies *in vivo*. Clinical trials have not been able to fully confirm those [23]. Kaempferol's anti-inflammatory effect is performed by inhibition of pro-inflammatory enzymes (COX, iNOS) and transcription factors like TNF-alpha, modulation of the expression of different adhesion molecules and intracellular pathways (MAPK, JAK/STAT, PI3K), anti-oxidant action and inhibition of metalloproteinases [24]. Jabbari et al. reported antinociceptive effect of kaempferol, possibly due to modulation of GABA-ergic and opioidergic systems [25]. Rutin also possesses anti-inflammatory [26] and antinociceptive properties [27]. In a meta-analysis of many controlled clinical trials, Fallah et al. demonstrated that dietary anthocyanins were able to decrease the levels of inflammatory markers like CRP, IL-6 and TNF-α [28]. Isolated phenolic acids detected in *Levisticum officinale* exert anti-inflammatory effect by inhibition of xanthine oxidase, COX-2 and other mechanisms [29-31]. In different animal models, phenolic acids were able to relieve pain as well [32-35].

***Anticancer effect***

Hydroalcoholic extract from *Levisticum officinale* was able to induce apoptosis in breast-cancer cell lines by increasing intracellular cGMP and inhibiting the enzyme $PDE_5$ (phosphodiesterase-5) [36]. Such extract revealed a cytotoxic potential also in prostate-cancer cell lines [37], by down-regulating the gene for zinc finger protein in cancer cells [38]. Ethanolic *Levisticum officinale* extracts induce apoptosis in several human leukemia cell lines [39], as well as in a head and neck squamous carcinoma cell line [40].

*Levisticum officinale* component quercetin has demonstrated significant hemopreventive and antigenotoxic properties in different cancer models (especially in colon cancer) [41]. Kaempferol has also revealed anti-cancer activity by induction of apoptosis and cell cycle arrest of cancer cells, modulation of PIP3-kinase signaling pathways and other mechanisms [42, 43]. Rutin is effective anticancer agent *in vitro* and *in vivo*, acting by modulation of different intracellular pathways [44]. Anthocyanins show suppressing activity in different cancer cell lines and animal models – of breast, prostate, colorectal, blood cancers etc. Protective role of dietary anthocyanins against gastrointestinal cancers was noticed [45]. Phenolic acids



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present in *Levisticum officinale* reveal significant anticancer potential in different *in vitro* and *in vivo* assays by induction of apoptosis and cell cycle arrest in malignant cells [31, 46, 47]. Chlorogenic acid may promote cancer-cells differentiation as well [48].

***Neuroprotective effects***

Methanolic *Levisticum officinale* extract exerts a strong acetylcholine-esterase inhibitory activity [49] probably due to terpenoid compounds [50]. Phytochemical compounds from lovage have shown promising results in inhibition of other Alzheimer's-disease-associated molecular targets. These were MAO-B (monoamine oxidase B), involved in amyloid-plaques formation; HMG-CoA (hydroxy methylglutaryl-CoA) reductase and BACE1 (beta-secretase 1), required for amyloid-beta production; and the glucocorticoid receptor, important for the normal functioning of the hypothalamo-pituitary axis and hence decreasing the risk of Alzheimer's development [51]. Indeed, *Levisticum officinale* extracts were able to reverse lipopolysaccharide-induced learning and memory deficits in rats, as well as to decrease the levels of the pro-inflammatory factor IL-6, increase the levels of the neurotrophic factor BDNF, and stimulate the neurogenesis in rat hippocampus [52].

Quercetin was able to induce antidepressant and anti-anxiety effects [53] and has been efficient in different models of Alzheimer's disease [54]. Quercetin and rutin were able to stimulate neuro- and synaptogenesis [55]. Neuroprotective properties of kaempferol include alleviation of Alzheimer's and Parkinson's disease, ischemic stroke, neuropathic pain and epilepsy, anti-depressant and anxiolytic effects [56]. Rutin and anthocyanins exhibit potent protection in different *in vitro* and *in vivo* models of neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's) [45, 57].

Neuroprotective effects of chlorogenic acid had been extensively studied *in vitro* and *in vivo* in animal models of neurodegenerative diseases. In epidemiological studies, increased intake of chlorogenic acid was linked to improved cognition and decreased risk for neurodegenerative diseases. Improved cognition after prolonged administration of chlorogenic acid has been demonstrated also in clinical trials [58]. This phenolic acid was effective in models of anxiety [59], and depression [60] as well. Ferulic, gallic and ellagic acids were also protective in different models of Alzheimer's and Parkinson's disease, in depression and anxiety [61-64]. Additional beneficial effect of chlorogenic and ferulic acids is to stimulate hippocampal neurogenesis and increase the levels of neurotrophic factors in CNS [65, 66].

***Antidiabetic and antiobesity effects***

In a study performed by Ghaedi et al., *Levisticum officinale* extract prevented harmful effects in streptozotocin-induced diabetic rats. The extract improved blood glucose and lipid profile, as well as insulin, creatinine, alanine aminotransferase and aspartate aminotransferase levels in the rat serum. Lovage restored the antioxidant status, inhibited renal sodium-glucose transporter 2 (SGLT-2), increased the expression of intestinal GLUT-2 transporter and inhibited alpha-amylase [67]. Alpha-glucosidase inhibitory activity of methanolic and aqueous *Levisticum officinale* extracts were reported earlier as well



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[68]. *Levisticum officinale* extracts inhibit the enzyme pancreatic lipase, important for triglyceride digestion [69]. Several isolated *Levisticum officinale* components were able to inhibit pancreatic lipase by themselves, e.g., quercetin, kaempferol, ferulic and ellagic acid [70].

*Levisticum officinale* extracts are rich in kaempferol, quercetin and rutin. These flavonols have also shown anti-diabetic and anti-obesity effects mediated by different mechanisms [71, 72]. Quercetin inhibits the intestinal absorption and tissue utilization of glucose, increases insulin secretion and improves insulin sensitivity of tissues [73, 74]. In mice fed high-fat diet, kaempferol reduced fat accumulation, improved lipid profile and glycemia by PPAR-gamma down-regulation [75]. This flavonol was also able to inhibit liver glucose production and increase muscle glucose utilization [76]. According to Ghorbani et al., rutin decreases intestinal carbohydrate absorption, inhibits gluconeogenesis, and stimulates tissue glucose uptake and insulin secretion [77]. Antidiabetic effect of anthocyanins is due to up-regulation of the enzyme AMP-kinase in adipose tissue and skeletal muscle [45]. Rutin was able to alleviate genetic and diet-induced obesity in rats by inducing brown-like adipocyte formation [78]. *In vitro* and animal studies indicate improvement of metabolic control of body weight and increased satiety by anthocyanins. Decreased risk of obesity and diabetes in high anthocyanin dietary intake is revealed by epidemiological studies as well [79].

The phenolic acids in lovage also show antidiabetic properties. Chlorogenic acid inhibits glucose intestinal absorption by inhibition of the enzyme alpha-glucosidase, sensitizes the tissues to insulin action, inhibits glycogenolysis and gluconeogenesis and increases muscle glucose uptake [80, 81]. Ferulic acid improves insulin sensitivity, increases glycogenesis and inhibits gluconeogenesis in liver [82]. It also inhibits the digestive enzymes alpha-amylase and alpha-glucosidase [83]. Gallic acid activates PPAR-gamma receptors and Akt signaling pathway in cell cultures and in different rodent models [84]. Ellagic acid increases insulin secretion and enhances glucose utilization in peripheral tissues [80]. Antiobesity effect has been reported in preclinical and even some clinical studies for chlorogenic [29], ferulic [85, 86], gallic [87] and ellagic acids [88].

***Antibacterial, antifungal, antiviral, antiprotozoal, insecticidal effects***

*Levisticum officinale* essential oil elicits suppressive activity against many bacteria like *S. aureus*, *E. faecium*, *E. coli* [89], *Ps. aeruginosa*, *A. baumannii* and *S. enteritidis* [90]. The essential oil and other components of this plant show a good antibacterial activity against multidrug-resistant *Mycobacterium tuberculosis* as well. One of these components - falcarindiol was active against methicillin-resistant *S. aureus* (MRSA) too [90, 91]. Different *Levisticum officinale* extracts (methanolic, chloroformic and water) were able to suppress the growth of Gram-negative bacteria and to potentiate the effect of antibacterial drugs, most probably by efflux inhibition [93]. Insecticidal effect of *Levisticum officinale* extract was also reported [94].



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Bacteriostatic properties have been attributed to quercetin (against *Ps. aeruginosa*, *H. pylori*, *E. coli*, *S. aureus*, *S. enteriditis*, etc.), as well as antiprotozoal (against *Toxoplasma*, *Babesia*, *Theileria*, *Trypanosoma*, *Leishmania*) and some antiviral activity [95]. Kaempferol reveals antibacterial (against *H. pylori*, *E. coli*, *S. aureus*, *S. enteriditis*, etc.) and antifungal activity [96-98]. Rutin also was able to suppress the growth of different bacteria, viruses and fungi [99]. A study by Ragunathan and Ravi suggests that the possible mechanism of antibacterial action of quercetin is inhibition of protein synthesis and that of rutin – inhibition of folic acid synthesis [100]. An intracellular target for quercetin in bacteria may also be the enzyme DNA-gyrase [101]. Kaempferol and quercetin were active against some fungi as well [102]. There are some data about possible antibacterial activity of anthocyanins [103].

The antibacterial activity of chlorogenic acid is due to disruption of cell membrane [104], especially in Gram-negative bacteria [105]. This phenolic acid has been effective against influenza A [106] and hepatitis B virus [107], as well as against some fungi [108]. Ferulic and gallic acids have also demonstrated antibacterial properties [109]. Gallic acid possesses antifungal [110] and antiviral activity [111]. Ellagic acid exerts antibacterial action against *H. pylory in vivo* [112]. Extracts with high concentration of ellagic acid have demonstrated activity against other bacteria [113, 114] and fungi [115] as well.

***Hepatoprotective effect***

*Levisticum officinale* water extract exerts protective effect in rat hepatocytes with reactive-oxygen-species-induced (by the pesticide paraquat) toxicity [116].

The flavonoids quercetin, kaempferol, rutin, and anthocyanins have been effective hepatoprotectors in different models of liver injury [117-120].

Chlorogenic acid was found to be hepatoprotective in different models of hepatotoxicity, such as carbon-tetrachloride-induced liver fibrosis [121] and LPS-induced chronic liver injury [122]. Ferulic, gallic and ellagic acids exert hepatoprotective effect in models of paracetamol-induced [123-125] and carbon-tetrachloride-induced [126, 127] hepatotoxicity, the protective effect of ellagic acid being comparable to that of silymarin [128].

***Protective effects in the genitourinary system***

*Levisticum officinale* exerts diuretic (aquaretic) effect [129]. *Levisticum officinale* extracts were able to stimulate the motility and viability of bovine spermatozoa [130].

The flavonols quercetin, kaempferol and rutin, and the anthocyanins found in *Levisticum officinale* exert nephroprotective effect in different models of renal injury. This renoprotection was due to modulation of intracellular pathways like ERK and NF-κB, leading to reduction of the expression of pro-inflammatory factors (NFκB, TNF-α, caspase-3) [131-134].



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Chlorogenic and ellagic acids were able to alleviate cisplatin-induced nephrotoxicity in mice [135,136]. Ferulic and gallic acids ameliorate gentamicin-induced renal damage in rats, probably through activation of PPAR-gamma receptors [137, 138].

Protective effect of quercetin, rutin, anthocyanins, chlorogenic, gallic and ellagic acids in different *in vitro* and *in vivo* models of male reproductive toxicity was observed [139-143].

***Additional effects of phenolic substances in L. officinale***

***Cardiovascular protection***

According to many *in vivo* studies, quercetin exerts versatile positive effects in the cardiovascular system, including antihypertensive, anti-dyslipidemic, anti-ischemic and anti-atherosclerotic [144]. Quercetin and kaempferol derivatives were able to prevent platelet aggregation *in vitro* [145]. Siti and al. found that rutin alleviates cardiac hypertrophy, remodeling and fibrosis and exerts cardioprotection [146]. There are some data about possible antihypertensive effect of this flavonoid [99]. Anthocyanins possess significant cardiovascular protective properties. These had been investigated in different cardiovascular-disease models. Epidemiological studies reveal significant decrease in the cardiovascular risk in people with high anthocyanin-rich-foods intake [45]. Chlorogenic, ferulic, gallic and ellagic phenolic acids were reported to possess antihypertensive action [29, 147-149].

***Antiosteoporotic effect***

Quercetin application causes improvement in the markers of bone mineral homeostasis and bone turnover [150]. Kaempferol alleviates osteoporosis *in vitro* and *in vivo* by interfering with ubiquitous signaling pathways, including BMP-2, NF-κB, regulation of estrogen receptor, MAP kinase, mTOR and others [151, 152]. Rutin was also able to prevent osteoporosis *in vitro* and in rodent osteoporosis models [153, 154]. Anthocyanins were able to suppress osteoclast and stimulate osteoblast function thus preventing osteoporosis in different models as well as human studies [155]. The phenolic acids chlorogenic [156, 157], ferulic [158, 159] and ellagic [160] prevent osteoporosis *in vitro* and *in vivo* by suppression of osteoclast function and other mechanisms.

***Other effects***

Quercetin's antioxidant, anti-inflammatory, neuroprotective, vasculoprotective and other actions contribute to beneficial effects in many ocular diseases including cataract, glaucoma and different types of retinopathies [161].

Kaempferol was reported to exert antiallergic (antiasthmatic) effect in a model of guinea-pig ovalbumin-induced allergic airway inflammation by improving chronic inflammation and other mechanisms [162].



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## Conclusion

*Levisticum officinale* is a plant exerting many beneficial health effects: antioxidant, anticancer, neuroprotective, metabolic regulatory, antibacterial, hepato- and nephroprotective. These effects are most probably due to the polyphenolic components of the plant. Flavonoids and phenolic acids found in lovage are reported to possess also other beneficial effects like cardioprotective and antiosteoporotic. More investigation is needed to reveal the full health-promoting potential of *Levisticum officinale*.

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