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REVIEW ARTICLE

The Pharmacology of *Apium graveolens.* - A Review

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ABSTRACT

Apium graveolens (celery) contained carbohydrates, flavonoids, alkaloids, steroids, glycosides, phenols, furocoumarins, volatile oils, sesquiterpene alcohols, fatty acids and wide range of trace elements. The previous pharmacologic studies showed that *Apium graveolens* exerted gastrointestinal, cardiovascular, cytotoxic, antimicrobial, antihelminthic, hypolipidemic, anti-inflammatory, central nervous and many other pharmacological effects. The objective of the present review is to highlight the chemical constituents and the pharmacological and therapeutic effects of *Apium graveolens.*

KEYWORDS

Apium graveolens, Pharmacology, Chemical constituents

INTRODUCTION

Apium graveolens (celery) belongs to the Apiaceae family is native for Eurasia, but it is nowadays cultivated and consumed all over the world[1]. The leaves, stalks and seeds of the plant are used for arthritis, rheumatism, gout, urinary tract inflammation, and specifically for rheumatoid arthritis with mental depression. Celery is also used as a diuretic, for regulating the bowels, for glandular stimulation, gall and kidney stones, as a prophylactic for nervous agitation, for the loss of appetite and exhaustion and as antihelminthic[2-3]. The preliminary phytochemical analysis revealed the presence of carbohydrates, flavonoids, alkaloids, steroids, glycosides and wide range of trace elements in the methanolic extract of seeds of *Apium graveolens*[8-9]. Celery also contained phenols, furocoumarins, volatile oils, sesquiterpene alcohols and fatty acids[10-27]. The previous pharmacologic studies showed that *Apium graveolens* exerted gastrointestinal, cardiovascular, cytotoxic, antimicrobial, antihelminthic, hypolipidemic, anti-inflammatory, central nervous and many other pharmacological effects[28-42]. The objective of the present review is to highlight the chemical constituents and the pharmacological and therapeutic effects of *Apium graveolens.*

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Physicochemical Properties

Moisture : 5-11% (seeds), 80.3-93.5% (leaves), total ash 6.9-11.0% (seeds), fiber 1.4-102% (seeds), cold water extract : 5.9-12.9 % (seeds), and ash soluble in acid : 0.5-4.0%[7]

Chemical Constituents

The preliminary phytochemical analysis revealed the presence of carbohydrates, flavonoids, alkaloids, steroids and glycosides in the methanolic extract of seeds of *Apium graveolens*[8].

The analysis of wild and three different regions celery showed that they contained 1.12-1.98% ash , 2.21-3.14 % fat, 5.68- 7.53 % protein, 15.87-18.28 % vitamin C and 1.89-2.97 mg / g beta carotene. They also contained the following minerals; Cr 0.11-0.73 , Se 0.08-1.32 , Cd 0.31-

1.66, Pt 0-2.63, Pb 2.37-5.12, Ni 2.01-5.5, Zn 11.96-15.61 , Mn 35.3-39.3, Cu 39.98-56.90, Fe 101.4-305.2, Mg 243-556, Ca 403-709, K 1235-2166, P 3243-4667, Na 4113-5333 mg / 100g.[9].

Celery contained phenols and furocoumarins. Furocoumarins included celerin, bergapten, apiumoside, apiumetin, apigravrin, osthenol, isopimpinellin, isoimperatorin, celereoside, and 5 and 8-hydroxy methoxypsoralen. Phenols (155.41-177.23mg/100g) included graveobioside A and B, apiin, apigenin, isoquercitrin, tannins (3.89-4.39 mg /100 g) and phytic acid (19.85-22.05mg/g)[9-16]. Celery seeds, stems and leaves oil (2.5-3.5%) contained volatile oils, sesquiterpene alcohols (1-3%) and fatty acids, the compound isolated were included selenine (10-15%) , limonene (60%), β-pinene, camphene, cymene, limonene, α-thuyene, α-pinene, β-phellendrene, p-cymene, γ-terpinene, sabinene terpinolene, myristicic, myristic, linoleic, petroselinic, palmitoleic, palmitic, oleic, myristoleic, stearic acid, santalol, β-eudesmol, α-eudesmol, sedanenolide, 3-n-butyl phthalide and phthalide. Celery tuber also contained methoxsalen (8-methoxypsoralen), 5-methoxypsoralen and the allergen profilin (Api g1)[17-27].

Pharmacological Effects

Gastrointestinal Effects

The antiulcerogenic activity of *Apium graveolens* extracts was evaluated in rats by the HCl/EtOH method. Inhibition of gastric lesions by *A. graveolens* extracts was dose-dependent for both aerial part (53–76%) and seeds (51–95%) extracts. The methanolic and aqueous extracts in a dose of 300 mg/ kg exhibited highly significant inhibition of gastric lesions (91% and 95%, respectively) which was similar to that induced by omeprazole (94%)[17]. *Apium graveolens* boiling water extract (5%) inhibited the mean height of rabbit jejunum smooth muscle contractions to 35% in comparison with normal contractions[28]. The methanolic extracts of the seeds of *Apium graveolens* possessed antihepatotoxic effect on rat liver damage induced by a single dose of paracetamol (3 g/kg orally) or thioacetamide (100 mg/kg sc) by histopathology and monitoring of liver functions (serum transaminases, alkaline phosphatase, sorbitol dehydrogenase, glutamate dehydrogenase and bilirubin in serum)[29].

Antimicrobial and Antihelminthic Effects

Essential oil and aqueous extract prepared from the aerial parts of *A. graveolens* were tested to determine their antibacterial activity. Essential oil of *A. graveolens* was strongly inhibitory against *Escherichia coli* and moderately inhibitory against *Pseudomonas aeruginosa* and *Staphylococcus aureus*[17]. *Apium graveolens* boiling water extract showed a wide zone of inhibition of *E.coli* growth in concentration of 5%[28]. The antimicrobial activity of *the* liquid carbon dioxide extracts of *Apium graveolens* were tested against *Escherichia coli*, *Listeria monocytogenes*, *Citrobacter freundii*, *Hafnia alvei*, *Salmonella typhimurium*, *Bacillus cereus*, *Enterococcus faecalis*, *Enterobacter aerogenes*, *Staphylococcus aureus* and *Proteus vulgaris*. It was found that all the investigated leaf extracts were effective inhibitors of *H. alvei*, *S. aureus*, *E. coli*, *Bac. Cereus*, *E. faecalis* and *E. aerogenes*, however the extracts isolated from the roots were less effective; all of them possessed high activity only against *B. cereus* and *E. faecalis.* *C. freundii* and *P. vulgaris* were resistant against celery extracts isolated both from roots and leaves[27].

The hexane, chloroform, methanol and water extracts showed various degrees of inhibition of bacterial growth when tested against *Escherichia coli*, *Bacillus subtilis*, *Shigella flexneri*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*, ranging between 6 to 14 mm (zone of inhibition). The methanolic extract of all the examined celery showed positive antibacterial activity against all strains. Similarly, antifungal potential of the celery was determined against *Trichphyton longifuss*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani and Candida glabrata* in concentration 200 µg/ml of dimethyl sulphoxide[9]. *A. graveolens* seeds have been proven to possess nematocidal activity

against *Caenorhabditis elegans* and *Panagrellus redivivus*, antifungal activity against *Candida albican*, *C. kruseii* and *C. parapsilasis*, and mosquitocidal effects against *Ae. aegypti* fourth-instar larvae[5,29-30]. *Apium graveolens*, was investigated for anti-mosquito potential, including larvicidal, adulticidal, and repellent activities against *Aedes aegypti*. The ethanol extracted *A. graveolens* possessed larvicidal activity against fourth instar larvae of *Ae. aegypti* with LD_{50} and LD_{95} values of 81.0 and 176.8 mg/L, respectively. The abnormal movement observed in treated larvae indicated that the toxic effect of *A. graveolens* extract was probably on the nervous system. In testing for adulticidal activity, celery extract exhibited a slightly adulticidal potency with LD_{50} and LD_{95} values of 6.6 and 66.4 mg/cm^2, respectively. It showed repellency against *Ae. aegypti* adult females with ED_{50} and ED_{95} values of 2.03 and 28.12 mg/cm^2, respectively. It also provided biting protection time of 3 h when applied at a concentration of 25 g%. Topical application of the ethanol-extracted *A. graveolens* did not induce dermal irritation. No adverse effects on the skin or other parts of the body of human volunteers were observed during 3 months of the study period or in the following 3 months, after stopping the treatment [31].

Regarding the active compounds, sedanolide and two senkyunolides were found to be active against nematode, mosquito larvae and fungi[32].

Cardiovascular and Hypolipidemic Effects

The effects of aqueous and ethanol extracts of *Apium graveolens* (0.5-15 mg/kg) was investigated on the mean blood pressure of anaesthetized rabbits and contractility of isolated atria of the rats. The intravenous administration of aqueous extracts induced the least hypotensive effects (14.35±2.94%), while the ethanol extract caused the greatest fall in the blood pressure (45.79±10.86%). Hypotensive effect of the extracts was partially blocked by atropine (0.3 mg/kg). Both aqueous and ethanol extracts of celery exhibit a negative chronotropic and inotropic actions. Aqueous extract decreased the rate of contractions by 12.88±2.74% and amplitude by 8.73±0.89%. Ethanol extract inhibited the rate of atria contractions by 34.26±5.69% and amplitude by 25.40±3.61%. Pretreatment of rat atria with atropine (1 μM) partially blocked the inhibitory response induced by aqueous and ethanol extracts of *Apium graveolens*[33]. Apigenin from *Apium graveolens* exhibited potent antiplatelet activity *in vitro*, inhibiting the aggregation of rabbit platelet induced by collagen, ADP, arachidonic acid and platelet aggregation factor, but not that induced by thrombin or ionophore A23187[34].

Many experimental studies showed that *Apium graveolens* significant lowered serum total cholesterol, triglycerides, LDL and VLDL and increased HDL level. *Apium graveolens* also reduced the formation of arterial plaques in experimental studies. However, the mechanisms suggested for lipid lowering action of *Apium graveolens* including inhibition of hepatic cholesterol biosynthesis, increasing faecal bile acid excretion and enhancing plasma lecithin: cholesterol acyltransferase activity and reduction of lipid absorption in the intestine. Some authors mentioned that blood lipids lowering effects was attributed to the compound 3n butylphthalideor (3nB) isolated from *Apium graveolens*, but, the active extract free from 3-n-butylphthalide has been reported to have lipid-lowering action. Instead, thin layer chromatography indicated that polar compounds with sugar or amino acid side chains(s) could be the hypocholesterolaemic constituents of celery extract[35-40].

In evaluation of the protective effects of ethanolic extract of *Apium graveolens* on ritonavir (a protease inhibitor) - induced dyslipidemia. It appeared that concurrent treatment with high dose of ethanolic extract of *Apium graveolens* (150mg/kg) in mice with ritonavir, showed significant improvement in blood lipid profile. However, using of low dose of ethanolic extract of *Apium graveolens* (75mg/kg) showed no significant effects[41].

Cytotoxic Activities

Apium graveolens seeds have been assessed for chemopreventive activity. The antiproliferative effect of the methanolic extract of *Apium graveolens* was evaluated *in vitro* on two human cell lines (DLA, Dalton's lymphoma ascites; L929, Mouse lung fibroblast). Typical morphological changes including cell shrinkage, chromatin condensation and characteristic DNA ladder formation were induced by *Apium graveolens*. Antitumor screening by the short-term cytotoxicity study with DLA cells showed that the *Apium graveolens* extracts exhibited a dose dependent inhibition of the growth. The extract was found to be cytotoxic towards L-929 cells in 72 hrs MTT assay and concentration required for 50% cell death was 3.85µg/ml[42]. In an *in vitro* study, sedanolide, a natural phthalide from celery seed oil, showed protective effects against hydrogen peroxide (H_2O_2) - and tert-butyl hydroperoxide (tBOOH)-induced toxicity in HepG2 and CaCo-2 cells [26].

Anti-inflammatory Activity

Apium graveolens exerted anti-inflammatory effects in the mouse ear test and against carageenan induced rat paw odema[43], therefore *Apium graveolens* was recommended in arthritis and back pain[3,21,44].

Central Nervous Effects

The anti-depressant effect of methanolic extract of *Apium graveolens* seeds (AGM) was investigated using two behavioral models in *in-vivo* study, the AGM (100, 200 mg/kg) produced significant anti-depressant effect on mice and rats in both forced swim test and tail suspension test , its action was found to be similar to imipramine. The anti-depressant effects of AGM were more prominent at 200 mg/kg when compared to lower dose of same fraction[8].

3, n-butylphthalide and sedanenolide isolated from celery oil showed weak sedative activity, prolonged pentobarbital narcosis, and induced sleep immediately following recovery from a prior barbiturate treatment in mice[45].

Contraindications and Adverse Effects

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages. Nevertheless, because of the kidney-irritating effect of the volatile oil, the drug should not be administered in the presence of kidney infections. Latent yeast infections of the plant could cause the furanocoumarins content of the fresh root to rise to 200 times its original level under storage conditions. For this reason, the relatively large amounts of furanocoumarins of yeast infected celery, could lead to phototoxicoses[3]. Celery should be used with caution in patients with fever. It is contraindicated in pregnant, lactating women and epileptic patients[46].

Dermatitis and phototoxic skin reactions from celery in some farm or grocery store workers were reported. However, after local application, hot sensations, or rashes were observed in the skin of human volunteers during the treatment[47-48].

Dosage

The daily dosage of the seeds is 1.2 to 4 g**.** Pressed juice of the fresh plant: 23 g (15 ml) 3 times daily[3].

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