REVIEW ARTICLE

A REVIEW ON ETHNO-MEDICINAL USES, PHYTO-CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL EVIDENCE OF *APIUM GRAVEOLENS* LINN.

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ABSTRACT

Apium graveolens Linn., popularly known as Karafs or Celery, belongs to family Apiaceae. It has been used in traditional system of medicine for a long time, for the treatment of the various ailments like bronchitis, asthma, liver and spleen diseases, gout, anuria, amenorrhoea, renal and vesicular calculi, renal colic, strangury and many more. *A. graveolens* Linn. contains a variety of chemical constituents which are medicinally important, such as flavonoids, alkaloids, glycosides, steroids. Whole plant contains medicinal value but seeds and roots are more commonly used therapeutically and are considered one of the best diuretic and lithotriptic drug according to Unani literatue. The present review is therefore, an effort to give a detailed study in pharmacognostical, phytochemicals and pharmacological properties.

Keywords: *Apium graveolens,* Tukhm-e-karafs, Unani medicine, Phytochemical, Pharmacological.

INTRODUCTION

Tukhm-e-Karafs are dried seeds of *Apium graveolens* Linn.[1] and monotypic genus of erect herb contains white flowers[2]. As per the Unani classical literature, it is of three types 'Sakhri (*Fitrasaliyun*); Nabti (*Akusaliyun*) and Tari (*Shamarfiyun*)'. Plant is native of Europe but now cultivated in India as a garden crop (Fig. 1), at the base of the North-West Himalaya and outlying hills in Punjab and Western India[4]. The seeds are used as spice[5](Fig. 2). It is an annual glabrous herb, upto 90 cm tall, branched and leafy[6]. The Arab physicians probably obtained their knowledge of it from the Greeks. Dioscorides describes five kinds of Karafs[7]. Wild growing in wet meadows and in ditches, it is acrid and poisonous; when cultivated in dry ground and partially blanched, it is the celery (Karafs) well known as a salad[8]. The plant grows from November to March, flowering and fruiting take place during February to March[1].

TAXONOMICAL CLASSIFICATION:

Kingdom : Plantae

Class : Magnoliopsida

Order : Apiales

Family : Apiaceae

Genus : Apium

Species : *A. graveolens* Linn.

VERNACULARS:

Arabic : Habb-ul-Karafs, Samarul Karafs, Bazrul Karafs; **Bengali**: Chanu, Chani, Randhuni; **Bombay**: Ajmud, Bodiajmoda; **Chinese**: Chin; **English**: Celery, Marsh Parsley, Smallage, Cultivated Celery, Smallage, Wild Celery Ache, Ache cultivee, Ache des malaris, Celerinavet, Celerirave, Celerisauvage; **German**: Eppich, Sellerie, Sumpfeppich, Wassereppich, Wassermark; **Gujarati**: Bodiajamoda; **Hindi**: Ajamo, Ajmud, Bhut-jata, Komal, Karafs, Ajmoda; **Kannada**: Selerina, **Marathi**: Amjoda; **Persian**: Tukhme Karaphas, Badiyane kohi, Tukhme Karafs; **Punjabi**: Bhutjhata, Bhutghata; **Russian**: Dikiy selderei, Selderei; **Sanskrit**: Ajmoda, Andhapatrika, Brahmakoshi, Brahmamusha, Dipyaka, Hastikavari, Karavi, Mayura, Moda, Modadhya, Modini, Ajamoda, Gandhadala; **Spanish**: Apio, Apiocomun; **Tamil**: Ashamtagam, Ajamoda, Celery-keerai; **Urdu**: Ajmod, Tukhme Karafs [1,3-5,7,9-19].

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GEOGRAPHICAL DISTRIBUTION

An erect, annual or biennial herb native to Europe[16], occurring wild in the foot of North-West Himalayas, outlying hills also in Punjab and Uttar Pradesh[1,10,20,21]. This species is distributed from Sweden to Egypt, Algeria, Ethopia, India, Baluchistan and Caucasus[6] and also found in Western Pakistan[22].

In India, Celery recently gained importance, more as a seed crop than as a vegetable. Large scale cultivation is done for procurement of seeds. Celery needs a cool climate and is moisture loving plant, requiring plenty of water and regular irrigation. The seedlings are transplanted later in December or in January and the seed crop is ready by the middle of May. For raising the seed crop, the seedlings are normally planted in the field in rows 45 cm apart. Hot water treatment of seeds is successful in reducing the incidence of blights. The seed crop is ready for harvest when the flowers lose their white colour and become reddish. The plants are cut and left in the field for 2-3 days for drying and then threshed with sticks to bring out the seeds. The seeds are winnowed through different sieves for grading[63].

MORPHOLOGY

A. graveolens Linn. plant is about 50 cm tall with a tap root[3]. This species is grown as an annual in India, which is herbaceous plant with erect stem. The leaves are compound pinnate with long stalks. The flowers are greenish-white in colour, appear in compound umbels[6], short-pedunculated or sessile[23]. The fruits are formed from two compressed carpels, enclosing the seeds, very small dark brown coloured cremocarp, with pungent taste and agreeable odour; roots are adventitious[2].

Macroscopic

The fruits of *A. graveolens* Linn. are mostly separated, the cremocarp is brown, roundish ovoid, laterally compressed and about 1.0-1.5 mm long, 1.5 mm wide and 1.5 mm thick. Each mericarp has five straight, scarcely prominent primary ridges; seeds are orthospermous[1]. The fruits are small in size and when the two mericarp are united it is almost globular, remarkable for its size and prominent ridges[3,7]. The fruit is laterally compressed and about 1.0-1.5 mm long, 1.6 mm wide and 0.5 mm thick[3].

Microscopic

Fruit - The sectional view of the fruit shows a wavy outline. Each mericarp has mostly five ridges having six to nine vittae. The epicarp consists of a single layer of rectangular, thin walled parenchymatous cells coated with irregular cuticles on the outer side. The mesocarp region is mostly composed of several layers of moderately thick walled parenchymatous cells which are polygonal to oval in shape. The sclereids of mesocarp are ovoid to elongate rectangular with a slightly sinuous outline. The walls are slightly thickened at corners. Innermost layer of mesocarp is made up of large brown parenchymatous cells which are elongated rectangular in shape and is attached to the endocarp. The endocarp consists of a single layer of rectangular to square thin walled cells. The testa, which is usually associated with the endocarp, is generally single layered; consisting of thin walled elongated rectangular and mostly collapsed cells, beneath which the endospermic region is composed of several layers of rectangular to polygonal, thick walled parenchymatous cells containing aleurone grains, which are oval to round and are joined in groups. Most of the endospermic cells contain microspheroidal crystals of calcium oxalate. A small amount of vascular tissue and reticulated parenchyma is present. The elements are small and are usually in groups; the vessels show spiral or reticulate thickenings[1,5].

Powder - Powder analysis of the crude drug reveals the presence of fragments of epicarp having stomata, vittae, endosperm, vessels, sclereids and aleurone grains and mirosperoidal crystals of calcium oxalate[1].

BOTANICAL DESCRIPTION ACCORDING TO UNANI LITERATURE

Depending upon the growing place, it is of many types Sahrai *(wild),* Bustani *(cultivated),* Kohi *(found at hilly areas)* and Ma'ai *(grows in water)* but when the term Karafs is used usually it appears to be Bustani *(cultivated)*. Cultivation starts from winter season. The length the plant attains is nearly 1 metre[26]. Roots are black in colour; seeds are 1.5 mm in diameter[22]. Leaves are round and seeds are also round, black, rough surface, bitter in taste[26], look like Anisoon *(Pimpinella anisum)*[18]. Flowers are white Karafs Rumi and Karafs Jabli are stronger than others[19].

PARTS USED

Seeds [5,18,22], Roots[5,10], Leaves[17] and Fruits [3,5,17].

TEMPERAMENT

Hot and Dry[9,14,27], Hot and Dry 2° [15,19,28,29,30,31], Hot 2° and Dry 2° [1,5,26], Hot and Dry3° [32], Hot and Wet[33].

DOSES

3-5 g[1,30], 5-7 g[5], 5-30g[12], 3 masha (2.91 g)[14,26]; 6 masha (5.82 g)[31]

ADVERSE EFFECT

Harmful for cold temperament[30]; pregnant women[94-97]; sometimes causes epilepsy[15,27,30,31].

CORRECTIVES

Anisoon *(Pimpinella anisum)*, Mastagi *(Pistacea lentiscus)*[5,26,34], Maghz-e-Badam *(Prunus amygdalus)* [35]; Ajwain Khurasani *(Hyocyamus niger)*[27,31]; Kahu *(Lactuca sativa),* Gulqand[26].

SUBSTITUTES

Saunf *(Foeniculum vulgare)*[5,26,31], Ajwain *(Tachyspermum ammi),* Zeera siyah *(Cuminum cyminum),* Afsanteen *(Artemisia absinthum)*[26], Ajwain khurasani *(Hyocyamus niger)*[5,27].

PHARMACOLOGICAL ACTIONS

Stimulant *(Muharrik)*[1,4,10,12,13,16,20,25], carminative *(Kasir-e-Riyah)*[1,4,5,7,10,12,13,15,16,25,27,37,38], diuretic (*Mudirr-e-Baul)*[2,4,7,9,13-15,26-28,30,31,32,35,37,39,98]; diaphoretic *(Muarriq)*[1,5], antiseptic (*Dafe ta'affun)*[25,37], emmenagogue (*Mudirr-e-Haiz)*[1,5,7,9,10,12,14-16,25,26,28,30,32,37,38], appetizer (*Mushtahi)*[1,5,9,27,39], lithotriptic (*Mufattit-e-Hasat)*[1,5,7,10,15,26,27,31,32,39], de-obstruent (*Mufatteh sudad)*[1,5,10,12,15,27,28,35], resolvent *(Mohallil)*[10,12,26], tonic (*Muqawwi)*[10,12,16,25,37,38,40], purgative (*Mushil)*[7,10,12,13,16], laxative (*Mulaiyyin)*[13], cardiotonic (*Muqawwi qalb)*[16,39], antiemetic (*Dafe Qai)*[26], sedative *(Musakkin)*[26], digestive *(Hazim)*[26], anthelmintic *(Qatil-e-Kirm)*[13,26,39,99], aphrodisiac (*Muqawwi-e-Bah)*[13,32], abortifacient *(Musqit-e-Janeen)*[13], stomachic *(Muqawwi-e-Meda*)[13], anti-inflammatory (*Dafe-Iltehab*)[3], astringent (*Qabiz)*[39], galactagogue *(Mudirr-e-laban)*[68].

MEDICINAL USES:

Bronchitis *(Warme shobat-ur-riya)*[9,10,12,13,16,19,25,27,28,37], cough (*Su'al)*[19,26], asthma *(Dama)*[13,16,19,25,27,37,31]; fever (*Humma)*[25], liver and spleen diseases *(Amraz-e-Jigar-wa-Tihal)*[10,13,25], flatulence *(Nafkh-e-Shikam)*[1,5,10], colic pain *(Qolanj)*[3,10,13,34], pleurisy (*Zat-ul-Janb)*[1,5], sciatica (*Irqun-Nasa)*[1,5,9,19,28,26], gout (*Niqris)*[1,5,10,16], backache (*Waja-uz-Zuhr)*[1,5], anuria (*Ehtebas-e-Baul)*[1,5,26], amenorrhoea (*Ehtebas-e-Tams)*[13], renal and vesicular calculi *(Hasat-e-Kuliya-wa-Masana)*[1,5,26], rheumatism[10,13,17], anasarca *(Istisqa)*[4,10,13,17,37], renal colic *(Wajaul Kuliya)*[10,16], jaundice *(Yarqan)*[2], constipation *(Qabz)*[12], hypertension *(Zagtud dam qawi)*[41], hypercholesterolemia[41], strangury *(Taqteer-ul-baul)*[15], vomiting (*Qai*)[13], inflammation *(Iltehab)*[13], chest pain *(Waja-us-sadr)*[13], nausea *(Gisyan)*[15], oliguria *(Qillate Baul)*[15,32], conjunctivitis *(Ramad)*[28]; spermatorrhoea *(Jaryan)* [4,26,39].

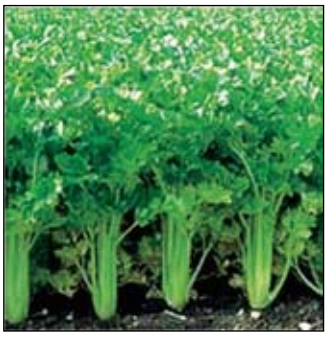

Fig. 1: Plant of tukhme karafs

Fig. 2: Market Sample of Tukhme Karafs

IMPORTANT FORMULATIONS

Jograjgogul, Dabeedulward, Namak Sulaimani[18]; Banadiq-ul-Buzoor, Habb-e-Khubs-ul-Hadeed, Majoon-e-Hajr-ul-Yahood, Majoon-e-Jograj Gugal, Majoon-e-Kalkalanaj, Zimad-e-Sumbul-ut-Teeb, Sikanjabeen Buzoori Moatdil,Safoof-e-Namak Sheikh-ur-Raees, Safoof-e-Moya, Majoon-e-Nankhwah, Safoof-e-Muhazzil[1]; Majoon Jalali, Majoon Fotnaji, Jawarish Zarooni Sada, Jawarish Shehreyaran[5].

PHYSICO-CHEMICAL PROPERTIES

Moisture 5-11% (seeds), 80.3-93.5% (leaves), total ash 6.9-11% (seeds), fiber 1.4-102% (seeds), cold water extract: 5.9-12.9% (seeds), and ash soluble in acid 0.5-4.0%[104].

Essential oil found to possess tranquilizing as well as anticonvulsant activity[42]. Isolation of 3-*N*-butylphthalide and 3-*N*-butyl-4, 5-dihydrophthalide from seeds; choline ascorbate from leaves; seselin, bergapten, rutaretin, celereoin, celeroside, apiumoside, vallein and nodakenin from seeds; octane-4, 5-dione, 2-isopropyloxy-ethane, sabinyl acetate and 1,4-butanediol detected in leaves[43].

Glycosides, steroids, phenolics, flavonoids, sodium, potassium, calcium and iron, essential oils, glucosides, apein[1]. Sulphur, lucosideapiin, volatile oil, lbumen, mucilage and salt[10], Glycosides (coumarins), Anthoxanthin glycosides (Graveobioside-A and Graveobioside-B). Graveobioside-B was shown to be a mixture of apein and chrysoeriol 7-apiosyl glucoside[16].

The seed oil consists of d-limomene, d-selenene, sedanoic acid, anhydride and sedamolide. The leaves and stalks contain vitamins A and C and iron[6]. Several substances have been isolated from the plant, including apein ($C_{26}H_{28}O_{14}H_2O$), graveobioside A ($C_{26}H_{28}O_{16}$), andgraveobioside B ($C_{27}H_{30}O_{15}$). On hydrolysis, a genin and two sugars are produced. Recently, non-glucose, DL-butylphthalide has been isolated from *A. graveolens*[41].

The steam-distillate of the seeds of an Indian sample gave: limonene, 72.2; β-selinene, 12.2; butylphthalide, 2.6; ligustilide, 2.4 and ∞-selinene, 2.1%. However, the major constitutes from a Libyan sample are: apiole, 23.2; sedanolide, 24.4; and 3-butylphthalide, 22.3%. The furocoumarin sangelicin, bergapten, psoralene, tri-methyl psoralene, xanthotoxin, isopimpinellin, oxypeucedanin and sphondin were identified in the plant extract[44].

The oil in general contains limonene (0.22%), β-phellendrene (0.38%), ∞-pinene (0.98%), β-pinene (1.02%), β-element (1.30%), ∞-humulene (1.90%), patchoulene (0.78%), β-selinene (29.23%), pentyl benzene (6.81 %), benzyl alcohol (1.02%), carveol (1.74%), eudesmol (3.0%), geraniol (0.46%), limonene glycol (6.19 %), linalool (0.81%), menthol (1.90 %), terpineol (1.62 %), thujol (0.28%), caryophyllene oxide (3.77%), citral (2.88%), methyl hepatanal (1.05%), caravone (5.93%), dihydrocaravone (3.49%), menthone (0.60%), phenyl ethyl ketone (1.89%), butyl phthalide (8.56%), geranyl acetate (0.85%), exoboranyl acetate (0.28%)[25]. Besides celereoside and nodakenin, three new furanocoumarin glucosides have been isolated from the seeds of *A. graveolens*. The new glucosides have been structurally assigned as (+)-2,3,-dihydro-9-hydroxy-2[1-(6-sinapinoyl) β-d-glucosyloxy-1-methylethyl]-7H-furo[3,2g] [1]-benzopyran-7-one, (–)-2,3-dihydro-9-*O*-β-d-glucosyloxy-2-isopropenyl-7H-furo[3,2*g*] [1]-benzopyran-7-one, and 5-methoxy-8-*O*-β-d-glucosyloxypsoralen[113].

PHARMACOLOGICAL STUDIES

Anti-inflammatory activity

It was found that the cyclooxygenase inhibitory and antioxidant bioassay-directed extraction and purification of celery seeds yielded sedanolide (1), senkyunolide-*N*(2), senkyunolide-J(3), 3-hydroxymethyl-6-methoxy-2,3-dihydro-1H-indol-2-ol(4), ltryptophan.(6), and 7-[3-(3,4-dihydroxy-4-hydroxymethyl tetrahydro-furan-2-yloxy)-4,5-dihydroxy-6 hydroxy methyl tetrahydropyran-2-yloxy]-5-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chromen-4-one. (7). The structures of compounds 1–7 were determined using spectroscopic methods. Compound 4 is reported here for the first time. 250 µg/ mL (COX-II) inhibitory activities at pH 7. The acetylated product (5) of compound 4 also inhibited COX-I and COX-II enzymes when tested at 250 µg/ mL. Compounds 6 and 7 exhibited good antioxidant activity at concentrations of 125 and 250 µg/ mL. Only compounds 1–4, 6 and 7 displayed prostaglandin hendoperoxide synthase-I (COX-I) and prostaglandin hendoperoxide synthase-II inhibitiry activity Compounds 1–3 exhibited topoisomerase-I and -II enzyme inhibitory activity at concentration of 100, 200 and 200 µg/ mL, respectively[45]. The anti-nociceptive and anti-inflammatory effects of the aqueous and hexane extracts obtained from *A. graveolens* L. seeds were evaluated on formalin and xylene-induced ear edema in mice. The hexane fraction was found to be effective against nociception while both fractions showed remarkable anti-inflammatory effect which supported the traditional use of *A. graveolens* in diseases associated with inflammation[46].

Another study showed that the anti-inflammatory activity was observed in croton oil-induced ear test model in mice. Results showed that the potency of the anti-inflammatory activity was seven times lower than the indomethacin. The mechanism involved in the anti-inflammatory activity may be due to the inhibitory activity of its active constituent apein against inducible nitric oxide synthase (iNOS) and nitride oxide (NO) production[78].

Apiuman, a pectic polysaccharide found in celery, has also been found to decrease interleukin-1β and increase interleukin-10 production and diminish the neutrophils migration, which may also be the cause of its anti-inflammatory activity[77]. The stems of the celery plant also possess significant anti-inflammatory activity due to the presence of polar constituents in the aqueous extract[79]. In another study, 70% ethanol was applied using the soaking method. Rats received 25, 50 and 100 mg/kg hydroxy extract of wild celery seed, respectively. Positive and negative control groups received 300 mg of aspirin and 5 mL/kg physiologic serum intraperitoneally, respectively. After half an hour, 100 Ll of 1 % carrageenan was subcutaneously injected to the paws of the rats in all groups and paw size changes were assessed using a plethysmometer every hour for 5 hours after the injection of carrageenan. All doses had an anti-inflammatory effect, and the 100 mg/kg dose of the extract had an antiinflammatory effect similar to aspirin in all of the measured times. Because there was no significant difference between the anti-inflammatory effect of the 100 mg/kg dose and aspirin, the 100 mg/kg dose was recognized as the optimal dose. The hydroalcoholic extract of the seeds of wild celery has a dose-dependent anti-inflammatory effect[105].

Diuretic activity

A. graveolens produced a significant reduction of blood urea nitrogen (5.7±0.05 vs 7.3±0.2 mmol/L), serum creatinine (87.2±0.63 vs 97.3±0.5 mmol/L) and serum Na+ levels (136.8±0.2 vs 142.16±0.7 mmol/L)with non-significant reduction in serum K+ (3.3±0.8 vs 3.8±0.03). There was a significant reduction in calcium deposition

in renal parenchyma in comparison to the control group after ten days of treatment. *A. graveolens* showed a significant diuretic effect that accentuated the excretion of urinary calcium[108]. Hydroalcoholic extract of Tukhm Karafs (seeds of *A. graveolens* Linn.) was studied for diuretic effect on Wistar albino rats. Animals were treated with 1 mL of distilled water, 4 mg/kg of furoseminde and 150 mg/kg and 300 mg/kg of the test drug by oral route with the help of a gastric cannula. The animals were placed singly in metabolic cages and urine sample of each animal was collected after 12 hours to determine the diuretic activity. The volume of the urine and the concentration of sodium and chloride in it were found to have increased significantly, showing diuretic activity. An increase in sum total of sodium and chloride and the sodium and potassium ratio demonstrated saluretic and natriuretic activity, respectively. The study demonstrated that Tukhm Karafs possesses diuretic, saluretic and natriuretic activity[110].

Antifertility

The petroleum ether, alcoholic (90%), aqueous and benzene extracts of the seeds at a dose of 100-150 mg/kg p.o. did not show any anti-implantation or resorptive activity in female rats. The 90% ethanolic extract of the plants at a dose of 250 mg/kg revealed 33.33% anti-implantation activity in female rats[16].

Anti-oxidant activity

The n-butanol extract of celery (*A.graveolens*) seeds ameliorated the lipid per oxidation and anti-oxidant status in streptozotocin-induced diabetic rats[47]. Another study reported that methanol and acetone extracts of *A. graveolens* Linn. has antioxidant activity[48]. *A. graveolens* is a big source of phenolic compounds, which provides a good source of antioxidants[72]. The anti-oxidant activity of Karafs leaf was investigated (by scavenging of the 1,1-diphenyl 2-picryl hydrazyl [DPPH] radical activity) and found to be a strong natural antioxidant by inhibiting oxidantion process[71]. It may be attributed to its antioxidant constituents including L-tryptophan and derivatives of methoxy-phenyl chromenone[45].

In another experiment, the organic and inorganic extracts of celery were tested and both of the extracts were found to a good scavenger of OH and DPPH radicals. *In vivo* experiments with CCl_4-induced toxicity also showed significant protective effects[73].

Anti-depressant Activity

The study showed that methanolic extract of *A. graveolens* seeds possessed significant anti-depressant activity in animal models at the dose of 200 mg/kg, when compared with standard drug mipramine at the dose of 20 mg/kg[49].

Anti-hyperuricemic activity

It is reported that roots of Karafs (*A. graveolens*) showed anti-hyperuricemic activity at the dose of 10 g once a day for the duration of 45 days in human subjects when compared with standard drug allopurinol 100 mg thrice a day for 45 days. It was found that test drug showed more significant anti-hyperuricemic activity[50].

Hepato-protective activity

The methanolic extract of the seeds (200 mg/kg p.o.) revealed hepato-protective activity against rat liver damage induced by a single dose of paracetamol or thioacetamide, as revealed by significant reduction by the extracts in the paracetamol and thio-acetamide induced increase in the levels of serum transminases, viz. glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), alkaline phosphatase (SALP), sorbitol dehydrogenase (SSDH), glutamate dehydrogenase (SGLDH) and serum bilirubin. The proportion of abnormal value percentage of the biochemical parameters in the rats treated with methanolic extracts of the plant revealed 61.9 % protection against paracetamol and thioacetamide-induced liver damage in rats, respectively. The protective effect of the extract was further confirmed by histopathological studies[16].

Another study reported that Karafs (celery) leaves exhibit hepato-protective effect on APAP induced toxicity in a fresh water fish, Pangasius sutchi [51]. Another study reported that methanolic extracts of *A. graveolens* Linn. showed hepato-protective activity when compared with standard drug silymarin[55]. It is also reported that metanolic extract of Tukhm-e-Karafs showed hepato-protective activity in rats against paracetamol induced hepatotoxicity[52]. The methanolic extract of *A. graveolens* seeds was found to have significant activity against paracetamol-induced and carbon tetra chloride-induced liver damage. *A. graveolens* extract dose dependently attenuated the rise in various hepato-toxicity markers including aspartate transaminase, alanine transaminase, alkaline phosphatase, albumin and total protein when compared with silymarin. Histo-pathological studies also showed the reversal of paracetamol induced structural changes of liver tissues[80].

In another study, dietary intake of celery along with chicory and barley attenuates the elevated serum liver enzymes, total cholesterol, triglycerides and improves lipid profile in cholesterol-fed diets[81].

Hypolipidemic activity

It is reported that ethanolic extract of *A. graveolens* revealed hypolipideamic effects in adult male albino rats[53]. Leaves of Karafs showed hypolipidemic effect in diabetic rats[54].

Another study revealed that ethanolic extract of *A. graveolens* (celery seeds) showed anti-dyslipidemic activity against ritonavir induced dyslipidemia in mice[55.] Another study reported that celery leaf extract reduces systolic BP, cholesterol, triglyceride, LDL and VLDL in animal model of fructose-induced hypertension[56].

Tranquillizer and anti-convulsant Activity

The essential oil from the seeds was found to possess tranquilizing activity, as revealed by potentiation of pentobarbital hypnosis in mice and loss of conditioned avoidance response in rats. The anti-convulsant activity of the oil was against supra- maximal electroshock seizure threshhold and metrazol seizure threshold in mice. The animals did not show signs of neural deficit at the ED_{50} levels. Alkaloid fraction isolated from the seeds was studied for its central effects. It showed tranquilizing activity in various animal tests, as evidenced by reduction in spontaneous motor activity, potentiation of pentobarbital narcosis and abolition of conditioned avoidance response. The extract also reduced mortality in aggregated mice by amphetamine. It protected mice in maximal electro-shock seizure pattern test but was ineffective against metrazol and strychnine convulsion in these animals[16].

Anti-microbial activity

The anti-bacterial activity of essential oils of *A. graveolens* (seeds) was detected against *E.coli, B. subtilis, B. pumilus, V. cholera, S. aureus, S. albus, Shigella dysenteriae, C. diphtheria, S. typhi, Sarcina lutea, S. faecalis, S. pyogenes, P. pyogenes, P. solanacearum* and *Micrococcus sp*. The oil obtained from the seeds in its pure form as well as 1:50 and 1:100 dilutions were reported to have anti-bacterial activity against *B.subtiles, E. coli, Sarcina lutea, S. aureus,* and *Pasteurella multocide* and antifungal activity against *A. niger, A. fumigatus, C.albicans, P. regulosum* and *M. gypseum*. The activity decreased with increasing dilutions[16].

Celery volatile oil has been shown to have antifungal activity and it is active against many bacteria viz., *Staphylococcus aureus*, *Staphylococcus albus*, *Shigella dysenteriae*, *Salmonella typhi*, *Streptococcus faecalis*, *Streptococcus pyogenes*, and *Pseudomonas solanacearum.* No activity was observed against *Escherichia coli* or *Pseudomonas aeruginosa*[59]. *A. graveolens* has been found to exhibit anti-bacterial activity against *E. coli*. The activity was more in the ethanolic extracts as compared to the aqueous and hexane extract[82].

Another studied showed the anti adhesive activity of fruits of *A. graveolens* extracts assessed by flowcytometry. Bioassay-guided fractionation revealed the presence of the phthalides senkyunolide and sedanenolide . Phthalides were identified as the main active compounds in polar and semi-polar extracts, which exert strong anti adhesive activity against uropathogenic *E. coli*. The current findings support the traditional use in phytotherapy for urinary tract infections[106].

Insecticidal activity

The seed's oil in doses of 5 and 2.5 % revealed 65 and 25 % inhibition, respectively, against *S. litura*. It did not exhibit any larval toxicity even in the highest dose of 0.01% against *A. aegypti* and *C. fatigans* cultures maintained in the laboratory. The seeds oil in 0.2% concentration after 2 h of application was lethal to *Musca domestica* to the extent of 2.22 % only[16].

Anthelmintic activity

The study has reported that 0.1 % emulsion of oil in 1% aqueous polysorbate 20 produced paralytic effect in 31 minutes and lethal effect in 78 minutes and 0.2% emulsion of oil in 1 % aqueous polysarbate 20 produced paralytic effect in 13 minutes and lethal effect in 44 minutes in comparision to 0.1 % piperazine citrate which produced paralysis in 24 minutes and lethal effect in 70 minutes and 0.2 % piperazine citrate which produced paralysis in 16 minutes and lethal effect in 44 minutes[57].

Anti-cancer activity

Celery contains compounds called coumarins that help prevent free radicals from damaging cells, thus decreasing the mutations that increase the potential for cells to become cancerous. Coumarins also enhance the activity of certain white blood cells, immune defenders that target and eliminate potentially harmful cells, including cancer cells[58].

The phthalides from celery are the most significant bioactive compounds exhibiting many health benefits like protection against cancer, high-blood pressure, and cholesterol. Sedanolide has been reported to be the most active of the phthalides in the reduction of tumors in laboratory animals. Sedanolide and 3-*n*- butyl phthalide isolated from celery seed oil exhibited high activities to induce the detoxifying enzyme glutathione S-transferase (GST) in the target tissues of female mice[61].

After treatment with 3-*n*-butyl phthalide and sedanolide, the tumor incidence was reduced from 68 % to 30% and 11%, re-spectively. About 67% and 83 % reduction in tumor multiplicity was also observed with 3-*n*-butyl phthalide and sedanolide, indicating that 3-*n*-butyl phthalide and sedanolide were both active in tumor inhibition and GST assays exhibiting a correlation between the inhibitory activity and the GST-inducing ability. These results suggest that phthalides, as a class of bioactive natural products occurring in edible umbelliferae plants, may be effective chemo-preventive agents. Oral administration of celery seeds extract 300 mg/kg body wt/day for six weeks prevented the rise in serum marker enzymes viz. glutamate oxaloacetates transami nase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatases (ALP), and levels of bilirubin in DEHP- induced rats. Similarly, reduction in oxidative stress markers has been observed in rat testes when treated with *A. greaveolens* extract[60].

Protection against DOX- induced toxicities

Study showed potential protective effect of *A. graveolens* against cumulative DOX-induced cardiac, hepatic, and hematologic toxicity in male rabbits, probably through a mechanism related to direct and indirect anti-oxidant effects[112].

Spermatogenesis activity

Study evaluated the effect of an aqueous extract of leaves on testicular tissue and spermatogenesis in healthy male rats. Results showed a remarkable increase in seminiferous tubules diameter, testes volume, and number of spermatogonia, primary spermatocytes and spermatozoa. Results indicate that celery leaf extract may improve the spermatogenesis process and sperm fertility parameters[62].

General pharmacology

The LD50 of 50 % ethanolic extract of the fruits has been reported to be more than 1000 mg/kg i.p. in mice and 1000 mg/kg i.p. in rats 21. The lethal doses of fixed and volatile oils extracted from fruits of *A. graveolens* Linn. were determined using Swiss albino mice by the method of probit analysis. The lethal doses (mL/kg) LD1, LD 10, LD 50, LD 90, LD 99 of *A. graveolens* Linn. essential oil were 0.706, 1.261, 2.568, 5.228, 9.333 and that of fixed oil were 0.789, 1.274, 2.291, 4.120, 6.647, respectively[64].

Effect on Central Nervous System

Its fraction (b.p.176^{0}C) containing α-Limonene was devoid of CNS activity. Maximum CNS activity was found in fractions (b.p.180^{0}C) and (b.p.265^{0}C) containing sedanolide and α-selinene, respectively. The ED50 values by the method of potentiation of pentobarbital narcosis and conditioned avoidance response were found to be 0.098 mL/100 g and 0.093 mL/100 g respectively. The ED50 value by the method of maximal electro shock seizures and metrazol seizure-thresholdtest were found to be 0.073 mL/100 g and 0.103 mL/100 g, respectively. The maximal activity of the reaction appears to be against maximal electro shock seizures (ED50 values being 0.073 mL/100 g)[66].

Alkaloid content from the seeds of Karafs was studied for its CNS activity by Kulshrestha. It was found to have tranquillizing effect in various animal models as evidenced by reduction in spontaneous motor activity, potentiating of pentobarbital narcosis and abolition of conditioned avoidance response. The extract was reported to reduce mortality in aggregated mice by amphetamine and protected mice in maximal electro shock seizure pattern test, but was ineffective against metrazole and strychnine convulsions in these animals. The ED50 values (in mg/100 g) were found to be 336 ± 5.5, 29.8 ± 1.4 and 24.3± 3.6 in potentiation of pentobarbital narcosis, conditioned avoidance response test and the test for spontaneous motor activity, respectively. However, ED50 value of reducing mortality in mice in amphetamine group toxicity test was found to be higher. The ED50 in mice was found to be 110.2 ± 7.6 mg/100 g. Thus the safety margin of the extract was shown to be two to three fold in animal experiments. The extract did not induce protection against metrazole and strychnine convulsions but did so against MEST in mice (ED50 – 34.6 mg/ 100g) indicating that the drug acts at a level higher than the brain stem in the central nervous system. This contention was further substantiated by the presence of potent tranquilizing activity in various animal tests. The higher margin of safety and presence of tranquilizing and anticonvulsant activities in the alkaloidal fraction suggest its therapeutic utility in various psychiatric conditions and in grandmal epilepsy[67].

The central depressant activities of 3 *n*-butylphthalide and a new compound, sedanenolide, were studied in mice. While neither compound affects ethanol sedation, they exhibit similar activities in both prolonging pentobarbital narcosis by prior administration of the test compounds and in inducing sleep immediately following recovery from a prior treatment with barbiturate. Weak sedative activity is also shown to reside in both compounds without potentiation[65].

A. graveolens Linn. has been reported to alleviate most of the Sodium valproate (Na-VPA) induced effect in

experimental animals suggesting its protective role through antioxidant activity. Apigenin content was estimated and was found as a major fraction of *A. graveolens* extract[70]. Pre-treatment with *A. graveolens* extract has effectively alleviated most of the Valproic acid (VPA) induced effects, suggesting a protective role of *A. graveolens* extract against experimental VPA-induced toxicity. Apigenin content was estimated and was shown as a major fraction of *A. graveolens* extract[93]. 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[103]. An important role for oxidative stress both as a consequence and as a cause of epileptic seizures has been suggested. Regarding the antioxidant and central nervous system depressant effects of *A. graveolens*, the effects of aqueous extract of the plant on the brain tissues oxidative damage in pentylenetetrazole (PTZ)-induced seizures model were investigated. Male Wistar rats were divided into 5 groups and treated control (saline), PTZ and three doses of the *A. graveolens* extract (100, 500 and 1000 mg/kg) before PTZ. Latency to the first Minimal Clonic Seizure (MCS) and the first Generalized Tonic-Clonic Seizures (GTCS) were recorded. The brain tissues were then removed for biochemical measurements. MCS and GTCS latencies in extract treated groups were significantly higher than that of PTZ group. The malondialdehyde (MDA) levels in the brain tissues of PTZ group were significantly higher than that of control animals. Pre-treatment with the extract resulted in a significant reduction in the MDA levels. Following PTZ administration, a significant reduction in total thiol content was observed in the brain tissues. Pre-treatment with the extract was not effective to prevent from the lowering effects of PTZ- induced seizures on total thiol concentrations in the brain tissues. The present study showed that aqueous extract of *A. graveolens* aerial parts possess anti-convulsant activity[111].

Gastro-intestinal activity

In another study, the effect of volatile oil of seeds of *A. graveolens* Linn. was studied on some hepatic enzymes including SGOT, SGPT and ALP in rats and also to identify the active components of volatile oils by GC/MS. The authors found D-limonene and myrcen as the major active components in volatile oil of *A. graveolens* Linn. They concluded that active ingredients of celery may act as an antioxidant or to decrease the production of free radicals, causing stabilization of hepatocyte membrane and decreasing the release of enzymes into the blood[69].

Larvicidal and mosquito repellent activity

The seed oil of the celery has a strong larvicidal, adulticidal and repellent activity against the A. aegypti larva, the vector of dengue hemorrhagic fever[74,75]. In another study, the mosquito repellent activity of celery oil (with 5 % vanillin) was found better than a number of commercially used repellent[76].

Anti-diabetic Activity

The anti-diabetic effect of the aqueous extract of the celery seed was tested on diabetic rats. It was found that intraperitoneal administration of the extract leads to changes in the lipid profile[83]. Another study revealed the anti-diabetic and antiglycation effects of *A. graveolens*. *S*treptozotozin-induced diabetic rats type 1 and 2 were orally treated with chloroform extract (AG-C) for 30 days. The extract showed good oral glucose tolerance, effect in both normoglycaemic and hyperglycaemic rats, an antioxidant effect decreasing in the serum level of TBARS and gave its optimum antioxidant enzymes, in liver, kidney and pancreas, decreas levels of glucose and glycosylated hemoglobin, reduced total cholesterol, low-density cholesterol and triglycerides, increased high-density cholesterol, aspartate, alanine aminotransferase, alkaline phosphatase, total bilirubin, total protein and insulin in serum and pancreas, and improved glucose metabolism by reducing insulin resistance and stimulating insulin production by protecting pancreatic β-cells from oxidative stress, inhibiting lipid abnormalities and have a hepatoprotective and renalprotective role. The close relationship between lipid peroxidation and nonenzymatic protein glycation (AGEs/ALEs) suggests that the antidiabetic activity of the celery could be due to the synergistic effect of antioxidant activity and antiglycation activity[107]. Another study was done on Wistar rats and divided into five groups (one normal and four diabetic groups). STZ was injected intraperitoneally to induce diabetes. The effects of hexane extract of celery seed and glibenclamide (as a positive control) were compared. Blood samples were analyzed on days 0, 18, and 33, and histopathological evaluations were performed at the end of the study. Glucose, triglycerides, and cholesterol levels significantly decreased, whereas insulin and high-density lipoprotein (HDL) levels increased in the extract-administered groups. Celery seed extract can be effective in controlling hyperglycemia and hyperlipidemia in diabetic rats, and demonstrated its protective effects against pancreatic toxicity resulting from STZ-induction[109].

Analgesic activity

The analgesic effect of celery is attributed to the involvement of celery in the cytochrome P450, which was found to be decreased in the liver homogenate[84].

Another analgesic activity was determined by hot plate method, tail immersion method, tail clip method and writhing test. Petroleum ether extract of seeds of *A. graveolens* (PEESAG) was tested in adult albino swiss mice weighing 20-30 g, at the dose of 50, 75, and 100 mg/kg body weight by different methods. The result show mild to moderate analgesic activity of celery seeds. The petroleum ether extract of celery seeds revealed mild to moderate analgesic activity[102].

Anti-ulcer activity

The ethanolic extract of celery seed significantly protects the indomethacin and cytodestructive agents (80 % ethanol, 0.2 M NaOH and 25 % NaCl) induced gastric ulcer. The results were assessed by biochemical and histopathological analysis of the control and treated samples. Extract significantly protects the gastric mucosa and suppresses the basal gastric secretion in rats possibly through its antioxidant potential that is evident from the presence of antioxidants compound (flavonoids, tannins) in the extract[85].

Anti-spasmodic activity

Ethanolic extract of the *A. graveolens* showed a significant anti-spasmodic activity. It inhibited the ileum concentration in a dose dependent manner. The activity may be attributed due to the presence of a flavonoid, apigenin[86,100].

Anti-platelet activity

A. graveolens has been found to have a potent anti-platelet activity. The effect is due to the presence of apigenin found in the extract. Apigenin inhibits the collagen, adenosine diphosphate (ADP) and arachiadonic acid induced aggregation of platelet. In addition, apigenin also inhibited collagen-ADP-induced aggregation in blood[87].

Cardiotonic activity

It was found that apigenin isolated from the celery inhibited the contraction of aortic ring caused by cumulative concentration of calcium in high potassium medium. This relaxation of thoracic aorta may be attributed to the Ca^{2+} ion suppressing effect of celery through both voltage and receptor operated calcium channels[88]. In another study, derivative of 3-butylpathalide isolated from the celery showed significance cardiotonic activity. It acts by inhibiting the calcium dependent and independent release of glutamate from synaptosomes. It also decreases the nitric oxide (NO) content and NOS activity in the global cerebral ischemia reperfusion model in rats. In addition, it also significantly inhibits the expression of the inducible NOS protein[89]. The celery juice has also been tested on the doxorubicin-induced cardio-toxicity in rats. The content of reduced glutathione, activity of catalase, xanthine oxidase, glutathione peroxidase and lipid peroxidation intensity in the liver homogenate and blood hemolysate was measured. The results showed the cardio-protective activity as compared to toxic group[90].

Cytotoxic activities

A. graveolens seeds have been assessed for chemo-preventive activity. The anti-proliferative effect of the methanolic extract of *A. 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 *A. graveolens*. Anti-tumor screening by the short term cytotoxicity study with DLA cells showed that the *A. graveolens* extract 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 3.85 µg/mL[91].

In another *in vitro* study, sedanolid- a natural phthalide from celery seed oil, showed protective effects against hydrogen peroxide (H_2O_2) and tetra-butyl hydroperoxide (tBOOH)-induced toxicity in Hep G2 and CaCo-2 cells[92].

DISCUSSION

A. graveolens has a significant value in traditional system of medicine. Its seeds have been explored exhaustively for its phytochemical and pharmacological activities such as stimulant, carminative diuretic, diaphoretic, emmenagogue lithotriptic, laxative cardiotonic, digestive, anthelmintic, aphrodisiac, stomachic, anti-inflammatory and astringent. Considering the available literature, the seeds are effective in vesicular calculi, urinary discharge, strangury, sexual debility, dysuria, burning micturation and ammenorrhoea. Though *A. graveolens* has been used extensively over the centuries and scientific evidence with respect to its pharmacological activities is also being generated, more studies at molecular level are needed to further understand the mechanism by which it inhibit the disease condition and the results should be correlated to the phyto-chemicals constituents present in the drug.

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