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Phyto-pharmacology of Celastrus Paniculatus: An Overview

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Abstract

Celastrus paniculatus(CP), a traditional Ayurvedic medicinal plant used for centuries as a memory enhancing, anti-inflammatory, analgesic, sedative and antiepileptic agent.The seed extract has been extensively investigated in several laboratories for their neuropharmacological effects and a number of reports are available confirming their nootropic action. In addition, researchers have evaluated the anti-inflammatory, anti-convulsant and other pharmacological effects of CP preaprations/extracts.Therefore, in view of the important activities performed by this plant, investigation must be continued in the recently observed in the recently observed actions described in this paper.Moreover, clinical studies have to be encouraged, also to evidence any side effects and possible interactions between this herbal medicine and synthetic drugs.

Keywords: Celastrus paniculatus, Ayurvedic, Medicinal plant, nootropic

INTRODUCTION

Celastrus paniculatus Willd. (CP) belongs to family Celastraceae is a large, woody, climbing shrub, distributed almost all over India up to an altitude of 1800 m is known for its ability to improve memory. It also found in middle and South Andamans. Ayurveda, the ancient Indian traditional system of medicine has used this plant seed for prevention and treatment of various diseases. The bark is abortifacient, depurative and a brain tonic. The leaves are emmenagogue and the leaf sap is a good antidote for opium poisoning. The seeds are acrid, bitter, thermogenic, emollient, stimulant, intellect promoting, digestive, laxative, emetic, expectorant, appetizer, aphrodisiac, cardiotonic, anti-inflammatory, diuretic, emmenagogue, diaphoretic, febrifuge and tonic, abdominal disorders, leprosy, pruritus, skin diseases, paralysis, cephalalgia,

arthralgia, asthma, leucoderma, cardiac debility, inflammation, nephropathy, amenorrhoea, dysmenorrhoea. The seed oil is bitter, thermogenic and intellect promoting and is useful in abdominal disorders, beri-beri and sores.

BOTONICAL ASPECTS

Botanical name: Celastrus paniculatus Willd
Family: Celastraceae
Synonym: Celastrus dependens
Vernacular names: Hindi – Malkangani; English – Staff tree; Kannada – Kariganne; Tamil – Valuluvai; Telugu – Malkangani.
Botanical description: Celastrus paniculatus Willd. is a climbing or scrambling shrub, with terete branches; the young shoots and branches are pendulous.
Leaves – glabrous, broadly ovate or obovate, acuminate or acute.
Flowers – unisexual, yellowish-green, borne in terminal, pendulous panicles (flowering throughout the year).
Fruit – capsule, globose, 3-valved, 3-celled, 3-6 seeded. Seeds are enclosed in complete red arillus, ovoid, brown.

PHYTOCHEMISTRY

Chemical examination of fixed oil from the CP seed showed presence of fatty acids, viz., oleic, linoleic, linolenic, palmitic, stearic, crude lignoceric acid, benzoic and acetic acid as volatile acids. The aqueous extract of CP seed contained traces of tannins, reducing sugars but no starch. The petroleum ether extract of husk from the seeds on saponification yielded palmitic and stearic acids. An unidentified sterol was obtained from unsaponifiable fraction.

Several sesquiterpene polyalcohols were reported to be present in the saponified 80% methanolic extract of seed oil and malkanguniol is one of the major constituent. Further, four related alcohols viz., polyalcohol A, polyalcohol B, polyalcohol C, polyalcohol D were isolated from the extract along with malkanguniol. Paraffinic hydrocarbons, β-sitosterol, β-amyrin and a pentacyclic triterpene diol paniculatadiol were isolated from the non-sapanifiable fraction of the CP seed oil. The triterpene diol was assigned structure as olean-12-ene-3β, 29 diol. The fatty acid composition of 4 lipid fractions of CP seed viz., normal triglycerides (20.2%), polar triglycerides (44.4%), polar nonglyceridic ester (23.5%) and non polar non glyceridic ester (11%) was reported. The components constituting the normal triglycerides were identified as palmitooleopalmitin, palmitooleostearin, palmitodiolein, palmitooleolinolein, stearodiolein, triolein and dioleolinolein. A new sesquiterpene polyol ester characterized as 1α, 6β, 8β-triacetoxy-9β-benzoyloxydihydro-beta-agarofuran, along with the three known compounds: 1α, 6β, 8α-triacetoxy-9α-benzoyloxydihydro-beta-agarofuran, angulatueoid C, and 1α, 6β, 8β, 14-tetraacetoxy-9α-benzoyloxydihydro-beta-agarofuran, was isolated from the carbon tetrachloride (CCl_4)-soluble fraction of CP methanolic seed extract. The fleshy arils of CP on extraction with petroleum ether

yielded a phytosterol designated as celastrol (0.15%), a semi-solid fat and a resinous colouring matter. The petroleum ether extract of the fruits showed presence of steroids/terpenoids, alkaloids and absence of flavonoids and saponins. A polyalcohol identified as dulcitol was isolated from the CP flowers. This was the first report of its occurrence in the genus Celastrus. The ethanol extract of CP bark showed presence of saponins and tannins and absence of alkaloids. The petroleum ether extract of the root bark yielded benzoic acid, n-triacontanol, pristimerin, a hydrocarbon, an uncharacterized quinine and a golden yellow oil. Celastrol, pristimerin, zeylasterone and zeylasteral are identified as quinone-methide and phenolic triterpenoids in the root outer bark of CP. A new sesquiterpene ester (Malkangunin) and three sesquiterpene alkaloids (celapanin, celapanigin, celapagin) were isolated from CP. The sesquiterpene alkaloids are derived from a new sesquiterpene tetra-ol (celapanol) which is alternately esterified with acetic, benzoic, nicotinic and β-furoic acids. The various mineral elements in the CP plant was reported as sodium, magnesium, aluminium, potassium, calcium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, molybdenum, silver while strontium and cerium were found to be absent. The 50% ethanolic extract of plant (excluding root) showed presence of tannins (3.52%).

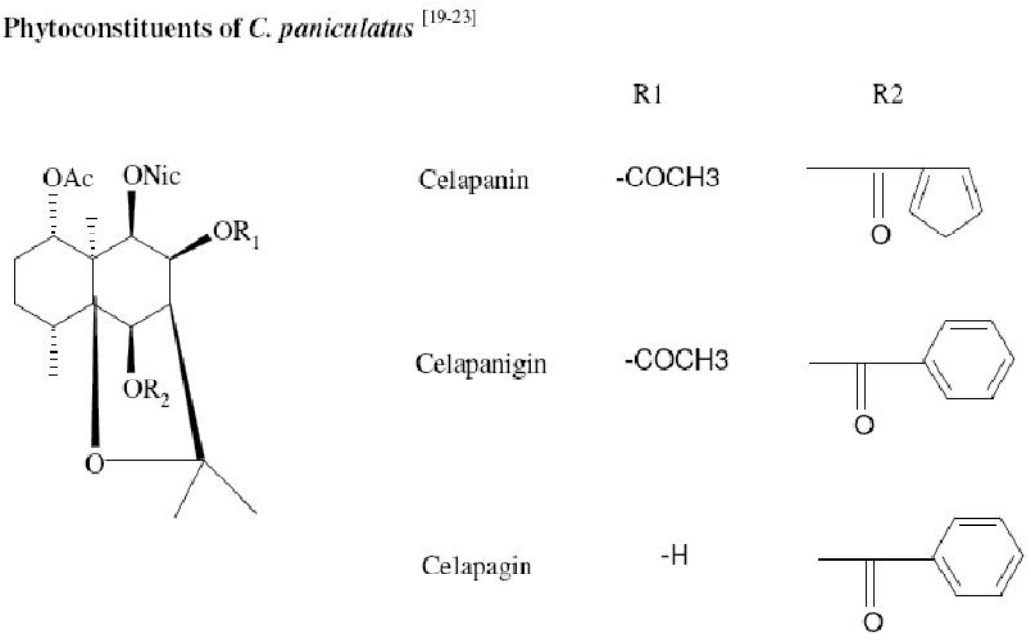
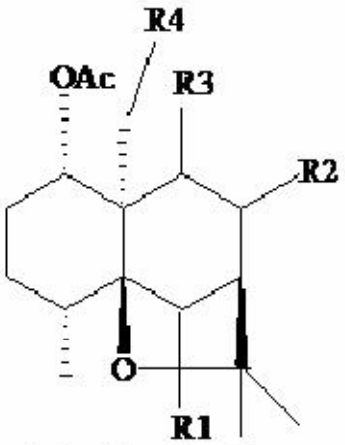


Figure 1. Sesquiterpene alkaloids in *Celastrus paniculatus*



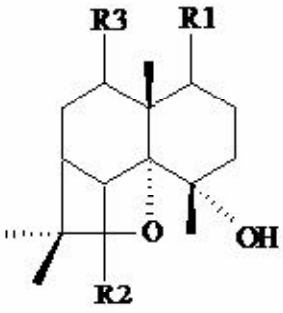
	R1	R2	R3	R4
1	b-OAc	b-OAc	b -OBz	H
2	b-OAc	a-OAc	a-OBz	a-OAc
3	H	b-OAc	a-OBz	a-OAc
4	b-OAc	b-OAc	a-OBz	a-OAc

1. 1a,1b, 8b-triacetoxy-9b-benzoyloxydihydro-b-agarofuran

2. 1a,1b, 8a-triacetoxy-9b-benzoyloxydihydro-b-agarofuran

3. Angulatueoid

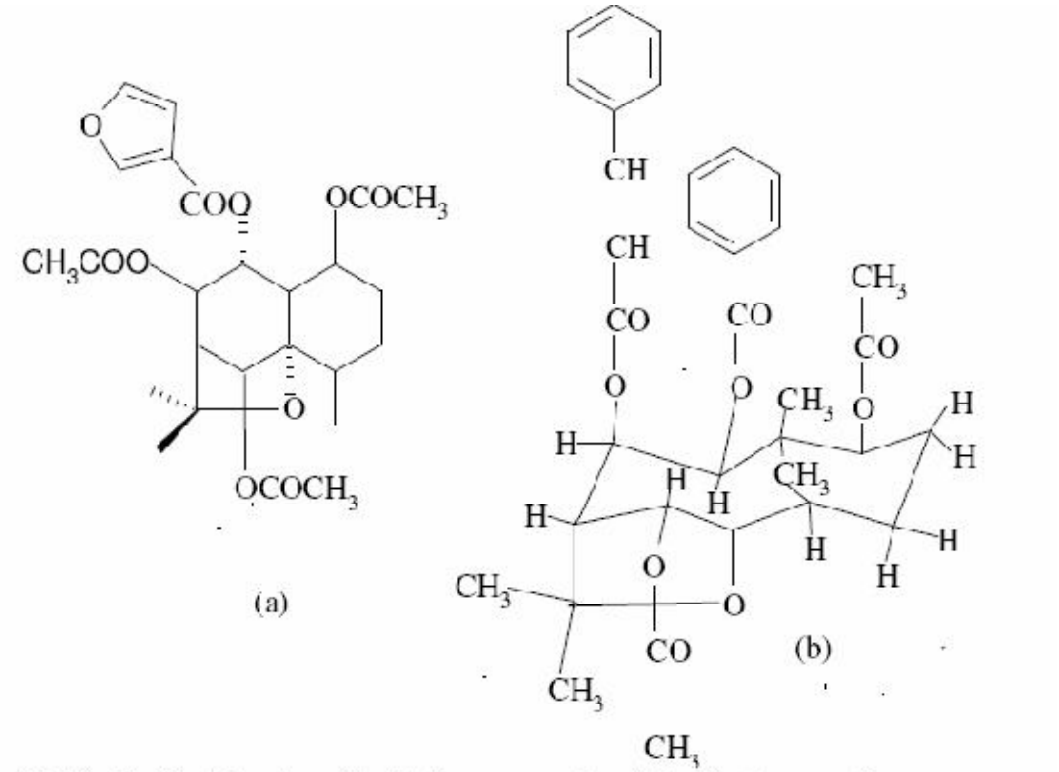
4. 1a, 6b, 8b-tetraacetoxy-9a-benzoyloxydihydro-b-agarofuran



	R1	R2	R3
1	OBz	OAc	OBz
2	OBz	OBz	OBz

1. 1b, 9a-dibenzoyloxy-4a-hydroxy-6a-acetoxy-b-dihydroagarofuran.

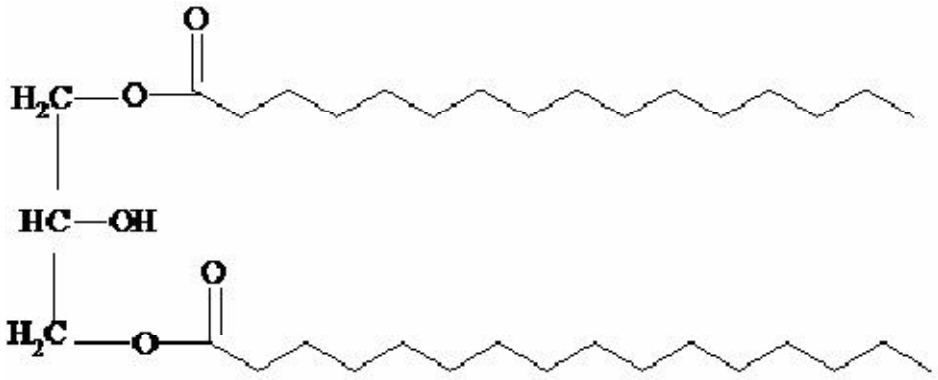
2. 1b, 6a, 9a-triibenzoyloxy-4a-hydroxy-6a-acetoxy-b-dihydroagarofuran.



(a). 1b, 6a, 8b-triacetoxy-9a-(b-furancaronyloxy)-b-dihydroagarofuran

(b). 1b, 6a, -diacetoxy-9b-benzoyloxy-8b-cinnamoyloxy-b-dihydroagarofuran

Figure 2. Sesquiterpene polyol esters from *Celastrus paniculatus*



a, a, Dipalmitoyl glycerol

Figure 3.Glycerol ester in *Celastrus paniculatus*

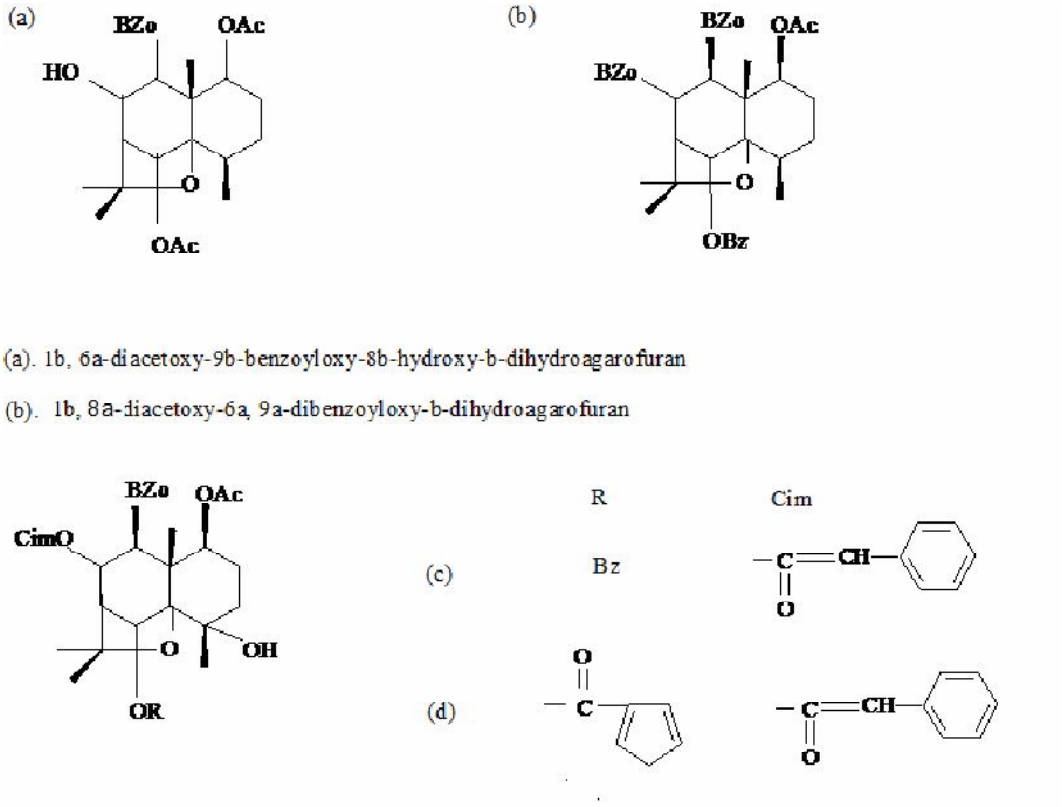


Figure 4. Sesquiterpenoids from *Celastrus paniculatus*

PHARMACOLOGICAL STUDIES

Central Nervous System

The crude CP seed oil administered orally, intramuscularly (i.m.) and intraperitoneal (i.p.) in a dose of 1 g/kg produced sedation in rats. The oil administered orally (100 mg/kg) as an emulsion showed no sedative effect in rabbits. The same emulsion (1 g/kg i.p.) to mice produced mild sedation. Administration of oil (1 g/kg i.m.) to mice showed a significant reduction of movement. CP seed oil given as emulsion showed tranquilizing effect on adrenaline and amphetamine-induced excitement in mice. The anticonvulsant activity of seed oil was examined against leptazole, picrotoxin and strychnine-induced convulsions in rats. It increased strychnine convulsions and reduced leptazole toxicity. It produced calming effect in injected rats, potentiated pentobarbitone sedation and exerted antispasmodic activity with respect to acetylcholine but did not significantly affect the amphetamine toxicity.

An active fraction, designated as Mal III/A was isolated from the CP seed oil. It produced a tranquillizing effect on rats, mice, monkeys and cats in a dose of 200 mg/kg. It potentiated the effect of hexobarbitone and produced hypothermia in mice. The fraction also decreased spontaneous motor activity, amphetamine-induced hyperactivity, orientation hyperactivity and oxygen consumption in mice.

Polyester isolated from CP seed oil when given in doses of 35 and 70 mg/kg, i.p. decreased amphetamine-induced hyperactivity and group toxicity in albino rats. It also reduced the rectal temperature of rats in both the doses. The analgesic effect of morphine at 2 mg/kg in rats was significantly prolonged by the drug in both doses administered 20, 40 and 60 min after injection of morphine. Oral administration of 1 ml of 5% emulsion of seed oil for 3 days enhanced the learning process in albino rats which was comparable to that of vasopressin. The memory process also improved which was more prominent in 7 days treated animals than in 3 days treated animals. The effects were comparable to that of vasopressin. Effects of administration of seed oil on learning and memory in a passive avoidance model as well as on brain contents of biogenic amines viz., norepinephrine (NE), dopamine (DA) and serotonin (5-HT) and their metabolites were studied. Significant improvement was observed in cognition ability of the drug treated rats. The drug did not produce any neurotoxic effect or change in pain threshold in rats. The contents of NE, DA and 5-HT and their metabolites in the brain were significantly decreased in the drug treated group. The effect of CP seed oil was studied using Morris water maze apparatus on the 6 day performance of young adult rats. Chronic oral administration of seed oil (50, 200, or 400 mg/kg) for 14 days completely reversed the scopolamine (0.5 mg/kg)-induced task performance deficit. On the other hand, acute treatment of CP (200 mg/kg) did not significantly reverse the scopolamine-induced impairment in maze performance. Thus, the seed oil of CP, when administered chronically, selectively reversed the impairment in spatial memory produced by acute central muscarinic receptor blockade, supporting the possibility that one or more constituents of the oil may offer cognitive enhancing properties. The aqueous, methanolic, chloroform and petroleum ether extracts of seeds of CP were investigated for their effect on cognitive functions in rats. Only the aqueous seed extract (200 mg/kg, b.w. for 14 days) showed an improvement in learning and memory in both the shuttle-box and step-through paradigms. The effect of aqueous seed extract was also evaluated on oxidative stress parameters and found to show antioxidant properties by decreasing the lipid peroxidation and augmenting endogenous antioxidant enzymes in brain. The aqueous extract of CP (100, 200 and 300 mg/kg for 21 days once a day) was investigated for its cognitive enhancing and antioxidant propery in model of alzheimer's disease in rats. The cognitive behavior was assessed using passive avoidance and elevated plus maze paradigms. Estimation of oxidative stress parameters (malondialdehyde, glutathione, superoxide dismutase and catalase) was carried out in the whole brain upon completion of the behavioral task. The aqueous extract of CP was found to be effective in preventing the cognitive deficits as well as the oxidative stress caused by ICV streptozotocin in rats.

Enriched forebrain primary neuronal cell (FBNC) cultures were used to study the neuroprotective effects of three water soluble extracts of CP seed (CP-WSE) (a room

temperature, WF; a hot water, HF; and an acid, AF) on glutamate-induced toxicity. Pre-treatment of neuronal cells with CP-WSE significantly attenuated glutamate-induced neuronal death. Electrophysiological studies using patch-clamp techniques on N-methyl-D-aspartate (NMDA)-activated whole-cell currents in FBNC were conducted to understand the molecular mechanism of action of CP-WSE. WSE significantly and reversibly inhibited whole-cell currents activated by NMDA. The results suggest that CP-WSE protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function. The petroleum ether extract of seeds was evaluated for antianxiety activity using behavioural disinhibition model of anxiety in rats. It showed significant inhibition of punishment related and reward related suppression of operant behaviour in rats, at dose level of 3.2 g/kg/day for 5 days. The Celastrus oil, extracted from seeds of CP tested at 2 dose levels (1 and 1.5 g/kg) in rats exhibited significant anxiolytic activity and did not produce tolerance. The non-sedative nature and reversal of anxiolytic property of 5-HT_{1A} partial agonist buspirone in the open field test point to the serotonergic mechanism underlying the anxiolysis.

Cardiovascular

The crude CP seed oil administered as emulsion (50-100 mg/kg) produced a gradual fall in cardiac output, bradycardia and marked increase in pulse pressure on isolated heart lung preparation in cat. A similar action with 1 g of emulsified oil was also observed in dogs. The aqueous extract of CP seed showed 50% angiotensin converting enzyme (ACE) inhibition; ethanol extract showed mild activity while the acetone extract was devoid of it.

Antifertility

The seed oil when given in a dose of 0.2 ml/animal/48 h to adult albino rats for 30 days showed antispermatogenic effects as evidenced by vacuolization of seminiferous tubules, germ cell depletion and exfoliation culminating into an arrest in spermatogenesis. The shrunken tubules revealed only sertoli cells and spermatogonia in the final stage of impairment of spermatogenesis. The livers revealed focal necrosis in animals receiving 0.2 ml (i.p.) seed oil for 30 days, but 45 days post treatment these lesions were absent. These results indicate that CP oil may have useful antifertility effects and that the degenerative changes seen in the liver are reversible with time.

Analgesic and Anti-inflammatory

Flowers of CP and whole plant of Tecomella undulata were extracted individually in absolute methanol. Using the hot water tail immersion test in mice and carrageenan induced paw edema in rats both extracts were tested for their oral analgesic and anti-inflammatory potentials. Results showed that CP had both analgesic and anti-inflammatory activities, while T. undulata had only analgesic potential when compared with aspirin.

The seed oil showed anti-inflammatory activity in carrageenan-induced rat paw oedema. The oil in doses of 5 and 10 ml/kg showed 66.60 and 78.78% inhibition of inflammation as compared to 75.75% shown by 100 ml/kg dose of ibuprofen.

Hypolipidaemic

Administration of 50% ethanolic seed extract at 500 mg/kg from day 1 to 120 to hyperlipidaemic rabbits, prevented accumulation of cholesterol and triglycerides in liver and aorta and regressed atheromatous plaques of ascending thoracic and abdominal aorta. The serum cholesterol and LDL-cholesterol levels were reduced by 60.10 and 71.70%, respectively. Increased faecal excretion of cholesterol was observed suggesting that modulation of adsorption was affected.

Antioxidant activity

The methanolic extract of CP plant was investigated for its free radical scavenging capacity and its effect on DNA cleavage induced by hydrogen peroxide UV-photolysis. CP extract showed a dose-dependent free radical scavenging capacity and a protective effect on DNA damage in human non-immortalized fibroblasts. The results indicate that the CP extract exhibit interesting antioxidant properties, expressed by their capacity to scavenge superoxide anion and hydroxyl radical and to reduce the hydrogen peroxide-induced cytotoxicity and DNA damage in human fibroblast cells. Three aqueous extracts (WSEs) obtained from CP seeds: a room temperature extract (WF); a hot water extract (HF); an acid extract (AF) were investigated for the free radical scavenging capacity. All the WSEs exhibited a dose-dependent free radical scavenging capacity for 1, 1-diphenyl-2-picryl-hydrazyl radical (DPPH) and also for superoxide-generated assays (in vitro assays). All the WSEs significantly attenuated hydrogen peroxide-induced neuronal death, and AF was the most effective in protecting the neuronal cells against oxidative injury caused by hydrogen peroxide (H_2O_2). The superoxide scavenging effects of CP seed oil (CPO) and two extracts, ethanolic extract (EE) and methanolic extract (ME), and their neuroprotective effects to H_2O_2-induced oxidative stress and glutamate-induced toxicity was investigated using an enriched neuronal cell culture. CPO and EE showed dose-dependent, free-radical-scavenging capacity, but to a lesser degree than observed for ME. The activity of cellular acetylcholinesterase (AChE) was not affected by CPO, ME, or EE, suggesting that the neuroprotection offered by CPO was independent of changes in AChE activity. Thus data suggest that CPO, ME and EE protected neuronal cells against hydrogen peroxide-induced toxicity in part by virtue of their antioxidant properties, and their ability to induce antioxidant enzymes.

Anti-arthritic activity

The anti-arthritic effect of oral administration of petroleum ether and alcoholic extracts of CP seed on Freund's adjuvant arthritis has been studied in Wistar albino rats. The body weight loss that was found during the arthritic condition was corrected on treatment with petroleum ether and alcoholic extracts of CP seed. The swelling of the paw during the secondary lesions was also markedly reduced. The results indicated that the seed of CP is endowed with anti-arthritic activity.

Wound healing activity

A triterpene compound lupeol isolated from petroleum ether extract of leaves of CP was screened for wound healing activity (8 mg/ml of 0.2% sodium alginate gel) by

excision, incision and dead space wound models on Swiss albino rats (175-225 g). In lupeol treated groups wound healing activity was more significant than the standard skin ointment nitrofurazone. Epithelialization of the incision wound was faster with a high rate of wound contraction as compared with the control group. In dead space wound model the weight of the granulation tissue of the lupeol treated animal was increased indicating increase of collagenation and absence of monocytes.

Antimalarial

Crude solvent extracts from the root bark and stem of CP were screened for antimalarial activity against Plasmodium falciparum using an in vitro culture system. A fraction of the chloroform extract of the root bark showed the highest antimalarial activity. An active principle was isolated and characterized from the chloroform fraction and indentified as a quinonoid triterpene, pristimerin. When tested in vitro against various multidrug resistant isolates of P. falciparum, pristimerin was less active than the conventional antimalarial drugs tested.

Antibacterial

The CP seed oil showed antibacterial activity against Micrococcus pyogenes var. aureus, Micrococcus pyogenes var. albus, Micrococcus pyogenes var. citreus, Bacillus subtilis, Corynebacterium diphtheriae, Salmonella typhosa, Salmonella paratyphi A and B, Escherichia coli, Proteus vulgaris, Pseudomonas pyocyana by cup-plate method. The concentration of oil ranging from 0.4-1% v/v was effective against Micrococcus pyogenes var. aureus and Salmonella typhosa.

The oil at different concentrations (20, 40, 60, 80 and 100%) was tested for in vitro antimicrobial activity against bacteria Escherichia coli, Staphylococcus aureus, Bacillus cereus, Salmonella dysentrica, Klebsiella pneumoniae and Proteus vulgaris and fungi Aspergillus niger, Aspergillus flavus, Penicillium sp. and Trichoderma sp. The oil showed weak antibacterial activity in terms of zone of inhibition against Proteus vulgaris, Staphylococcus aureus and Salmonella dysentrica at 100% concentration.

The aqueous extract of CP seed showed potent antibacterial activity against Bacillus cereus, Klebsiella pneumoniae, Proteus morganii, Proteus vulgaris, Salmonella marcescens, Salmonella typhosa, Salmonella partyphi A, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus lutea, Staphylococcus aureus but was found inactive against Bacillus subtilis and Salmonella paratyphi B.

Antifungal activity

Twenty-eight South Indian medicinal plants were screened for their anti-fungal activity against six species of fungi (Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton soudanense, Candida albicans, Torulopsis glabrata, and Candida krusei). Three plant species extracts, Celastrus paniculatus, Eriodendron anfractuosum and Ficus glomerata showed inhibitory activity against 6 species of fungi.

Acute toxicity studies

CP seed oil was administered orally at a dose of 0.5, 1, 2, 3, 4 and 5 g/kg, b.w. to different groups of rats (n = 8, in each group). During the first 4 h after the drug administration, the rats were observed for gross behavioural changes. The parameters observed were hyperactivity, grooming, convulsion and sedation, loss of righting reflex, increased respiration and hypothermia. Celastrus oil administration up to the highest dose (5 g/kg b. w.) did not produce any toxic effect on the normal behaviour of the rats. No mortality was observed even with the highest dose of CP. The acute oral toxicity study was carried out as per the guideline set by the Organization for Economic Co-operation and Development (OECD). One tenth of the medium lethal dose (LD_{50}) was taken as an effective dose. The LD_{50} cut-off dose for petroleum ether extract and alcoholic extract were found to be 5000 mg/kg and 3000 mg/kg body weight respectively. Hence, the therapeutic doses were taken as 500 mg/kg and 300 mg/kg body weight for petroleum ether and ethanolic extracts respectively.

CP, a traditional Ayurvedic medicinal plant has been used for centuries as a memory enhancing, anti-inflammatory, analgesic, sedative and antiepileptic agent. The seed extract has been extensively investigated in several laboratories for their neuropharmacological effects and a number of preclinical reports are available confirming their nootropic action but the exact mechanism of its actions is still uncertain. It has been suggested that CP, exhibits neuroprotective and cognitive enhancing effects, in part due to its, capacity to modulate the cholinergic system and to contrast oxidative stress. In addition, researchers have evaluated the analgesic, anti-inflammatory, anxiolytic and other pharmacological effects of CP preparations/extracts. Therefore, in view of the important activities performed by this plant, investigation must be continued in the recently observed actions. Moreover, clinical studies have to be encouraged, also to evidence any side effects and possible interactions between this herbal medicine and synthetic drugs.

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