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Biological Studies of the Plants from Genus *Pluchea*

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ABSTRACT

Pluchea is a genus of flowering plant in the Asteraceae family. The genus Pluchea (Asteraceae) comprises 80 species distributed mainly in North and South America, Africa, Asia and Australia. These are native to tropical and warm temperate areas. The plants of Pluchea genus have been used traditionally used as astringent, antipyretic, anti-inflammatory, hepatoprotective, diaphoretic in fevers, smooth muscle relaxant, nerve tonics, laxatives and for the treatment of dysentery, lumbago, leucorrhoea, dysuria, haemorrhoids, gangrenous ulcer and disorders causing cachexia. The chemical investigations on the genus have shown the presence of eudesmane-type sesquiterpenoids, monoterpenes, lignan glycosides, triterpenoids and flavonoids. The present review summarizes the various biological studies done on the extracts and bioactive phytoconstituents from the plants of the genus Pluchea over the past few decades.

Key-words: *Pluchea*, Biological activity, Pharmacological activities, Asteraceae.

INTRODUCTION

An estimated 70% of population around the world use traditional medicines derived from plant species for their treatment and cure[1]. *Pluchea* is a genus of flowering plant in the Asteraceae family. The genus *Pluchea* (Asteraceae) comprises 80 species distributed mainly in North and South America, Africa, Asia and Australia [2]. These are native to tropical and warm temperate areas. The plants of *Pluchea* genus have been used traditionally used as astringent, antipyretic, anti-inflammatory, hepatoprotective, diaphoretic in fevers, smooth muscle relaxant, nerve tonics, laxatives and for the treatment of dysentery, lumbago, leucorrhoea, dysuria, haemorrhoids, gangrenous ulcer and disorders causing cachexia [3-9]. The chemical investigations on the genus have shown the presence of eudesmane-type sesquiterpenoids, monoterpenes, lignan glycosides, triterpenoids and flavonoids. The flavonoids include quercetin,

isorhamnetin, hesperidin, a dihydroflavonol- taxilolin 3-arabinoside and an isoflavonoid-formononetin. The chemical constituents also include lignan glycosides, terpenic glycosides, tertiary bases, a large number of water-soluble quaternary bases, including pluchine 7-O-glucoside [10-20].

In this review, we summarize the various biological studies done on the extracts and bioactive phytoconstituents from the plants of the genus *Pluchea* over the past few decades.

Biological Studies

Anti-inflammatory and Antinociceptive Activities

The anti-inflammatory activity of aqueous extract and dichloromethane extract of *Pluchea sagittalis* was evaluated by carrageenan-foot oedema test. There was a significant inhibition *(p<O.OS)* in rats treated with a single dose of 100mg/kg. The aqueous extract and dichloromethane extract of *Pluchea sagittalis* produced a total inhibition of 50.85% and 41.16% respectively. This study shows that the aqueous and dichloromethane extract of *Pluchea sagittalis* had an antiinflammatory effect in the carrageenan-foot oedema test [21].

The effect of the methanol fraction of *Pluchea indica* and certain standard drugs were evaluated on platelet activation factor (PAF)-induced inflammation, gastric necrosis, ulceration and haematological picture. Administration of PAF (i.v.) for 20 min produced significant alteration in haematological profiles, considerable inflammation, severe gastric mucosal vasocongestion, necrosis and ulceration. Pre-treatment with *P. indica* and certain standard drugs significantly inhibited inflammation and incidences of lowered gastric damage [22].

The influence of the methanol fraction of *Pluchea indica* Less root extract (PIRE) was evaluated *in vivo* for anti-inflammatory activity. PIRE produced significant anti-inflammatory activity against glucose oxidase induced paw oedema [23].

The anti-inflammatory and antinociceptive activities of the ethanolic extract (EE) from aerial parts of *Pluchea quitoc* DC. (Asteraceae) were evaluated in mice and rats. Oral treatment with the EE (1–2 g/kg, p.o.) decreased the paw oedema induced by carrageenan in rats, showed anti-nociceptive effects on the tail-flick test and on acid-induced writhing in mice, and inhibited both phases of pain (neurogenic and inflammatory) of the formalin test in rats. Topical application (EE 1.25, 2.5 and 5.0 mg) inhibited the ear oedema induced by croton oil in mice. The results support the folkloric use of the plant in inflammatory processes [24].

The ethanolic extract of *Pluchea lanceolata* exhibited significant anti-inflammatory activity, which was further investigation after fractionation. The result showed that activity was localized in the hexane fraction, from which □-taraxasterol acetate was isolated which proved to be one of the active constituents. Taraxasterol acetate, isolated from hexane fraction, accounted for only part of the activity of that fraction. It is obvious that there are other active substances present in the hexane fraction which need to be isolated and characterised [25].

Neolupenol, a pentacyclic triterpene isolated from *Pluchea lanceolata* flowers, was studied to determine its anti-inflammatory activity against carrageenin-induced rat-paw edema. The degree of edema inhibition was found to increase with dose as well as time interval and was found to be

maximum at 300 min. Neolupenol, when administered at 100 mg/kg, p.o. was found to exhibit 70% edema inhibition which was greater than that of the reference compound, ibuprofen (50 mg/kg, p.o., 65% inhibition, and 300 min) [26].

Ethanolic extract of *Pluchea indica* leaf (PIL) was used to investigate its anti-inflammatory and antinociceptive activities by using carrageenan- induced oedema model and acetic acid induced writhing test. PIL exhibited significant and dose-dependent anti-inflammatory activity at a dose of 300 mg/kg when administered orally. It was also demonstrated that the i.p administration of PIL at a dose of 10, 30, 100 and 300 mg/kg produced significant inhibition of abdominal constriction induced with 0.6% (v/v) acetic acid in dose dependent manner. These results indicate that PIL exhibits significant anti-inflammatory and antinociceptive effects [27].

The effect of the methanolic fraction of *Pluchea indica* Less root extract was evaluated on various models of inflammation and ulcer to assess the role of fraction on the 5-lipoxygenase pathway of prostaglandin synthesis. Studies presented here reveal significant anti-inflammatory activity of the fraction on arachidonic acid, platelet activation factor and compound 48/80-induced paw oedema. There was significant inhibition of spontaneous as well as compound 48/80-induced histamine release from mast cells. Ulcer studies revealed significant protective action of the fraction on indomethacin, alcohol and indomethacin-alcohol induced ulceration. There was significant decrease of gastric volume and acidity in pylorus ligated rats. Studies also showed, significant protective action of the same on gastric mucosa [28].

A methanolic fraction of a chloroform extract of defatted *Pluchea indica* roots was investigated for its anti-inflammatory potential against several models of inflammation. The extract showed significant inhibitory activity against carrageenin-, histamine-, serotonin-, hyaluronidase- and sodium urate-induced pedal inflammation. The extract inhibited protein exudation and leucocyte migration. The extract also inhibited carrageenin- and cotton pellet-induced granuloma formation as well as turpentine-induced joint oedema and adjuvant-induced polyarthritis. The present observations establish the efficacy of the extract in the exudative, proliferative and chronic stages of inflammation [29].

The ethanolic extract of *Pluchea indica* root exhibited significant anti-inflammatory activity, which was further localized in the hexane fraction, from which Ψ-taraxasterol acetate was isolated which proved to be one of the active constituents [30].

The methanolic fraction of the root extract of *Pluchea indica* Less was investigated for anti-inflammatory effects. The extract, in doses of 50 mg/kg and above (i.p.), was found to cause a significant inhibition of carrageenin-induced oedema in rats. Significant inhibition of granuloma formation was found to occur with the extract in doses of 100 mg/kg and above (i.p.) when tested by the cotton pellet granuloma test in rats. The extract in doses of 100 mg/kg and above caused a significant reduction of paw-diameter in formaldehyde-induced arthritic rats. Significant antipyretic action was also observed to occur with the root extract in doses of 50 mg/kg and above (i.p.), when tested against yeast-induced pyrexia in rats. It may be concluded from the results of the present study that *P. indica* root extract possess potent anti-inflammatory action against both exudative and proliferative phases of inflammation and also significant antipyretic activity [31].

Venom Neutralizing Capacity

The methanol root extracts of *Pluchea indica* (Less) were explored for the first time for neutralization of snake venom *(Viperu russellii)* activity. The *P. indica* root extracts significantly neutralized the viper venom-induced lethality and haemorrhagic activity in albino rat and mouse. Venom-induced coagulant and anticoagulant activity was also antagonized by both the extracts. No precipitating bands were observed between the plant extract and polyvalent snake venom antiserum. These observations confirmed that certain Indian medicinal plants like *Pluchea indica* possess significant snake venom neutralizing capacity and need further examination for their active constituents [32].

The neutralization of viper and cobra venom by β-sitosterol and stigmasterol isolated from the root extract of *P. indica* Less. (Asteraceae) was evaluated in experimental animals. Cobra venom-induced lethality, cardiotoxicity, neurotoxicity, respiratory changes and PLA2 activity were also antagonized by the active component. It potentiated commercial snake venom antiserum action against venom-induced lethality in male albino mice. The active fraction could antagonize venom-induced changes in lipid peroxidation and superoxide dismutase activity. This study suggests that β-sitosterol and stigmasterol may play an important role, along with antiserum, in neutralizing snake venom induced actions [33].

Neuropharmacological Studies

Neuropharmacological studies were conducted in rodents with *Pluchea indica* Less root extract. On investigation with different experimental models it was found that the extract produced alteration of behaviour pattern, reduction in spontaneous motility, prolongation of pentobarbitone-induced sleep, suppression of aggressive behaviour pattern and of the conditioned avoidance response. The observations suggest that the root extract of *P. indica* possesses a potent central nervous system depressant action [34].

Antioxidant Activities

Cadmium intoxication induces lipid peroxidation and causes oxidative damage to various issues by altering antioxidant defence system enzymes. At 24 h after treatment with a single intraperitoneal dose of cadmium chloride (5mg kg $^{-}$1), swiss albino mice showed a significant increase in the levels of malanodialdehyde and xanthine oxidase ($P < 0.001$), and a concomitant depletion of renal glutathione, catalase ($P < 0.001$) and other antioxidant enzymes. $CdCl_2$ also led to a simultaneous increase in micronuclei formation ($P < 0.001$) and chromosomal aberrations ($P < 0.05$) in mouse bone marrow cells. Oral pre-treatment with *Pluchea lanceolata* extract at doses of 100 and 200 mg kg^{-1} for 7 consecutive days before $CdCl_2$ intoxication caused a significant reduction in malanodialdehyde formation and xanthine oxidase activity ($P < 0.001$). A significant restoration of the activity of antioxidant defence system enzymes such as catalase, glutathione peroxidise ($P < 0.05$), glutathione-S-transferase and glutathione reductase ($P < 0.001$) was observed. A significant dose-dependent decrease in chromosomal aberrations and micronuclei formation was also observed ($P < 0.05$). The results indicate that pre-treatment with *P. lanceolata* attenuates cadmium chloride induced oxidative stress and genotoxicity by altering antioxidant enzymes and reducing chromatid breaks and micronuclei formation [35].

The methanol fraction of *Pluchea indica* Less root extract (PIRE) was evaluated *in vitro* for free radical-scavenging activities, CCl_4-induced lipid peroxidation and the metabolism of arachidonic

acid by lipoxygenase. PIRE showed inhibition of hydroxyl radical and superoxide generation, lysis of erythrocytes induced by hydrogen peroxide, CCl_4-induced lipid peroxidation and also dioxygenase activity of lipoxygenase (both in the presence and absence of hydrogen peroxide) [23].

Extracts from *Pluchea indica* were screened for flavonoid content, total phenolics, and antioxidant activity. *Pluchea indica* Less. extracts inhibited linoleic acid oxidation and had the DPPH, ABTS, and ferric cyanide antioxidant capacities. Therefore, the plant may contribute to dietary antioxidant intake [36].

The antioxidant activity of *Pluchea arabica* was investigated using *in vitro* DPPH and phosphomolybdenum assay methods. The aqueous ethanol extracts of *Pluchea arabica* showed the inhibition of DPPH radical at 89–93%, after 15 min of incubation at a test concentration of 50 lg/ml. The total antioxidant capacity as gallic acid equivalents of 1790 mg/g of ethanol extracts were obtained for *P. crispa* in the phosphomolybdenum assay [37].

The scavenger activity of the hydroxyl radical produced in Fenton reaction was evaluated. The oxidation of L-epinephrine to adrenochrome permitted the detection of the hydroxyl radical by spectrophotometry and its possible scavenging by hydroquinone, a well known antioxidant. The method was used to evaluate the antioxidant activity of *Pluchea carolinensis* leaves [38].

The antioxidant activities of the methanolic root extract of tissue cultured *Pluchea indica* (L.) Less. (Family: Asteraceae) was evaluated in various in vitro models. The hydrogen donating ability of the methanol extract of *Pluchea indica* (MEPI) was measured in the presence of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical. A 400 μg/ml of MEPI and Ascorbic acid exhibited 91.23% and 96.35% inhibition, respectively, and the IC_{50} values were found to be 12.35μg/ml and 67.65 μg/ml for MEPI and ascorbic acid respectively. The effect of MEPI on reducing power was studied according to the reaction of Fe^{+3} to Fe^{+2}. The reducing power of the extract increased with the increasing amount of the concentration. The methanolic root extract showed effective reducing power, and inhibition of β-carotene bleaching. All the above in vitro studies clearly indicate that the methanolic extract of *Pluchea indica* (MEPI) has a significant antioxidant activity [39].

Antiulcer Activity

The methanolic fraction of *P. indica* root extract was found to possess significant antiulcer activity in different experimental animal models. In preventive antiulcer tests, significant protective actions in acetylsalicylic acid, serotonin and indomethacin-induced gastric lesions were observed in experimental rats. The extract also afforded significant protection to chemically-induced duodenal lesion in guinea pigs. Significant enhancement of healing process in acetic acid-induced chronic gastric lesions was also observed in the extract-treated animals [40].

Trypanocidal Activity

Four compounds active against the epimastigote forms of *Trypanosoma cruzi*, the causative agent of Chagas' disease, were isolated from the hexane extract of *Pluchea quiroc* L. (Compositae). The flavone casticin, identified on the basis of its spectroscopic characteristics,

along with PQU19B, 19G and *BA*, the structures of which are in the process of identification, did not show significant activity against the infective bloodstream trypomastigote forms of the parasite. Despite their considerable activity against epimastigotes, the compounds isolated from *P. quitoc* were much less effective as blood chemoprophylactics than gentian violet. As a consequence, a reinvestigation of *P. quitoc* using the more laborious and risky assay with the infective blood form will have to be carried out in order to detect substances active against the trypomastigotes [41].

Hepatoprotective Activity

The methanol fraction of the extract of *Pluchea indica* roots exhibited significant hepatoprotective activity against experimentally induced hepatotoxicity by carbon tetrachloride in rats and mice. The extract caused significant reduction of the elevated serum enzyme levels (AST, ALT, LDH and serum alkaline phosphatase) and serum bilirubin content in acute liver injury. A significant increase of reduced serum total protein, albumin and albumin/globulin ratio was also observed on extract treatment. The extract significantly reduced the prolonged pentobarbitone-induced sleeping time and also caused a significant reduction of plasma prothrombin time in comparison with CC1,-treated animals. The extract caused significant reduction of the increased bromosulphalein retention by CCl_4 treatment. These findings suggested a potent hepatoprotective effect of the extract of *Pluchea indica* roots [42].

Larvicidal Activity

The volatile fractions obtained by hydrodistillation of the fresh leaves of *Pluchea dioscoridis* were analysed by GC-MS technique. Of 36 components were identified in the volatile oil of *P. dioscoridis*. Farnesol was the major component (16.50%) accompanied by a high percentage of sesquiterpene alcohols. Oxygenated sesquiterpenes (26.43%) and sesquiterpene hydrocarbons (39.43%) represented the main constituents in the oil. *P. dioscoridis* showed a marked mosquito larvicidal activity against *Culex pipiens* (LC50 71.86ppm) [43].

Cytotoxic Effects

The n-hexanic and ethanolic extracts from *Pluchea sagittalis* (Lam.) Cabrera was investigated in various biological assays, targeting different aspects in this complex process. The extracts were investigated on NF-κB DNA binding, p38α MAPK, TNF-α release, direct elastase inhibition and its release as well as on caspase-3. Fibroblasts migration to and proliferation into the wounded monolayers were evaluated in the scratch assay, the agar diffusion test for antibacterial and the MTT assay for cytotoxic effects. The result showed significant wound healing effects of the investigated medicinal plant [44].

The anti-neoplastic potential of *Pluchea odorata* was investigated against severe inflammatory conditions such as neuritis, rheumatism, arthritis, coughs, bruises and tumours. The freeze dried extracts from five solvents of increasing polarity was tested against HL-60 and MCF-7 cells. The inhibition of proliferation and the induction of cell death were investigated as hallmark endpoints to measure the efficiency of anti-cancer drugs. Western blot and FACS analyses elucidated the underlying mechanisms. The dichloromethane extract of *P. odorata* exhibited pronounced anti-cancer activity [45].

Aqueous and organic extracts of was tested *in vitro* for cytotoxic activity against human solid tumour cell lines. The extracts were screened against HT29 human colon adenocarcinoma cells and NCI-H460 human non-small cell lung cancer cells. The *Pluchea sagittalis* extracts produced differential sensitivity across the cell lines [46].

Anti-inflammatory and Antioxidant Activities

Plucheu sagittulis (Lam.) Cabr., a popular medicinal herb grown in South America, was studied for anti-inflammatory and antioxidant activities. The anti-edema action of *P. sugittulis* aqueous extract was assayed in different models of inflammation *viz*. the mouse ear edema test induced by arachidonic acid & croton oil, the rat hind-paw edema test produced by several inflammatory inductors: carrageenan, dextran. zymosan, platelet-activating factor (PAF) and arachidonic acid and a subacute model based on the rat carrageenan air-pouch granuloma test. Blood leukocyte free radical production was measured by flow cytometry with 2',7'-dichlorofluorescin diacetate (DCFH-DA) *in vivo*, in rats with induced air-pouch granuloma, and in a model *in vitro*, stimulating leukocytes with hydrogen peroxide. The aqueous extract of *P. sugittulis* showed a marked anti-inflammatory effect in both ear edema tests, dextran and carrageenan hind-paw edemas and carrageenan air-pouch model. It also had a potent antioxidant activity in blood leukocytes, both *in vivo* and *in vitro*. The results correlate the reduction of free radical production with the anti-inflammatory effect of this plant [47].

Anti-amoebic Activities

Seven compounds were isolated and purified from the methanolic root extract of *Pluchea indica* by column chromatography. The compounds were identified by spectroscopic analyses. The anti-amoebic activities of the pure compound R/J/3 was investigated against the HM1 strain of *Entamoeba histolytica*. The compound, R/J/3 showed the most pronounced anti-proliferative activity at a dose of 50 μg/ml. It also showed a marked activity on cell lysis of trophozoites, 4 h after administration. The cell lytic activity was compared with metronidazole (5 μg/ml) as positive control [48].

Immunoregulatory Role

Pluchea quitoc has been previously found to modulate the hematopoietic response during bacterial infection. A study was designed to investigate the effects of *P. quitoc* on the growth and differentiation of bone marrow granulocytemacrophage progenitor cells (CFU-GM) in Ehrlich ascites tumor-bearing mice. In contrast to the myelosuppression developed in the tumor-bearing animals, treatment with *P. quitoc* ethanolic extract (250, 500 or 1000 mg/kg) for 3 consecutive days after tumor challenge reversibly stimulated myelopoiesis, restoring the number of CFU-GM to normal. This same dose-schedule also increased colony formation in normal mice as compared to controls. In addition, *P. quitoc* significantly enhanced survival of tumor-bearing mice. These results suggest an immunoregulatory role for *P. quitoc* in counteracting the tumor-induced myelopoietic suppression as well as usefulness as adjuvant treatment of cancer [49].

The immunosuppressive potential of 50% ethanolic extract (PL) of *Pluchea lanceolata* and its bioactive chloroform fraction (PLC) was investigated with basic models of immunomodulation, such as, the humoral antibody response (hemagglutination antibody titers), cell-mediated immune response (delayed-type hypersensitivity), skin allograft rejection test, in vitro (*C.*

albicans method), and in vivo phagocytosis (carbon clearance test). The findings revealed that *P. lanceolata* causes immunosuppression by inhibiting Th1 cytokines [50].

Antimicrobial Activity

The in vitro antifungal activity of the aqueous, ethanol, chloroform, petroleum ether, and residue extracts from *Pluchea ovalis* was evaluated using the agar well diffusion assay against four filamentous fungi and two yeasts monitored by standard antifungal disks. The results showed that all the extracts from *Pluchea ovalis* revealed elevated inhibitory effect against all microbes evaluated [51].

The *Pluchea indica* aqueous extract was tested against both gram positive and gram negative bacteria's using agar diffusion susceptibility test. The positive result showed the possibility of using *P. Indica* as an alternative therapy in the treatment of urinary tract infections [52].

The methanolic root extract of tissue cultured *Pluchea indica* (L.) Less was tested for its antibacterial potentiality against 18 strains of *Shigella* species which is well known gram-negative *Bacillus* functioning as common pathogen in humans. In the in vitro MIC study total 18 *Shigella* strains were tested, among them *Sh. boydii* 10, *Sh. dysenteriae* 1, *Sh. dysenteriae* 7 and *Sh. flexneri* 2a NK 307 were inhibited at 250 µg/ml. Again *Sh. boydii* 8, *Sh. boydii* 10, *Sh. boydii* B 22461, *Sh. dysenteriae* 1, *Sh. dysenteriae* 2, *Sh. dysenteriae* 3, *Sh. dysenteriae* 6, *Sh. flexneri* 5a 18603 were inhibited at a concentration of 500 µg/ml, while the stain like *Sh. boydii* D 13624, *Sh. dysenteriae* 8 were inhibited at a concentration of 1000 µg/ml. The extract was found to be bacteriostatic in nature against *Sh. flexneri* 2a NK 307. In the in vivo experiment using the rabbit ileal loop model two different dosages of *P. indica* root extract (500 µg/ml and 1000µg/ml) were able to protect the animals when they were challenged with *Sh. flexneri* 2a NK 307 in the ileum. The results obtained suggest marked antibacterial activity of the root extract of tissue cultured *Pluchea indica* [47].

Alteration in the Gastrointestinal Absorptive Characteristics

Pluchea sagittalis (Lam.) Cabrera, (qultoco or erva lucera) is commonly used to treat digestive disorders in Southern Brazil and countries of the South Cone. The aqueous extracts from the leaves, stalks or flowers were used in pharmacological studies to determine the gastrointestinal transport of water, sodium, and potassium in rats. The extracts from the leaves and stalk have reduced the absorption of water in the jejunum and ileum, respectively with relation to the control. There was absorption of sodium with the administration of these extracts, especially those from the flowers, when compared with that of the control. There was an increase in the absorption of potassium in different parts of the gastrointestinal tract in comparison to that of the control, being increased in most parts with the application of extracts from the stalks. It could be concluded that the extracts from the stalk, leaves and flowers of *P. sagittalis* have substances that alter the absorptive characteristics of several portions of the gastrointestinal mucosa [53].

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