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CHEMICAL CONSTITUENTS, PHARMACOLOGICAL AND THERAPEUTIC EFFECTS OF *EUPATORIUM CANNABINUM*- A REVIEW

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Abstract:

Phytochemical analysis of Eupatorium cannabinum showed that it contained volatile oil, sesqiterpene lactones- the major one being eupatoriopicrin, polyphenols, flavonoids, pyrrolizidine alkaloids, tannins, terpenoids, saponins and immunoactive polysaccharides. The previous pharmacological studies revealed that the plant possessed cytotoxic, antimicrobial, antioxidant, antiinflammatory, immunological, choleretic, hepatoprotective, insecticidal and repellent effects. The current review highlights the chemical constituents and pharmacological effects of Eupatorium cannabinum.

Keywords: *constituents , pharmacology, therapeutic, Eupatorium cannabinum*

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INTRODUCTION:

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals [1]. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [2-32]. Phytochemical analysis of *Eupatorium cannabinum* showed that it contained volatile oil, sesqiterpene lactones- the major one being eupatoriopicrin, polyphenols, flavonoids, pyrrolizidine alkaloids, tannins, terpenoids, saponins and immunoactive polysaccharides. The previous pharmacological studies revealed that the plant possessed cytotoxic, antimicrobial, antioxidant, antiinflammatory, immunological, choleretic, hepatoprotective, insecticidal and repellent effects. The current review will highlight the chemical constituents and pharmacological effects of *Eupatorium cannabinum*.

Synonyms:

Chrone heterophylla Dulac, *Eupatorium allaisii* Sennen, *Eupatorium argenteum* wallich, *Eupatorium birmanicum* DC., *Eupatorium cannabinum* subsp. *cannabinum*, *Eupatorium cannabinum* var. *cannabinum*, *Eupatorium cannabinum* var. *indivisum* DC., *Eupatorium cannabinum* subsp. *syriacum* (Jacq.) H.Lindb., *Eupatorium cannabinum* var. *syriacum* (Jacq.) Boiss., *Eupatorium cannabinum* subsp. *syriacum* (Jacq.) Nyman, *Eupatorium caucasicum* Steven, *Eupatorium corsicum* Req. ex Loisel., *Eupatorium dicline* Edgew., *Eupatorium finlaysonianum* wallich ex DC., *Eupatorium heterophyllum* DC., *Eupatorium hyrcanicum* Steven, *Eupatorium lambertianum* wallich, *Eupatorium lemassonii* Biau, *Eupatorium longicaule* wallich ex DC., *Eupatorium mairei* H.Lév., *Eupatorium ponticum* Georgi, *Eupatorium punduanum* wallich ex DC., *Eupatorium simonsii* C. B. Clarke, *Eupatorium soleirolii* Loisel., *Eupatorium suaveolens* wallich, *Eupatorium trifidum* Vahl, *Eupatorium trifoliatum* hort. dorp ,ex Stev, *Eupatorium variifolium* Bartl., *Eupatorium viscosum* wallich, *Eupatorium wallichii* var. *heterophyllum* (DC.) Diels and *Mikania longicaulis* wallich [33].

Taxonomic classification:

Kingdom: Plantae, **Subkingdom**: Viridiplantae **Infrakingdom**: Streptophyta, **Superdivision**: Embryophyta, **Division**: Tracheophyta, **Subdivision**: Spermatophytina, **Class**: Magnoliopsida, **Superorder**: Asteranae, **Order**: Asterales, **Family**: Asteraceae, **Genus**: *Eupatorium*, **Species**: *Eupatorium cannabinum* [34].

Common names:

Arabic: Khad Albint, Ghaffath, Ghafith, Ghafith Kinnabi, Kinab maa, **English**: hemp-agrimony, water hemp, hemp Eupatorium; **French**: eupatoire chanvrine; **German**: gewöhnlicher Wasserdost, Wasserhanf; **Italian**: Canapa acquatica, **Swedish**: hampflockel [35].

Distribution:

The plant was distributed in **Africa** (Algeria and Morocco), **Asia** (Armenia, Azerbaijan, Georgia, Russian Federation, Iran, Iraq, Palestine, Lebanon, Syria, Turkey, Nepal and China), **Europe** (Estonia, Latvia, Lithuania, Moldova, Russian Federation, Ukraine, Austria, Belgium, Czech, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Denmark, Finland, Ireland, Norway, Sweden, United Kingdom, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Macedonia, Montenegro, Romania, Serbia, Slovenia, France, Portugal and Spain), **Northern America** (Canada and USA) **Australasia** (New Zealand) [35].

Description:

It is perennial, 50-150 cm tall. Rhizomes robust, with many fibrous roots. Stems erect, purplish red, simple or only apically corymbose branched, puberulent; synflorescence branches and peduncles more densely hairy, glabrescent in median lower part by anthesis. Leaves opposite, shortly petiolate; petiole ca. 5 mm; median and lower leaves irregularly lobed; central lobe elliptic or narrowly lanceolate, large, 6-11 × 2-3 cm, base cuneate or broadly cuneate, apex acuminate or long acuminate; lateral lobes same shape as central lobe, smaller; upper stem leaves gradually smaller, irregularly lobed or simple; lower stem leaves shed by anthesis; all stem leaves scabrid, rather thick, sparsely puberulent and glandular, more densely hairy abaxially and on veins, pinnately veined, lateral veins 5- or 6-paired, margin serrate, undulate. Synflorescences terminal, of densely compound corymbs. Capitula numerous, 3-7-flowered; involucre campanulate, ca. 6 mm; phyllaries 2- or 3-seriate, imbricate; outer phyllaries short, ovate-lanceolate, ca. 2 mm, puberulent; median and inner phyllaries gradually longer, with membranous margin and purplish tip; corollas purple-red, pink, or whitish, ca. 5 mm, outside sparsely yellow glandular. Achenes black-brown, cylindric, ca. 3 mm, 5-ribbed, with yellow glands; pappus setae white [36].

Traditional uses:
It was used in different religious and socio-cultural activities including the ritual purification functions of dead. It was used in folk medicine of Taiwan for treatment of hepatitis, headache, diarrhea, hypertension, and diabetes mellitus. Moreover, the plant had several ethno-medicinal applications. An infusion (100 ml) prepared from the tender leaves was given orally to women once a day for five days in excess bleeding during menstruation period. Leaves and stems juice was applied to cuts and bruises to stop bleeding. It was also used as detoxifying herbs and for the treatment of fevers, cold, flue and viral conditions [37-40].

Leaves and roots of *Eupatorium cannabinum* were also used a cholagogue, laxative, diuretic and hypocholesterolemic and for wound healing, diarrhea and livers diseases [42-44].

Chemical constituents:
Eupatorium cannabinum contained volatile oil, sesqiterpene lactones- the major one being eupatoriopicrin, polyphenols, flavonoids, pyrrolizidine alkaloids, tannins, terpenoids, saponins and immunoactive polysaccharides [45-46].

Twenty one thymol, benzofuranoid, and phenylpropanoid derivatives compounds were isolated from the aerial part of *Eupatorium cannabinum* included: 9-O-angeloyl-8,10-dehydrothymol; 9-(3-methylbutanoyl)-8,10-dehydrothymol; Eupatobenzofuran; 2-hydroxy-2,6-dimethylbenzofuran-3(2H)-one; 1-(2-hydroxy-4-methylphenyl)propan-1,2-dione; 9-acetoxy-8,10-epoxythymol 3-O-tiglate; 9-acetoxy-8,10-dehydrothymol 3-O-tiglate; 9-acetoxythymol 3-O-tiglate; 9-hydroxy-8,10-dehydrothymol; 9-isobutyryloxy-8,10-dehydrothymol; 8-methoxy-9-O-isobutyrylthymol; 8-methoxy-9-O-angeloylthymol; 10-acetoxy-8-hydroxy-9-O-angeloylthmol; 30,40,4a0,9a0-tetrahydro -6,70-dimethylspiro[benzofuran-3(2H),20-pyrano[2,3-b]benzofuran]-2,4a0-diol; 1-[2-hydroxy-4-(hydroxymethyl)phenyl]ethan-1-one; hofmeisterin II; euparin; 2H-chromen-2-one; taraxasterol acetate; mixture of β-sitosterol and stigmasterol [47].

Two new thymol (=5-methyl-2-(1-methylethyl)phenol) derivatives: 8,10-didehydro-9-(3-methylbutanoyl)thymol 3-O-tiglate and 9-O-angeloyl-8-methoxythymol 3-O-isobutyrate were isolated from the root of *Eupatorium cannabinum* ssp. asiaticum [48].

Seven benzofurans were isolated and identified from the root cultures of *Eupatorium cannabinum*. Studies on the biosynthesis of the benzofurans were carried out by feeding ^{14}C-labelled compounds and stable isotopes to the root cultures of *Eupatorium cannabinum*. The results showed that the aromatic ring, as well as the C-acetyl substituent linked to the aromatic ring, originate from the shikimic acid pathway via phenylalanine and cinnamic acid. The C-acetyl substituent was shown to arise directly from the phenylpropanoid side chain [49].

Pyrrolizidine alkaloids of the *Eupatorium cannabinum* were included echinatine isomers, lycopsamine and intermedine, and a number of their beta-acetyl, beta-angelyl/tiglyl and beta-(iso)valeryl esters. Pyrrolizidine alkaloids without a substituent at C-7 were tentatively identified as supinine and amabiline. In addition to a number of these alkaloids, some beta-(iso)butyryl, beta-angelyl/tiglyl, and beta-(iso)valeryl esters of supinine or amabiline were detected in subterranean parts of the plant. Pyrrolizidine alkaloids with a saturated necine base trachelanthamine isomers and some beta-anglyl/tiglyl esters which were detected in the root material only. A C-9-viridifloryl/trachelanthyl ester of a saturated amino-alcohol like turneforcidine and one of its beta-angelyl/tiglyl esters have also been found [50-52].

From the alkaline aqueous extract of *Eupatorium cannabinum*, polysaccharides were isolated and identified as 4-*O*-methylglucuronoxylans [53].

Polyphenolics levels in the aerial parts of *Eupatorium cannabinum* subsp. *cannabinum* (g/kg on dry matter) were: chlorogenic acid 14.67 ±0.73; 3,5 dicaffeoylquinic acid 22.74 ±1.13; 4,5 dicaffeoylquinic acid 4.23 ± 0.23; total caffeoyl derivatives 41.64, total dihydroxycinnamic derivatives 65.72 ± 3.37, total flavonoids 8.10 ± 0.41, total dihydoxycinnamic derivatives 73.82 and total polyphenolic compounds 81.47 ±3.75 [54]. The hydroalcoholic extract of *Eupatorium cannabinum* from Romania contained 56.86 mg% caffeic acid, 1.26 mg% eupatorin, 18.06 mg% eupatilin, 97.03 mg% quercetin, 762.63 mg% rutin and 68.8 3mg% β-ecdysone [55].
The total phenol and flavonoid contents were found 64.82 mg/g and 25.05 mg/g gallic acid and quercetin equivalent respectively in the ethanolic extract of the leaves of *Eupatorium cannabinum* [56].

Flavones and flavonol glycosides were isolated from the aerial parts of *Eupatorium cannabinum*, these included: 6-methoxyflavones hispidulin and eupafolin, flavonol glycosides astragalin, kaempferol-3-rutinoside, hyperoside, isoquercitrin and rutin [57].

Flowers of *Eupatorium cannabinum* from Iran, gave 0.1% and leaves, 0.2% oils based on dry weight. Thirty one compounds were identified from *Eupatorium cannabinum* flowers oil. The major components of this oil were found to be germacrene D (27.3%), germacrene B (12.4%), valencene (10.5%) and β-caryophyllene (8.7%). Thirty one compounds were identified from leaves oil. The main constituents of pale yellow leaves oil were shown to be germacren D (37.1%), germacrene B (11.7%), β-

caryophyllene (10.2%) and delta-2-carene (8.5%). However, the compounds identified in the *Eupatorium cannabinum* flowers and leaves oils and their percentage (respectively) were: α-pinene 0 and 0.2, camphene 0 and 0.2, sabinene 0 and 0.1, myrcene 0 and 0.1, delta-2-carene 0.4 and 8.5, α-phellandrene 1.3 and 4.9, *p*-cymene 1.6 and 0.8, limonene 0.1 and 0.4, (Z)-β-ocimene) 0 and 0.2, benzenacetaldehyde 0.4 and 0, (E)-β-ocimene 0.2 and 1.5, terpinolene 0.1 and 0.2, linalool 0.1 and 0.1, nonanal 0.4 and 0.2, phenyl ethylalcohol 0.3 and 0, α-terpineol 0.5 and 0.1, decanal 0.1 and trace, nerol 0.5 and 0 , thymol (methyl ether) 6 and 4.3, thymoquinone 6.2 and 0, bornyl acetate 0.1 and 0.1, thymol 0.6 and 0, hexyl tiglate trace and 0.1, neryl acetate 8.7 and 3.3, geranyl acetate 0.2 and 0, β-cubebene 0.3 and 0.3, β-elemene 0 and 0.4, longifolene 0 and 0.2, β-caryophyllene 8.7 and 10.2, coumarine 0.6 and 0, α-guaiene 0.2 and 0, α-humulene 1.3 and 1.7, α-patechoulene 1.8 and 0.6, germacrene D 27.3 and 37.1, valencene 10.5 and 6.7, bicyclogermacrene 0.9 and 1.6, β-himachalene 0 and 0.5, δ- cadinene 2.7 and 1.2 and germacrene B 12.4 and 11.7 [58].

The essential oil from aerial parts of *Eupatorium cannabinum* subsp. corsicum from Corsica contained one hundred and forty-seven components. The main constituents were germacrene D (28.5%), alpha-phellandrene (19.0%) and para-cymene (5.2%). The specificity of this essential oil was the presence of monoterpene esters derived from nerol, lavandulol, borneol, thymol and 8,9-dehydrothymol [59].

Senatore *et al*., found that the aerial parts of *Eupatorium cannabinum* contained 0.37% (v/w) essential oil, on a dry weight basis. The oil composed of fifty-nine compounds. Germacrene D (33.5%) was the most abundant component with appreciable amounts of α-farnesene (12.9%) and δ-2-carene (6.5%). Among the oxygen containing components, elemol (2.8%) and α-cadinol (2.7%) were the most abundant [60].

Linoleic acid ethyl ester; 9,12,15-Oktadekatrienoic acid; ethyl ester; (Z,Z,Z)- and Hexadecanoic acid, ethyl ester were the main components among the constituents of the oil of *Eupatorium cannabinum* from Azerbaijan [61].

In contrast to the essential oil from the aerial parts, the essential oil from the roots was characterized by a high content of oxygenated compounds (61.0%), particularly oxygenated monoterpenes (54.0%). In the root oil, 106 components were identified, it was dominated by the monoterpenes esters (33%), neryl isobutyrate (17.6%), thymyl methyl oxide (15.1%), delta-2-carene (14.5%) and beta-pinene (5.7%) [62].

Pharmacological effects:

Cytotoxic effect:

The cytotoxic effects of *Eupatorium cannabinum* ethanolic extract was studied in colon cancer cell line HT29. Severe loss of HT29 cell viability was detected for 50 µg/ml *Eupatorium cannabinum* ethanolic extract after 24 h of exposure. All other used concentrations (0.5, 5 and 25 µg/ml) caused significant decrease in cell viability after 96 h. Exposure to 25 µg/ml *Eupatorium cannabinum* ethanolic extract for 48 h induced irreversible cell damage causing a drastic decrease in cell viability even after 72 h recovery in *Eupatorium cannabinum* ethanolic extract -free medium. After 48h exposure, 25 µg/ml *Eupatorium cannabinum* ethanolic extract treatment induced alteration of colony morphology, H3K9 hyperacetylation, transcriptional upregulation of p21 and downregulation of NCL, FOS and AURKA, indicating reduced proliferation capacity. The treatment also induced drastic mitotic nuclear disruption denoting induction of cell death. *Eupatorium cannabinum* ethanolic extract /doxorubicin co-exposure decreases cell viability in relation to doxorubicin for all *Eupatorium cannabinum* ethanolic extract concentrations, without affecting the doxorubicin-induced cell cycle arrest [63].

Eupatoriopicrin, a sesquiterpene lactone from *Eupatorium cannabinum* showed cytotoxic activity against different tumors *in vitro*. Eupatoriopicrin showed significant cytotoxic activity at a concentration of 1.0–5.2 molar, particularly against leukaemia tumor and ZNS tumor cells (V 251) [64].

The cytostatic effect of eupatoriopicrin was studied against FIO 26 cells *in vitro* with the aid of a clonogenic assay and *in vivo* by tumour growth delay in FIO 26 and Lewis lung tumour-bearing mice. *In vitro* the IC_{50} for 1 h exposure to eupatoriopicrin was 1.5 microgram/ml (4.1 nmol/ml). This concentration depleted about 25% of its cellular GSH concentration. Pretreatment of FIO 26 cells with buthionine sulphoximine (BSO), resulting in greater than 99%. GSH depletion, enhanced the cytotoxic effect of eupatoriopicrin. The dose-enhancement factor at the level of 10% cell survival was 2.3. Growth inhibition of the Lewis lung carcinoma and the FIO 26 fibrosarcoma, solidly growing in C57Bl mice, was found after iv injection of 20 or 40 mg/kg eupatoriopicrin, at a tumour volume of about 500 microliters. Pretreatment with BSO at a dose of 4 mmol/kg ip, 6 h before eupatoriopicrin administration, resulted in a significantly stronger growth delay of both tumours compared with eupatoriopicrin only. At the time of eupatoriopicrin treatment, cellular GSH in the tumours was reduced by BSO treatment to about 60% [65].

After 2 hr incubation of Ehrlich ascites tumour cells with eupatoriopicrin, the DNA damage, was observed at concentrations only slightly higher than those causing cell death (1-10 micrograms/ml). Glutathione (GSH) depletion of the cells to about 99%, by use of buthionine sulphoximine (BSO), enhanced the extent of DNA damage [66].

The viability of Jurkat cells treated with increasing concentrations of *Eupatorium cannabinum* hydroalcoholic extract (7- 500 µg/ml) for 24 and 48 hours was studied using the MTS assay. The extract significantly inhibited the growth of Jurkat cells in a dose- and time-dependent manner, especially when exposed for 48 hours. Cell proliferation consistently decreased, from 60.64±0.06% viability for the 125µg/ml dose at 24 h to 26.51±0.013% for the same concentration at 48 h. The inhibitory capacity of *Eupatorium cannabinum* extract at the dose of 250 µg/ml was comparable to 5-FU (200µg/ ml). The IC_{50} value of the extract determined at 48 hours was 73.3 µg/ml[55].

Among the isolated compounds, thymol derivatives (9-acetoxy-8,10-epoxythymol 3-O-tiglate) was the most cytotoxic with IC_{50} values of 0.02±0.01, 1.02±0.07, and 1.36±0.12 µg/ml, respectively, against DLD-1, CCRF-CEM, and HL-60 cell lines. 10-acetoxy-9-O-angeloyl-8-hydroxythymol and eupatobenzofuran exhibited cytotoxicities, with IC_{50} values of 1.14±0.16 and 2.63±0.22, and 7.63±0.94 and 2.31±0.14 µg/ml, respectively, against DLD-1 and CCRF-CEM cell lines [48].

The cytotoxic effect of essential oils of *Eupatorium cannabinum* was studied using brine shrimp (Artemia sp.) assay. The determined LC_{50} value was 16.3-22.0 µg/ml [41].

Hispidulin, eupafolin and rutin, isolated from the aerial parts of *Eupatorium cannabinum*, were screened for cytotoxicity *in vitro* against Ehrlich Ascites tumour (EAT). The lowest active dose of the flavonoids causing growth inhibition of the EAT cells was 2.6 nmol/ml for rutin, 9.8 nmol/ml for eupafolin and > 21 nmol/ml for hispidulin. While eupatoriopicrin, isolated from *Eupatorium cannabinum*, was used as a reference, possessing a lowest active dose of 0.8 nmol/ml [57].

Antimicrobial effect:

The antibacterial effect of the essential oil of the aerial parts of *Eupatorium cannabinum* was studied against Gram positive (*Staphylococcus aureus*, *Streptococcus faecalis*, *Bacillus subtilis* and *Bacillus cereus*) and Gram negative (*Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli* and *Salmonella typhi* Ty2) bacteria. The results showed a significant antimicrobial activity against all the tested microorganisms, mostly against Gram positive bacteria, particularly *Streptococcus faecalis*, while, *Pseudomonas aeruginosa* showed the highest resistance to the oil [60]. Different extracts of *Eupatorium cannabium* (chloroformic, water and hydroalcoholic extract) were tested for their antimicrobial activity against Gram positive bacteria (*Bacillus cereus*, *Staphylococcus aureus* and *Enterococcus faecalis*), Gram negative test bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus niger*). The chloroformic and hydroalcoholic extracts of the Eupatorium cannabium showed inhibitory activity against *Escherichia coli* and *Bacillus cereus* only, as well as on the dimorphic yeast *Candida albicans*. No clear inhibition have been noticed against *Staphylococcus aureus*, *Enterococcus faecalis* and *Aspergillus niger* [67]. The essential oil of *Eupatorium cannabinum* possessed fungicidal action against *Aspergillus niger*, and fungistatic effect against *Trichoderma lignorum* and *Fusarium oxysporum* [61].

Antioxidant effect:

The DPPH antioxidant assay was used to determine the antioxidant effect of hydro-alcoholic extract of *Eupatorium cannabinum* (at doses of 0.1-10mg/ml). EC_{50} of the extract was determined at 2.91mg/ml [55]. The antioxidant activities of caffeoyl derivatives isolated from the aerial parts of *Eupatorium cannabinum* subsp (individually) were: chlorogenic acid (EC_{50} = (13.80 ±0.36) µmol/l), 3,5-dicaffeoylquinic acid (EC_{50} = (7.62 ± 0.22) µmol/l), 1,5-dicaffeoylquinic acid (EC_{50} = (7.85 ±0.23 µmol/l) and 4,5-dicaffeoylquinic acid (EC_{50} = (7.99 ±0.31 µmol/l) [54].

Antiinflammatory effects:

9-Acetoxy-8,10-epoxythymol 3-O-tiglate; 9-acetoxy-8,10-dehydrothymol 3-O-tiglate (7), 9-acetoxythymol 3-O-tiglate; 8-methoxy-9-O-isobutyrylthymol; 10-acetoxy-8-hydroxy-9-O-angeloylthymol; and 1-[2-hydroxy- 4-(hydroxymethyl)phenyl]ethan-1-one isolated from the aerial part of *Eupatorium cannabinum* exhibited potent inhibition (IC_{50} value of 18.4 µM) of superoxide anion (O^{2-}) generation by human neutrophils in response to fMLP/CB [47]. 9-(3-Methylbutanoyl)-8,10-dehydrothymol; eupatobenzofuran; 9-isobutyryloxy-8,10-dehydrothymol; 10-acetoxy-8-hydroxy-9-O-angeloylthymol and 1-[2-hydroxy- 4-(hydroxymethyl)phenyl]ethan-1-one isolated from the aerial part of *Eupatorium cannabinum* inhibited fMLP/CB-induced elastase release with IC_{50} value of 18.3 µM [43].

Immunological effects:

The polysaccharides isolated from the alkaline aqueous extract of *Eupatorium cannabinum* showed a phagocytosis enhancing effect as determined in three immunological test systems (carbon clearance, granulocyte- and chemiluminescence test) [53]. Polysaccharide fractions were isolated from the water or alcaline-water extracts of *Eupatorium cannabinum*.

They showed significant immunostimulating activities according to the granulocytes- and carbon clearance tests [68].

Choleretic and hepatoprotective effects:

The influence of *Eupatorium cannabinum* was evaluated on the sites of bile formation by quantitative determination of bile flow, bile acids output, and [^{14}C]-erythritol clearance and to determine the anti-hepatotoxic potency of *Eupatorium cannabinum* using CCl_4 in *in vivo* model in rats. Bile flow was significantly increased after a single injection of various doses of *Eupatorium cannabinum* aqueous extract (125, 250, 500, 1000 mg/kg) reaching the maximum efficiency within 30 to 90mm (19% at 250mg/kg). The extract also possessed anti-necrotic properties against $CC1_4$-induced hepatotoxicity. Pretreatment (30 min before $CC1_4$), with *Eupatorium cannabinum* showed a significant decrease of GPT levels at 250, 500, and 1000 mg/kg [42].

An aqueous extract of the plant exhibited anti-necrotic activity against carbon tetrachloride-induced hepatotoxicity in rats. The effect was attributed to the presence of flavonoids (rutoside, hyperoside and quercetin) and phenolic acids, caffeic and chlorogenic; and not due to the presence of eupatoriopicrin. Acrylic acid and the lactic, malic and citric acids, present in the plant, also exhibited protective effect against acute toxicity induced by ethanol in mice [46].

Insecticidal and repellent effect:

The methanol and chloroform fraction of *Eupatorium cannabinum* were effective for the control of *Callosobruchus chinensis*. They possessed maximum repellent activity 90% at 250ppm concentration [69]. The toxicity of *Eupatorium cannabinum* against the second and fourth instar larvae of *Culex quinquefasciatus* and *Aedes aegypti* was studied using four different concentrations from 20 to 50 ppm. Acetone extract of *Eupatorium cannabinum* caused dose dependent larval motility against second and fourth instar larvae of *Aedes aegypti* and *Culex quinquefasciatus*. The purified fraction was more effective than the crude extract, the IC_{50} values for the 100 ppm of purified fraction against second and fourth instar larvae of *Aedes aegypti* were 40.11 and 34.10 ppm respectively [70].

Side effects and toxicity:

Mice were given 125mg/ 20g bw, of the extract by intragastric gavage, then the animals were monitored and observed every hour the first day, and by the end of 14 days were subjected to observation at least twice a day. The dose reduced spontaneous motility, caused drowsiness and ptosis. Phenomena were spontaneously reversible and no other behavioral changes were noticed by the end of the observation period. No deaths were recorded [55]. Because of the pyrrolizidine alkaloid content with 1,2- unsaturated necic parent substances, hepatotoxicity and carcinogenicity are likely consequences of internal use[71].Eupatoriopicrin from *Eupatorium cannabinum* showed a weak sensitizing capacity in guinea pigs [72].

CONCLUSION:

The current review discussed the chemical constituents and pharmacological effects of *Eupatorium cannabinum* as a promising plant for many pharmacological purposes as a results of effectiveness and safety.

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