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EUPHORBIA HELIOSCOPIA: A REVIEW ON PHARMACOLOGICAL ACTIVITIES

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Abstract

Pharmacological activities reveal favorable or unfavorable effects of chemicals or compounds under study. *Euphorbia helioscopia* has been investigated for number of pharmacological activities because of its great use as folklore remedy. This article reviews all the pharmacological activities that have been found till today.

Keywords: Pharmacological activity, *E. helioscopia*, Folklore remedy

Introduction

Euphorbia helioscopia belongs to *Euphorbiaceae* family which contains 8000 species. It is used in the treatment of various ailments like warts cure, skin diseases, intestinal parasites, migraine, gonorrhea. [1, 2] Traditional uses of leaves and stems of *E. helioscopia* are vermifuge and febrifuge actions, roosted pepper mixed with seeds are used in cholera , seeds oil used in constipation, and roots are being used as anthelmintic.[3,4] Madwoman's milk, Cats milk, Sun euphorbia, Sun spurge, Umbrella Milkweed, Wart Spurge, Wart Weed, Wart Grass are vernacular names of this plant. [5] Locally, it is called Hirruseeah and Mahubi in Hindi and Gandabhuti, Duadai Kulfadodak, and Chatriwal in Punjabi [4]. The plant is an annual weed having cosmopolitan distribution and contains white lacteal juice. It has thin and cylindrical root, green or reddish stalks in upright or prostrate position (either single or numerous, simple or ramified) with 5.0 – 50.0 cm length. Leaves are broadened toward apex with rounded, finely toothed or serrated ends, narrowed toward petiole base, with the greatest width in distal third. Main stem/ray branches into 3 secondary rays, which in turn branch into 2 tertiary rays. Flowers are small, unisexual and greenish-yellow, inconspicuous and may aggregate in complex inflorescences. March to June is the blossoming season while fruits occur in June-July. [6] The plant is found throughout the Punjab while grown in Nilgiri Hills [7]. Various types of secondary metabolites reported in the plant include triterpenoids [8], diterpenoids, [9-14] flavonoids, [15,16] Tannins, [17] steroids and lipids [14].

According to Zhang and Guo, (2006) this plant has 24 secondary metabolites, which are euphoheliosnoid D, euphornin, euphornins B, euphornins C, euphoscopins A-C, euphoscopins F, euphoscopins J, epieuphorscopins A, epieuphorscopins B, helioscopinolide B, 2 alpha hydroxy helioscopinolide B, guaiane lactone, hemistepsin, 4,5-dihydroblumentol A, and aglycon of icariside B2, licochalcone A, 2', 4, 4'-trihdroxy chalcone, echinatia, licochalcone B, galabrone, 4', 5,7-trihdroxyflavanone, helioscopinolide C. [18]

It has been explored by number of researchers for various pharmacological activities. This review was planned to give detailed analysis and summary of pharmacological activities of *E. helioscopia* that support the medicinal importance of this plant.

Material and Methods

Anti-nociceptive, anti-inflammatory and anti-pyretic activity

Prostaglandins are mediators of pain, inflammation and pyrexia. A pain stimulus reaches to brain via central and peripheral pathways. Acetic acid induced writhing test, and formalin test (late phase) were performed to explore peripheral anti-nociceptive effect. Central anti-nociceptive effect was explored with hot plate test and formalin test (early phase). Anti-inflammatory activity was explored carrageenan induced paw edema test in mice. Anti-pyretic effect was evaluated with brewer's yeast induced pyrexia in mice. Leaves methanol extract and latex exhibited dose dependent central and peripheral anti-nociceptive effect, anti-inflammatory and anti-pyretic effect. Leaves methanol extract and latex of *E. helioscopia* were examined for central and peripheral pain protection using acetic acid induced writhing, formalin tests and hot plate test in mice and found concentration dependent anti-nociceptive effect. Carrageenan induced paw edema test was performed to assess anti-inflammatory activity in mice and highest activity (81.25 %) was displayed by leaves methanol extract at dose 300mg/kg. Anti-pyretic effect was evaluated with brewer's yeast induced pyrexia in mice and leaves methanol extract at 300mg/kg exhibited maximum (45.36 %) anti-pyretic activity. [19]

Genotoxic and mutagenic potential

COMET assay was performed for genotoxicity study and Ames test was used for mutagenic potential determination. Latex (1000-1.6µg/mL) and leaves methanol extract (10-0.625 µg/mL) were used in this study. Latex did not present signs of genotoxicity and mutagenicity whereas extract displayed genotoxicity and mutagenicity at 10µg/mL concentration only. [20]

Teratogenic and embryo-toxic effects

To explore the teratogenic effect, latex and leaves methanol extract were given to mice at doses 100, 300, 500, 700, 1000, 1500, and 2000mg/kg body weight on 7th day of conception via intra-peritoneal route. No abnormality was seen in the born litters.

Embryo-toxic effect was studied in white leghorn chicken embryos of 5th day of incubation. Latex and leaves methanol extract (10 - 120µg/200µL) were administered to embryos through chorioallantoic membrane and incubated. After two days, eggs were transferred from incubator to chilled freezer and embryos were observed for malformation. No

abnormal sign of growth was observed. Hence, it is concluded that *E. helioscopia* is safe in pregnancy at therapeutic doses/concentrations. [21]

Anti-Allergic and anti-asthmatic activity

Helioscopinin-A, a polyphenol isolated from *E. helioscopia*, inhibited the pharmacological response of leukotriene D4 and release of histamine from mast cells in asthmatic models of rat and guinea pig. These results indicated anti-allergic and anti-asthmatic activities of *E. helioscopia*. [22]

Insulin secretagogue activity

Ethanol extract of whole plant of *E. helioscopia* was investigated at different concentrations ranging from 1 to 40µg/mL for insulin secretagogue potential by using insulinoma cell line (INS-1). It showed statistically significant (P>0.05) activity at 10µg/mL. [23]

Inhibition of multidrug resistance causing P-glycoprotein and breast cancer resistance protein (BCRP)

Barlie et al., (2008) and Corea et al., (2009) isolated diterpenes from *E. helioscopia* and tested them for their pharmacological activity against P-glycoprotein (ABCB1: ATP binding cassette, subfamily B, member 1) and BCRP (ABCG2; ATP binding cassette, subfamily G, member 2). P-glycoprotein efflux the cytotoxic drugs that results in resistance of the body against cytotoxic drugs thus, decrease their cytotoxicity. BCRP genes are associated with self-renewal of cancer cells. *E. helioscopia* displayed strong inhibitory action against P-glycoprotein and non-significant activity for BCRP. [24, 25]

Cytotoxic Potential of E. helioscopia against cancer cell lines HL-60 and LA795.

HL 60 cell line was isolated from acute myeloid leukemia patient and LA 795 is adenocarcinoma cell line of lungs. Tao et al., (2008) and Chen et al., (2011) isolated a macrocyclic diterpenoid named "Euphornin" from *E. helioscopia* and analysed for cytotoxicity against LA 795 cell line and HL 60 cell line respectively. Both studies concluded that euphornin exhibited cytotoxic potential against cancer cells. [9, 26]

Cytotoxicity on epithelial Vero cell line

Leaves methanol extract and latex were tested with MTT assay at concentrations ranging from 1000-0.0128 µg/mL. IC_{50} value, calculated from linear regression equation for leaves methanol extract, was 5.27 µg/mL. IC_{50} value could not be found out for latex at experimental concentrations because at 1000 µg/mL latex had 57% cell survival. [27]

Vasodepressor activity

Barla et al., (2006) isolated compounds from the arial parts of *E. helioscopia* and tested them for vasodepressor activity. Femoral vein and artery were cannulated for measuring blood pressure with a polygraph. There was found decrease in blood pressure which was might be due peripheral vascular resistance. [28]

Antibacterial activity

According to Saleem et al. (2015c) study, *Staphylococcus aureus* (ATCC No. 25923), *Escherichia coli* (ATCC No. 25922), *Salmonella enterica* (ATCC No. 10708) showed susceptibility to leaves methanol extract of E. helioscopia but *Bacillus subtilis* (ATCC No. 6633) was resistant to it. Hence, the above mentioned microbes were found resistant to latex.

Uzair et al., (2009) tested antibacterial activity of dichloromethane and methanol extracts of ariel parts of E. helioscopia against *Eschericha coli, Bacillus subtilis, Shigella flexenari, Staphylococcus aureu, Pseudomonas aeruginosa* and *Salmonella typhi.* Both the extracts exhibited non-significant activity against *Bacillus subtilis* and *Salmonella typhi.* [29]

Chaudhry et al., (2001) study also found antibacterial activity of methanol extract of *E. helioscopia* against *Sarcina leutea.* [30]

Antifungal activity

Dichloromethane and methanol extracts of aerial parts *E. helioscopia* were investigated for anti-fungal activity against Trichphyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani and Candida glabrata. Only Fusarium solani was inhibited 90% with dichloromethane extract and methanol extract was found inactive against all the selected fungi. [29]

Dichloromethane, petroleum ether and methanol extracts were tested against fungi "Cladosporium cucumerinum" and found no antifungal activity. [30]

Anti-viral activity

Methanol extract prepared by soxhlet and ethanol extract prepared by ethanol were tested for antiviral activity. Bacteriophage CP51 was used in this study. Methanol extract at 0.75 mg/mL inhibited phage growth and reproduction more than 50% and ethanol extract also showed the same result at 0.125mg/mL. [31]

Anti-tumor activity

Helioscopinolide compound showed anti-tumor activity by inhibiting cell (MCF-7 cell line) proliferation. Water extract of root of *E. helioscopia* displayed anti-tumor activity when administered to S-180 and H-22 strains of mice. [32-34] Another study showed that ethyl acetate fraction (EAE) of aqueous-ethanol (maceration) extract of the plant has cytoprotective effect against five human cancer cell lines, three were hepatocellular carcinoma cell lines; SMMC-7721, BEL-7402 and HepG2, one gastric carcinoma cell line; SGC-7901, and colorectal cancer cell line SW-480. The major active substance in the EAE extract found using high-performance liquid chromatography (HPLC) was flavonoid (quercetin). [35] Ten compounds were isolated from *E. helioscopia* and investigated for anti-tumor activity against LA795 cell line. Among those compounds, gallic acid and hypersoide exhibited anti-tumor power. [36]

***In-vitro* and *in-vivo* antioxidant activity**

In-vitro anti-oxidant activity of latex and water, ethanol, petroleum ether, chloroform and methanol extracts of leaves and stem of *E. helioscopia* were investigated by employing four electron transfer reactions; DPPH, total antioxidant capacity, FRAP, and ferric thiocyanate assay (FTC) and one hydrogen atom transfer reaction; ß-carotene linoleate bleaching assay. In all assays Latex and leaves methanol extract (among all extracts) showed greatest antioxidant potential. A significant positive pearson correlation was found among all the methods. [37] In another research, dichloromethane and methanol extract of arial parts of *E. helioscopia* were studied for *in-vitro* antioxidant activity by TLC (thin layer chromatography) autography assay. Only methanol extract showed antioxidant activity. Methanol extract of flowers showed strong antioxidant activity with IC_{50} value of 26.66 µg/mL. [29, 38]

To find out *in-vivo* antioxidant potential of latex and leaves methanol extract of *E. helioscopia,* experiment was performed in mice. Superoxide dismutase, catalase, glutathione peroxidase and melondialdehyde (*in-vivo* antioxidant biomarkers) were quantified in liver, heart, brain and kidney homogenates and result showed promising antioxidant activity of leaves methanol extract. [39]

Anthelmintic activity

It was determined by *in-vitro;* egg hatch assay and worm motility inhibition assay and *in-vivo*; faecal egg count reduction assay. Methanol and aqueous extracts of arial parts of E. helioscopia were used in this study. Both, *in-vivo* and *in-vitro*, assays concluded anthelmintic potential of this plant. [40]

Wound healing property

Ethanol and aqueous extracts were tested in rats for wound healing property. Incision, excision and dead space wound models were used in the study. Ethanol extract showed more prominent wound healing as compared to standards. [41]

Molluscicidal activity

Methanol, acetone and hexane extracts were tested against *Biomphalaria pfeifferi* and *Bulinus wright* for molluscicidal activity and found positive for above mentioned activity. [42-45]

Pesticide Potential

Elyassaki and El-Sayed (1996**)** explored pesticide potential of *E. helioscopia* against *Culex pipiens* larvae and *Biomphalaria alexandrina* snails and found positive results. [46]

Allelopathic / Phytotoxic effect

Water extract from root, stem, leaf, and fruit of *E. helioscopia* had allelopathic potential against chickpea, and lentil resulting in reduced seed germination and germination index in chickpea and lentil. [47] Aqueous extract (1 – 10% w/v) shoot was tested for its effect on germination and early growth of seedling of pea (Pisum sativum L.) and wheat (Triticum aestivum L.). Germination of seeds was affected; it increased with rise in concentration. [48]

Anti-angiogenic activity using in-vivo CAM assay

Latex, and leaves extracts, prepared in water, ethanol, petroleum ether, chloroform and methanol were evaluated for anti-angiogenic activity by employing chorioallontoic membrane assay (CAM). Blood vessels of CAM were quantified using SPIP software. % inhibition of angiogenesis was calculated and greatest anti-angiogenic activity (11.64%) was found with leaves methanol extract. Quercetin was used as standard anti-angiogenic drug. [49]

Acute oral toxicity

OECD guidelines were followed to calculate LD_{50} of leaves methanol extract of *E. helioscopia* after oral administration and it was found greater than 2000 mg/kg. [50]

Conclusion

The use of plant as medicinal agent is quite safe as

toxicity data on E. helioscopia gathered from acute oral toxicity study, teratogenicity,cytotoxicity, mutagenicity and genotoxicity studies revealed safety of the plant. Number of pharmacological activities make this medicinally important.

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