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RESEARCH ARTICLE

ETHNOPHARMACOLOGICAL PROPERTIES AND THERAPEUTIC USES OF OPHIORRHIZA MUNGOS LINN : A REVIEW

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Abstract

Ophiorrhiza mungos L, is an Ayurvedic herb ,belonging to the family Rubiaceae, commonly known as"Mongoose plant" is an ethnobotanically important plant containing Camptothecin as a potent natural bioactive compound. The genus Ophiorrhiza is known to be a natural source of Camptothecin and diverse biological activities. Camptothecin (CPT), a cytotoxic quinoline indole alkaloid is an important source for the synthesis of some of the major anti-cancer agents such as irinotecan and topotecan.

O.mungos is a plant which yields contain Camptothecin in a significantly high amount. The plant is gaining recognition due to its diversified medicinal value; however it has been categorized as an endangered plant. Alternative method of propagation like tissue culture, cell suspension culture, root culture, seedling culture etc aims at large scale production of the plant. Scientific literature regarding the Ophiorrhiza plants revealed their wide distribution across Asia and the neighbouring countries, where they were utilised as traditional medicine to treat various diseases. Several secondary metabolites like alkaloids, flavonoids, steroids, terpenoids, and fatty acids etc, exhibiting anti-bacterial, anti-viral, anti-ulcer, anti-helminthic and anti-venom properties are extracted from various parts of the plant. Here we aim to provide an overview of the importance of Ophiorrhiza mungos , a member of genus Ophiorrhiza its botanical properties, phytochemical and pharmaceutical aspects with interest on camptothecin and its future prospects. The review is an attempt to provide insights in our gap of knowledge that needs concern and bridge the gaps between its bioactive compound, traditional uses and pharmacological activities; in an approach to provide long term benefits to society.

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Introduction:-

Since ancient times herbal medicines and their therapeutic agents are in use by herbal medical practitioners to treat various forms of diseases including cancer. The demand for herbal drugs have ever since increased due to its lesser side effects and toxicity compared to commercialized drug. The genus Ophiorrhiza belonging to family Rubiaceae ,is an Indo Malaysian genera , distributed widely in the wet forests across tropical and subtropical Asia, Australia, New Guinea, and the Pacific Islands. [1,2]. At present the genus is represented by 321 species and 5 varieties and one subspecies of which 46 species and five varieties are mainly distributed in the north-eastern states and Western Ghats of India [2]. The greatest diversity of the genus is observed in New Guinea and south eastern Asia, the former is considered as the centre of origin of the genus[3]The plant is known to contain bioactive constituents like alkaloids (indole alkaloids and quinoline alkaloids), secoiridoid monoterpenes, sesquiterpenes, steroids, quinines and phenyl propanoids [4] which finds use in therapeutic. These bioactive compounds exhibit anti-bacterial, anti-viral, anti-ulcer, anti-helminthic and anti-venom properties [5]. Some of the compounds from this family, such as caffeine, quinine, emetine, and camptothecin, are of major pharmaceutical importance [6]. One such ethnomedicinally important plant is Ophiorrhiza mungos, which is known to contain several important bioactive constituents exhibiting antihelminthic, anti venom, stomachic, anti ulcers properties ,from decoction obtained from various parts of the plant [7]. A potent phytoconstituents found in majority of species of Ophiorrhiza is Camptothecin (CPT) is an essential precursor of semisynthetic chemotherapeutic agents (irinotecan, topotecan, etc.) used for treatment of various forms of cancers throughout the world[8]. Exploration of new species of Ophiorrhiza is important to identify more potent medicinal sources.

Ophiorrhiza mungos Linn , Rubiaceae commonly known as mongoose plant is identified by characters like presence of interpetiolar stipules, gamopetalous corolla and inferior ovary. The leaf drug is identified by the presence of rubiaceous stomata, septate, multicellular trichomes containing crystal sand inclusion, resinous content in the cells of ground tissue , vessels with spiral and pitted thickening which serve as useful pharmacoeial properties[9]. Plant is a suffretescent herb, 45-60 meter height[10]. Leaves are dorsiventral, simple, petiolate, membranaceous, greenish on the upper surface and greenish–white on the lower surface, minutely pubescent beneath, lamina and petiole shrivelled and curved when dry . It has a bitter taste with a characteristic pungent odour [9],elliptic-lanceolate, acuminate; long attenuate at base, flowers white, in sub-umbellate cymes. Fruits compressed, coriaceous, seeds numerous angular, pale brown[10].O. mungos var. angustifolia is distributed all over peninsular India and Sri lanka.[11].

Ethnopharmacological uses of Ophiorrhiza sp:

Different species of Ophiorrhiza have been known to be used as traditional herbal medicines and as sources of secondary metabolites.

O. mungos ,is specifically known as ‘snakeroot’ due to its ability to treat snakebite [7]. Traditionally the decoction of roots, leaves and bark of O.mungos are given as a stomachic. Leaves are used for dressing ulcers. It is also used as an antihelmintic counteracts poisonous effects of scorpion sting, rat, and snake bites and also heals ulcers. Leaves and stems of O. mungos contain hydrocyanic acid. Leaves contain alkaloid camptothecin, 10-methoxycamptothecin and β-sitosterol. Roots contain starch and a light brown resin [12]. In Ayurveda, roots of the plant is used for treatment of cancer, leprosy etc [13].Luteolin-7-O-Glucoside, a flavonoid is isolated from leaves [14]. The bruised roots are used as an application for various forms of cutaneous eruptions. The leaves are said to possess alterative properties and the flowers are prescribed as a stimulant and cardiac tonic in rheumatism and heart ailments. Sri Lankans use the entire plant of O.mungos to treat snakebite, rabies, cancer and also a bitter tonic [15,16].

Camptothecin:

Camptothecin (CPT), a monoterpene indole alkaloid is regarded as one of the potent inhibitor of topoisomerise 1.Nuclear topoisomerase 1 are important human enzymes are the only known target of the alkaloid Camptothecin[17]. The two major semi synthetic derivatives of CPT, topotecan and irinotecan, are Food and Drug Administration (FDA) approved drugs effectively used for treating different cancer types and sold under the trade names Hycamtin and Camptosar are drugs currently

used in ovarian and colorectal carcinoma [18]. Camptotheca acuminata Decne. and Nothopodytes nimmoniana (Graham) Mabb.are prominent woody plants known to be traditional sources of Camptothecin, however increasing demands for Camptothecin have threatened their level of existence[4] so other wild plants are in demand to meet its increasing needs. Among the Ophiorrhiza species , O.mungos is known to contain highest CPT levels (0.02 % g dw). CPT level was determined in plants before flowering (0.074 ± 0.003 % g dw) and at flowering (0.052 ±0.002 % g dw) [18]. Topotecan is presently indicated as a second-line therapy for advanced ovarian cancer and small cell lung cancer. Irinotecan is approved for use in the treatment of advanced colorectal cancer, both as first-line therapyin combination with 5-fluorouracil and as salvage treatment in 5-fluorouracil refractory disease [19]. There are several camptothecin analogues (topotecan, irinotecan, 10-methoxy camptothecin, 11-hydroxy camptothecin, desoxy camptothecin, 20-hexanoyl-10-methoxy camptothecin, 7-ethyl-10-hydroxy camptothecin, 9-amino camptothecin) which are at various stages of clinical evaluation [20].

Ophiorrhiza mungos var. angustifolia is a variety of Ophiorrhiza mungos , a HPTLC densitometry study was performed and it demonstrated the presence of high amount of camptothecin in this plant compared to other species of Ophiorrhiza[21].Apart from its potential anticancer activity, camptothecin is also active against the fowl plague virus [22], Trypanosomes leishmania [23], the Human Immuno Deficiency virus(HIV), and the equine infectious anaemia virus [24].

Pharmaceutical compounds :
The family Rubiaceae is known to possess diverse bioactive metabolites such as iridoids, indole alkaloids, anthraquinones, terpenoids (i.e., diterpenes and triterpenes), flavonoids,and many other derivatives of phenolic compounds, which result in their respective significant pharmacological activities [25] .The phytochemical analysis of O. mungos have revealed the positive presence of phytochemicals like alkaloids, carbohydrates and glycoside , fixed oils and fats, phytosterols , flavonoids , phenolic compounds and tannins etc [9]. Camptothecin and its derivatives,namely pumiloside, luteolin, harman, tetrahydroalastonine, bracteatine, blumeanine, strictosidinicacid, and lyalosidic acid are important phytochemicals found in most Ophiorrhiza species[26]. These compounds derived from Ophiorrhiza species are proven to be a potential source of drug for curing various diseases including the potent cancer replacing synthetic anticancer drugs with various side effects .

1 **Alkaloids**:
Camptothecin, a modified monoterpene indole alkaloid is found in abundance in O.mungos and O. mungos var.angustifolia have potent anticancer property[27]. It consists of a pentacyclic ring structure, which includes a pyrrole(3,4β) quinoline moiety and an asymmetric centre within the alpha-hydroxyl lactone ring with 20S configuration[28].

2 **Flavonoids:**
Luteolin-7-O-glucoside, is a flavonoid reported to have found in O.mungos Linn. In particular Luteolin-7-O-glucoside [29] possess three aromatic ring structure with the characteristics of 5,7,3',4 oxygenated flavones. Hydrolysis of Luteolin-7-glycoside with acid will generate luteolin-7-O-β-glucosides.[29]Luteolin-7-O-glucoside[29] typically yield potent anti-oxidant, anti-inflammatory and anti –cancer properties[30], besides it is known to protect the GI tract from ethanol and indomethacin-induced gastric ulcer upon its remodelling in rats[31].

Pharmacological mechanism of action:
Ophiorrhiza mungos encompasses diverse structurally active biological compounds which finds use in traditional medicines. The major group of compounds reported from preliminary screening of hexane and methanol extract revealed the presence of phenolics, flavonoids, coumarins, steroids, terpenoids, saponins, carbohydrates and alkaloids[26] . These compounds have
1 **Antiviral activity**: The ethanolic extract of root , stem and leaves of O. mungos showed antiviral activity, especially against the Herpes virus [16]. Camptothecin and 10-methoxycamptothecin isolated from the leaves of O. mungos have been noted to yield an active activity against the herpes virus [31].
2 **Anti venom activity** : Root extract of O. mungos acts as an antidote to neutralize Russells piper venom in intro and in vivo [32].

3 **Cytotoxic activity**: Antioxidant and cytotoxic activities of different parts of O. mungos have beenstudied[33,34] and later shown to possess high cytotoxic activity .

4. **Anti bacterial and antifungal activity** : Hexane extract of O. mungos var. angustifolia showed activity against gram positive bacteria; Bacillus subtilis and gram negative bacteria; E. coli, Klebsiella pneumonia, Staphylococcus aureus.

Hexane extract also showed moderate activity against the fungi Colletotrichum gloeosporioides and Aspergillus niger[26].

Ethyl acetate,and methanol extracts of leaves and stem of the O. mungos showed potent antimicrobial activity against nine microorganisms (B. subtilis, L. lactis, S. aureus, M. luteus, P. aeruginosa, S. typhimurium, K. pneumonia, P. vulgaris, E. coli.)[35].

Ethanolic extract of fresh flower of O . mungos showed antimicrobial activity with six pathogens B. subtilis (20 mm), K. pneumonia (19 mm), P.aeruginosa (14 mm), S. aureus (14 mm), S. mutans(11 mm), C. albicans (16 mm)[36].

5.**Anticancer activity**: Normal cells grow and divide for a limited time period but due to altered gene expression of DNA certain cells proliferate and divide in an uncontrollable manner which are cancerous in nature , consequently resulting in the resistance of apoptosis and continuous divison [37].Furthermore natural antioxidants found in the body control production of free radicals and Reactive oxygen species (ROS) or destroys them , if not controlled severe damage to tissue cells may occur but cancer cells continue to proliferate actively[30].Synthetic anti cancer drugs have various side effects such as fatigue, sleep disturbances, appetite loss, nausea , hair loss etc so nature derived alternatives are preferred as a substitute to overcome the side effects[37]. Phytochemical analysis and HPTLC of aqueous and alcohol extracts of leaves of O.mungos were carried out and it indicated the presence of camptothecin[9] a potent anticancer compound, with CPT levels highest in O.mungos species[16,38]. Methanol extract using high performance liquid chromatography revealed the level of CPT was 297.94 ±2.27µg/g dry weight[26]. Besides O. mungos other species of Ophiorrhiza also contain considerable amount of Camptothecin.

Conservation Strategies:

Natural regeneration is poor in Ophiorrhiza so tissue culture is opted for regeneration of plantlets . With the growing demands for CPT, the importance for conservation of the Ophiorrhiza species urges for alternative strategies for propagation of the plants in mass scale ; with CPT levels highest in O .mungos [16,38].

Studies on the effect of Jasmonic acid in cell suspension culture of O. mungos species has revealed suspension's ability to significantly increase the production of camptothecin[39].Influence of silver nitrate and yeast extract on cell growth, showed camptothecin accumulation and cell viability, thereby leading to a significant enhancement in the production of biomass and camptothecin[40].

Different concentration of various auxins in O. mungos var angustifolia have reported to influence the biomass camptothecin production, whereby results showed the explants showed growth in presence of Murashige and Skoog(MS) medium and no growth in absence of exogenous hormones[41].

Root culture of transformed O. mungos species reported to have high production of CPT[42].Similarly seedling culture[43] and shoot culture[44] established for O.mungos species showed favourable in-vitro higher amount production of Camptothecin when compared to naturally grown plants.

Conclusion:-

In the recent times improved health is the foremost priority of human population , so herbal medicine or drugs are preferred over commercialized clinical formulations in order to ameliorate the quality of life. Most of the members of genus of Ophiorrhiza are known to contain active constituents and secondary metabolites among which camptothecin is a potent constituents ; however the quantity of these constituents may vary due to geographical factors, climatic conditions, time or period of collection of plant, abiotic stress etc. So, it is job of the researchers to emphasize the significance of the plant in an attempt to further explore its potentiality as a drug , and to find other new bioactive molecules, which may prove to be a remedial source for various other diseases as well. At the same time alternate methods of propagation like tissue culture and various in vitro methods of propagation should be encouraged for its sustainable production. This would reduce pressure on the plant due to its high demand .

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