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Pharmacological Potential and Therapeutic Applications of Inula racemosa: A Comprehensive Review of Ethnopharmacology, Phytochemistry, and Bioactivity

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Abstract: Inula racemosa, also known as Pushkaramula, is a well-documented medicinal plant in India, belonging to the Asteraceae family. This review article aims to comprehensively gather and examine scientific research on the ethnopharmacology, phytochemistry, and bioactivity of I. racemosa, encompassing its isolated phytoconstituents and extracts. Traditionally, the plant has been utilized for its anti-inflammatory, cardiovascular, hypoglycemic, antianginal, analgesic, and antibacterial properties, which have been validated through experiments on various animal models. Furthermore, the plant's distribution, physical characteristics, and traditional uses are emphasized, highlighting its potential for further exploration and utilization in the field of pharmacology. The diverse range of pharmacological effects exhibited by Inula racemosa, particularly the bioactivities of alantolactone and isoalantolactone, underscores the plant's importance and the possibility of discovering novel chemical compounds for further application.

Index Terms **- Inula racemosa, ethnopharmacology, phytochemistry, bioactivity.**

I. INTRODUCTION

Inula racemosa is widely present in India, China, and Europe, thriving in the temperate and alpine regions of the Western Himalayas at elevations ranging from 1300 to 4500 meters. Its distribution spans the temperate alpine Himalayas, ranging from altitudes of 1500 to 4200 meters, extending from Kashmir to Kumaon, Afghanistan to Central Nepal. In its natural habitat, it can be found growing among robust alpine scrub vegetation in the cold, arid environment of the NW Himalayas, specifically between 2700 and 3500 meters in the eastern Ladakh (Leh) region of Kashmir.

Domesticated forms of this incipient cultigen are cultivated on borders of agricultural fields of wheat, barley and buckwheat both in Kashmir and Lahaul valley of Himachal Pradesh[1]. The plant is a stout shrub, bearing large leaves arranged in a racemose manner. The stem is grooved and all vegetative parts are scabridtomentose. Lower leaves are narrowed to a winged leaf stack. Upper leaves are lanceolate and stem clasping. The abaxiallaminal face is densely tomentose. The fresh root is brown and becomes grayish on drying. The fresh roots resemble the aroma of camphor. The fruits, slender achenes have long pappus hairs. Root stock is branched. Sometimes a number of roots are found in the collar zone, though usually few occur in each clump. These roots have a dull brownish skin with yellowish colour inside. They possess a sweet and somewhat camphoraceous odour and have a bitter taste[2].

Inula racemosa is known to be used in traditional medicine throughout the world, especially East Asia and Europe. Apart from being used for other ailments, the plant extract and its isolated active constituents show promising activity against abdominal pain, acute enteritis, bacillary dysentery, expectorant and tonic[2]. Inula

racemosa is also used in combination with other plant extracts and used for various conditions including hyperlipidemia, angina and patients with Ischemic Heart Disease[3]. Various active constituents have been isolated from the plant, most important being sesquiterpene lactones Alantolactone (ALT), and isoalantolactone (IALT) that show anti-inflammatory and decreased proteolytic activity[4-5]. This review is therefore aimed to comprehensively collect all the literature regarding ethnopharmacology, phytoconstituents, and biological activity of Inula racemose.

II. ETHNOPHARMACOLOGY

Inula racemosa has been used as traditional medicine in East Asia and Europe. In China it has been prescribed for abdominal pain, acute enteritis and bacillary dysentery. The roots are widely used as indigenous medicine, as an expectorant and in veterinary medicine as a tonic[2]. Native Americans use this plant for treatment of tuberculosis[6]. Root powder is reportedly hypoglycemic and hypocholesterolemic in human subjects[7]. It brought about a beneficial improvement in ST-T changes in ECG of patients with ischemic heart disease (IHD)[8].

Combination therapy of Inula racemosa with other plants and extracts has also shown substantial biological activities. It is anti-anginal and hypolipidemic when used in combination with guggulu in patients with Ischemic heart disease[3]. It exerts cardioprotective effect in isoproterenol induced myocardial ischemia in rats when used in combination with drugs Terminalia arjuna and Commiphora muku[l9]. It reduced corticosteroid induced hyperglycaemia in mice when used with Gymnema leaf extract[10].

The drug exhibited negative chronotropic effect and positive ionotropic effect on isolated frog heart with petroleum ether extract(200mg/kg). Further, increase of dose to 400mg/kg exhibited adrenaline-induced beta blocking activity in rats[11]. Petroleum ether extract exhibited less hepatoprotective activity as compared to the aqueous, methanolic and total aqueous extract[12]. Moreover, with the alcoholic extract significant protection against egg albumin induced passive cutaneous anaphylaxis was provided and the alcoholic extract is non-toxic upto 2100±60mg/kg i.p in rats[13]. Furthermore, anti dermatophytic and anti-cholinergic activities were exhibited by the crude alcoholic extract, the former reportedly localized in the hexane soluble fraction[14].

III. ISOLATED PHYTOCHEMICAL CONSTITUENTS FROM INULA RACEMOSE

Inula racemosa yields large amounts of sesquiterpene lactones as-Alantolactone (ALT) and isoalantolactone (IALT)4, Dihydroalantolactone, dihydroisoalantolactone, inunolide[15], dihydroinunolide, neoalantolactone, isoalloalantolactone[16], alloalantolactone[17], inunal, isoinunal[18], alantodiene and isoalantodiene[19] are other sesquiterpene lactones isolated from the non-polar fractions of the root. Daucosterol, D- mannitol and Beta sitosterol have also been reported in good quantities from the roots[20]. Roots of 'mano' from Kashmir is reported to yield 5.7-6.2% petroleum ether extract while those from Lahaul valley, Himachal Pradesh reportedly yield 8.5%w/w constituted of 83%lactones[1]. The major lactones ALT and IALT are in the ratio 4:6. Investigation on the aerial parts of Inula racemosa reported the presence of several other sesquiterpene lactones namely ivalin acetate, 2d-OH alantolactone, 1- desoxy-8-epi-ivangustin, 8-epiisoivangustin, 9β-OH costunolide, 9β-propionyloxycostunolide, 9β-(2-methylbutaryloxyl) costunolide, 4β-5α-epoxy-10 α, 14H inuviscolide, 4β, 5α-epoxy-4,5-cis-inunolide, 4H-tomentosin, 4H carborne.

IV. BIOLOGICAL ACTIVITIES OF ISOLATED COMPOUNDS

"Sesquiterpene lactones are important because of their various biological activities and generic inhibition of enzymes[21]. They provide protection to the plant against various pathogenic organisms, insects and mammals. They are secondary metabolites of plant exerting various biochemical effects on other flora and vertebrate poisoning[22].

The main sesquiterpene lactones found in Inula racemosa are ALT and IALT5 .Amixture containing both the lactones is called Inula camphor (Helenin). In antiquity Inula helenium (Elecampane) contains both ALT and IALT. It was added to food as a seasoning in the middle age and later, it came to be used for medicinal purposes. Now a days, this mixture is the active principle of drug Alanton which is used for ulceration[23]. The drug is anti-inflammatory, antiproteolytic and is used to regulate the acidic function of the stomach. Alanton also promotes mucin formation and stimulates the regenerative capacity of the gastric mucosa[5].

ALT and IALT promotes the growth in number of rootlets of Phaseolus aureus by a factor of 2-2.5 as compared to control in the experiment[24]. IALT is herbicidal because of its lipophilicity. It gets incorporated into cell membrane and does not reach to other regions of the plant[25].

ALT and IALT showed an increase in the antioxidant activity of lipids at doses of 100-200 mgkg-1, their action considerably more than antioxidant activity of α-tocopherol and ubiquinone. The anti-tussive activity of helenin in guinea pigs has been seen, but it is half that of codeine[5,26].

Both ALT and IALT possess antibacterial activities against many of gram positive and gram-negative bacteria. ALT is completely inhibitory to Bacillus subtilis, while IALT exhibited weak antibacterial activity towards Bacillus subtilis and Bacillus vulgaris. ALT and helenin possessed pronounced inhibitory effect against Staphylococcus aureus and Mycobacterium tuberculosis at 31.2-62.5 and 31.22µg/ml respectively.

The antifungal activity has been studied in relation to more than 16 different cultures for both ALT and IALT, inhibited the growth of all the fungi studied, but the effects for each individual culture differed greatly. For zoophilic fungi Microsporium cookie and Trichophyton mentagrophytes both ALT and IALT exhibited their greatest inhibitory effect[27]. The antibacterial and antifungal activity of sesquiterpene lactones has been mainly due to the presence or absence of α - methylene group in the lactone ring alone[28]. This has been proved by the SAR of several sesquiterpene lactones.

V. BIOLOGICAL ACTIVITY OF DIFFERENT EXTRACTS OF INULA RACEMOSE

Anti-Inflammatory Activity

The anti-inflammatory activity of the ethanol extract of the roots of Inula racemosawas evaluated by carageenan-induced paw edema in rats. Ethanol extract showed maximum inhibition (34.17%) at a dose of 200 mgkg−1 , body weight (b.w.) after 2 h of drug administration in carageenan-induced paw edema. Aspirin (100 mgkg−1) was used as standard drug produced 17.50% of inhibition in paw edema[29]. In another study, aqueous extract of the roots of I. racemosa showed maximum inhibition(60%) at a dose of 400mgkg-1b.w. after 8 h of drug administration in carageenan-induced paw edema in rats, whereas standard drug indomethacin (20 mgkg−1) produced 69% of inhibition[30].

Analgesic Activity

Analgesic effect of ethanol extract of the roots of Inula racemosa was performed in albino rats of either sex using hot plate. Ethanol extract of the plant showed latency in percentage protection (42.99%) at a dose of 200 mg/kg, b.w. after 2 h of drug administration. Standard drug aspirin (100 mgkg−1) produced 65.47% latency of percentage protection 41. Also, analgesic effect of aqueous extract of the roots of Inula racemose was performed in albino mice of either sex by acetic acid-induced writhing and tail immersion methods. Aqueous extract of plant at a dose of 400 mgkg-1 showed higher latency of percentage protection (63%), whereas in tail immersion model the highest enhanced reaction time was observed at 400 mgkg-1 (8.65 ± 1.63 at 3 h)[31].

Cytotoxic Activity

In-vitro cytotoxic activity of 95% ethanol extract of Inula racemose roots and its different fractions (n-hexane, chloroform, n-butanol and aqueous) was evaluated on colon, ovary, prostate, lung, CNS and leukemia cancer cell lines using sulphorhodamine-B dye and MTT assay for HL-60 cell line. The major constituents of hexane fraction i.e. alantolactone and isoalantolactone was studied for its mode of action in HL-60 cells. The lowest IC50 value (10.25 µgmL−1) was found for n-hexane fraction for Colo- 205, a colon cancer cell line, whereas 17.86 µg·mL−1 was the highest IC50 value found for CNS cancer cell line (SF-295)[30]. Ma et al isolated racemosalactones A, alantolactone, isoalantolactone, alloalantolactone, 5-α-epoxyalantolactone, α-epoxyisoalantolactone and isotelekin from the methanol roots extract of Inula racemosa. All the isolated compounds were evaluated for their antiproliferative activities using human non-small-cell lung cancer (A-549), hepatocellular carcinoma (HepG-2) and human fibrosarcoma (HT-1080) cells using CCK-8 dye. All the tested compounds exhibited anti-proliferative activities with IC50 values ranging from 0.38 to 4.19 µgmL-1 against human non-small-cell lung cancer. A-549, hepatocellular carcinoma HepG-2, and human fibrosarcoma HT-1080 cells. Isolated compounds alantolactone and isoalantolactone were evaluated for antiproliferative activity against human umbilical vein endothelial cells (HUVECs). IC50 values for these two compounds were found to be 2.4 and 2.5 µgmL−1 , respectively[32].

Antioxidant Activity

Antioxidant activity of 70% ethanol extract of the roots of Inula racemose was performed in Albino rats. The effect of daily oral administration of alcoholic extract (suspended in 1% gum acacia) of the roots of Inula racemose to rats for 21 days was investigated for lipid peroxide formation and reduced glutathione 51 content. The level of GSH in blood and liver was found significantly higher in treated animals as compared to control (1%gum acacia). Result showed that Inula racemose has antioxidant properties because greater availability of GSH to the cell would lead to higher rate of destruction of deleterious hydrogen peroxide and lipid peroxides by glutathione peroxidase[13].

Anti-Allergic Activity

Mast cell stabilizing activity of 90% ethanol root extracts of Inula racemosa was evaluated on degranulation of rat peritoneal mast cell induced by compound 48/80 and egg albumin. Effect of plant extract on egg albumin induced mast cell degranulation in rats at concentration of 5, 10, 20 and 40 μgmL−1 produced dose related inhibition of 18.85, 39.96, 58.97 and 71.65% respectively. Whereas, kitotifen (standard drug, 10 μgml−1) was found to inhibit degranulation to avc n extent of 78.22%. Effect of Inula racemosa extract on compound 48/80 induced mast cell degranulation in rats at same concentration showed reduction in degranulation to 20.36, 37.08, 59.52 and 41.28% respectively while standard drug kitotifen was found to inhibit degranulation to an extent of 77.52%[33].

VI. CONCLUSION

Inula racemosa is a medicinal plant of immense importance with a diverse pharmacological spectrum. There is a great scope for further screening of the plant against various respiratory, antihistaminic and cardiovascular disorders. The plant can also be evaluated against hyperglycemia, cytoprotective and hepatoprotective properties. Thus, the broad spectrum of the biological activities of alantolactone and isoalantolactone completely justifies the Russian name of the compound from which these compounds were isolated – devyasil (nine powers). Moreover, the phytochemical screening can also be performed to explore new chemical entities present in the plant for further exploitation of species.

REFERENCES

1) Singh, G.; Paul, V.; Handa, K., Chemical composition of the essential oil of Inula racemosa roots from plants growing in Jammu and Kashmir. J. Sci. Indust. Res. B 1959,18, 351-352.
2) Chopra, R. N.; Nayar, S. L.; Chopra, I. C., Glossary of Indian medicinal plants. New Delhi.: C SIR 1956.
3) Singh, R.; Singh, R.; Batliwala, P.; Upadhyay, B.; Tripathi, S., Puskara-Guggulu, an Anti-anginal and Hypolipidemic Agent in Coronary Heart Diseases (CHD). Jour. Res. Ay. & Siddha 1991,12.
4) Arora, R.; Maheshwari, M.; Chandel, K.; Gupta, R., Mano (Inula racemosa): Little known aromatic plant of Lahaul valley, India. Economic Botany 1980,34 (2), 175-180.
5) Milman, I., Alanto-and isoalantolactones. Chemistry of Natural Compounds 1990,26 (3), 251-262.
6) Moerman, D. E. Medicinal plants of native America; 1986.
7) Tripathi, S.; Tiwari, C.; Upadhyay, B.; Singh, R., Screening of hypoglycemic action in certain indigenous drugs. Journal of Research in Indian Medicine, Yoga and Homeopathy 1979,14, 159-169.
8) Tripathi, S.; Upadhyaya, B.; Gupta, V., Beneficial effect of Inula racemosa (pushkarmoola) in angina pectoris: a preliminary report. Indian journal of physiology and pharmacology 1983,28 (1), 73-75.
9) Seth, S.; Maulik, M.; Katiyar, C.; Maulik, S., Role of Lipistat in Protection against Isoproterenol Induced Myocardial Necrosis in Rats: A Biochemcial and Histopathological Study. Indian journal of physiology and pharmacology 1998,42, 101-106.
10) Gholap, S.; Kar, A., Effects of Inula racemosa root and Gymnema sylvestre leaf extracts in the regulation of corticosteroid induced diabetes mellitus: involvement of thyroid hormones. Die Pharmazie-An International Journal of Pharmaceutical Sciences 2003,58 (6), 413-415.
11) Tripathi, Y.; Tripathi, P.; Upadhyay, B., Assessment of the adrenergic beta-blocking activity of Inula racemosa. Journal of ethnopharmacology 1988,23 (1), 3-9.
12) Rao, K.; Mishra, S., Hepatoprotective activity of Inuta racemosa root. Fitoterapia 1997,68 (6), 510-514.
13) Sharma, V.; Hem, K.; Sharma, D.; Singh, V. P.; Singh, N. K., Journal of Natural Products and Resources.
14) Tripathi, V.; Agarwal, S.; Srivastava, O.; Rastogi, R., Antidermatophytic constituents from Inula racemosa Hook f. Indian Journal of Pharmaceutical Sciences 1978,40 (4), 129-131.
15) Raghavan, R.; Ravindranath, K.; Trivedi, G.; Paknikar, S.; Bhattacharyya, S., Inunolide--a new sesquiterpene lactone from Innula racemosa root. Indian journal of chemistry 1969.
16) Ravindranath, K.; Raghavan, R.; Paknikar, S.; Trivedi, G.; Bhattacharyya, S., Structure and stereochemistry of inunolide, dihydroinunolide and neoalantolactone. 1978.

17) Bhandari, P.; Rastogi, R., Alloalantolactone, a sesquiterpene lactone from inula-racemosa. Council scientific industrial research publ & info directorate, new delhi 110012, india: 1983; Vol. 22, p. 286-287. Qurba Firdous et al / Int. J. Res. Ayurveda Pharm. 9 (1), 2018 101
18) Kalsi, P.; Goyal, R.; Talwar, K.; Chhabra, B., Epoxy alantolides: isoinunal—a new potent plant growth regulator from Inula racemosa. Phytochemistry 1988,27 (7), 2079- 2081.
19) Kalsi, S.; Goyal, R.; Talwar, K.; Chhabra, B., Stereostructures of two biologically active sesquiterpene lactones from Inula racemosa. Phytochemistry 1989,28 (8), 2093-2096.
20) Tan, R.; Tang, H.; Hu, J.; Shuai, B., Lignans and sesquiterpene lactones from Artemisia sieversiana and Inula racemosa. Phytochemistry 1998,49 (1), 157-161.
21) Matthews, V.; Åström, M.-B.; Chan, M.; Bruce, C.; Krabbe, K.; Prelovsek, O.; Åkerström, T.; Yfanti, C.; Broholm, C.; Mortensen, O., Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia 2009,52 (7), 1409-1418.
22) Ober, A. G.; Fischer, N. H., Sesquiterpene lactones from Calea septuplinervia. Phytochemistry 1987,26 (3), 848-849. 23. Fu, B.; Su, B.-N.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O., A bissesquiterpene and sesquiterpenolides from Inula macrophylla. Phytochemistry 2001,58 (7), 1121-1128.
23) Kashman, Y.; Lavie, D.; Glotter, E., Sesquiterpene lactones from Inula helenium. Israel Journal of Chemistry 1967,5 (1), 23-27.
24) Al-Yahya, M. A.; Khafagy, S.; Shihata, A.; Kozlowski, J. F.; Antoun, M. D.; Cassady, J. M., Phytochemical and biological screening of Saudi medicinal plants, Part 6. Isolation of 2α-hydroxyalantolactone the antileukemic principle of Francoeuria crispa. Journal of natural products 1984,47 (6), 1013-1017.
25) Topçu, G.; Öksüz, S.; Shieh, H.-L.; Cordell, G. A.; Pezzuto, J. M.; Bozok-Johansson, C., Cytotoxic and antibacterial sesquiterpenes from Inula graveolens. Phytochemistry 1993,33 (2), 407-410.
26) Kaur, B.; Kalsi, P., Stereostructures of inunal and isoalloalantolactone, two biologically active sesquiterpene lactones from Inula racemosa. Phytochemistry 1985,24 (9), 2007-2010.
27) Picman, A. K., Biological activities of sesquiterpene lactones. Biochemical Systematics and Ecology 1986,14 (3), 255-281.
28) Vidari, G.; De Bernardi, M.; Vita-Finzi, P.; Fronza, G., Sesquiterpenes from Lactarius blennius. Phytochemistry 1976,15 (12), 1953-1955.
29) Pal, H. C.; Sehar, I.; Bhushan, S.; Gupta, B. D.; Saxena, A. K., Activation of caspases and poly (ADP-ribose) polymerase cleavage to induce apoptosis in leukemia HL60 cells by Inula racemosa. Toxicology in vitro 2010,24 (6), 1599-1609.
30) Dalvi, R.; Singh, B.; Salunkhe, D. K., A study on phytotoxicity of alantolactone. Chemico-biological interactions 1971,3 (1), 13-18.
31) Jagdale, A. C. S. C., Antibacterial activity of isolated constituents and extract of roots of Inula racemosa. Research Journal of Medicinal Plant 2007,1 (1), 7-12.
32) Xu, R.; Zhou, G.; Peng, Y.; Wang, M.; Li, X., Pharmacokinetics, tissue distribution and excretion of isoalantolactone and alantolactone in rats after oral administration of Radix Inulae extract. Molecules 2015,20 (5), 7719-7736.
33) Ohta, Y.; Andersen, N. H.; Liu, C.-B., Sesquiterpene constituents of two liverworts of genus Diplophyllum: novel eudesmanolides and cytotoxicity studies for enantiomeric methylene lactones. Tetrahedron 1977,33 (6), 617-628.