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A review on the anti-cancerous activity of an important medicinal plant *Inula racemosa* Hook. F.

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ABSTRACT

The word" Cancer" is an umbrella term with a group of approximately 200 diseases. Cancer has emerged as a major problem globally. It is the second largest health problem of the world after cardiovascular diseases both in developed and in developing countries. At present, there is no specific treatment for the cure of cancer as allopathic medicines provide only short time relief from symptoms or severity. Radiotherapy or chemotherapy also gives a way for temporary relief but at the cost of severe side effects. Surgical interventions, chemo and radio therapies have failed consistently to cure many varieties of cancers. This hopeless situation demands for newer kind of therapeutic interventions which may not be the conventional modes of therapy. Scientific research interest is drawing its attention towards naturally-derived compounds as they are considered to have less toxic side effects. Inula racemose Hook. F. has proved to be a great success for the treatment of this deadly disease. The plant has several anti cancerous properties which make it very effective in the treatment of all types of cancer. The review discusses the important role of I. racemose in the treatment of cancer and it types.

Keywords: Cancer, Radiotherapy, Chemotherapy, Anti-cancerous, Inula racemosa

I. INTRODUCTION

Cancer is a major burden of disease worldwide. Each year, tens of millions of people are diagnosed with cancer around the world, and more than half of the patients eventually die from it. In many countries, cancer ranks the second most common cause of death following cardiovascular diseases. With significant improvement in treatment and prevention of cardiovascular diseases, cancer has or will soon become the number one killer in many parts of the world. As elderly people are most susceptible to cancer and population aging continues in many countries, cancer will remain a major health problem around the globe. Based on the GLOBOCAN database, there were about 10,862,496 new cancer cases (excluding skin cancer) in the world in 2002. Of these, 5,801,839 (53.4 percent) were male and 5,060,657 (46.6 percent) were female. Nearly 45 percent of the new cases were diagnosed in Asia, 26 percent in Europe, 15 percent in North America, 7 percent in Latin America, and 6 percent in Africa. For males and females combined, the most common cancer site worldwide was lung (965,446 male and 386,875 female cases per year). The second most common site was colon (550,513 males and 472,743 females), followed by stomach (603,003 males and 330,290 females). Among women, the number one cancer site was breast (1,152,161 new cases per year), followed by cervix (493,100 cases), and colon

(472,743 cases). Among men, the three most common cancer sites were lung (965,446 cases), prostate (679,060 cases), and stomach (603,003 cases) (Ma and Yu, 2006).

The number of deaths caused by cancer worldwide in 2002 was 6,723,887, among which 3,795,991 were male and 2,927,896 were female. Lung cancer led to most cancer deaths in the world. In 2002, the total death toll due to lung cancer was 1,179,074, of which 848,321 were male and 330,753 were female. The second on the list was stomach cancer, which resulted in a total of 699,803 deaths, including 445,691 in males and 254,112 in females. Liver cancer was the number three cause of cancer mortality. A total of 598,412 deaths (416,926 male and 81,486 female) were attributed to liver cancer in 2002. For women, the top three sites for cancer mortality were breast (411,093 deaths), lung (330,753 deaths), and cervix (273,449 deaths), while lung (848,321), stomach (445,691), and liver (416,926) constituted the top three sites for cancer mortality in men. In 2002, Asia had the largest number of cancer deaths in the world, a total of 3,355,928 deaths, including 1,983,473 males and 1,372,455 females, followed by Europe (1,701,472), and North America (631,971). The World Cancer Report tells us that cancer rates are set to increase at an alarming rate globally. Although many different approach such as surgery, radiation therapy, hormone therapy, biological therapy, gene therapy, vaccine therapy and others are employed for cancer treatment but complete cure of cancer is still not possible. Treatments for cancer went through a slow process of development. Early in the 20th century, the only curable cancers were small and localized enough to be completely removed by surgery. Later, radiation was used after surgery to control small tumor growths that were not surgically removed. Finally, chemotherapy was added to destroy small tumor growths that had spread beyond the reach of the surgeon and radiotherapist. The beginnings of the modern era of cancer chemotherapy can be traced directly to the discovery of nitrogen mustard, a chemical warfare agent, as an effective treatment for cancer of the lymph nodes called lymphoma. This agent served as the model for a long series of similar but more effective agents (called "alkylating" agents) that killed rapidly proliferating cancer cells by damaging their DNA. Not long after the discovery of nitrogen mustard, a compound named aminopterin related to the vitamin, folic acid, produced remission in acute leukemia in children. Aminopterin blocked a critical chemical reaction needed for DNA replication. That drug was the predecessor of methotrexate, a commonly used cancer treatment drug today. Over the years, the development and use of chemotherapy drugs have resulted in the successful treatment of many people with cancer.

Currently there are four major classes of chemotherapeutic agents like the taxanes (paclitaxel and docetaxel), the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), and the camptothecin derivatives (topotecan and irinotecan) are used to treat different type of cancer. All the above mentioned cancer chemotherapeutic agents are mainly derived from plants. Therefore, plants are being actively explored as a source of new molecules that can curtail cancer growth and possess enormous potential to provide drugs being the reservoir of natural chemicals.

For thousands of years medicine and natural products have been closely linked through the use of traditional medicines (Grabley and Thiericke, 2000; Mann, 2000; Newman *et al.*,2000). The therapeutics use of plant products (herbal medicine) is perhaps the oldest medical practices (Mukherjee *et al.*,2007).

Inula racemosa Hook.F. commonly known as Pushkarmula (Asteraceae family) is a well documented Indian medicinal plant. Puskaramula is one of the herbs mentioned in all Ayurvedic scriptures. It possesses various synonyms like kasari an enemy of cough, sulahara – pain killer, svasari – an enemy of breathlessness, kasmira – grows abundantly in Kashmir, sughandhika – fragrant etc. The great sage Caraka has categorized it as hikka nigrahana – stops hiccup and svasahara – hana – stops hiccup and svasahara – alleviates the breathlessness, asthma. It is also as the best medicament for pleurisy along with cough and asthma. Puskaramula is highly acclaimed to be the drug of choice for pleurisy (parsvasula).

II. CLASSIFICATION

Kingdom- Plantae
Phylum -Magnoliophyta
Class -Magnoliopsida
Order- Asterales
Family- Asteraceae
Tribe -Inuleae
Genus- Inula
Species- *I. racemosa*

Inula, exists as more than 100 species, and it is found mainly in Europe, Africa, and Asia. The plant, Inula racemosa is widely distributed in India, China and Europe. The plant grows in temperate and alpine Western Himalayas from 1300 to 4500 meters elevation. The plant is a stout herb growing 0.33-2 meters in height. The stem is grooved, rough and very hairy. The leaves are elliptical, large, 3-6 cm long and 2-3 cm broad, and have long petioles. The fruits, slender achene's, 0.4 cm long, bearded with 0.75 cm long pappus hairs. The flowers are yellow, many in heads, 0.5-1 cm in diameter. The fresh root is brown and becomes grayish on drying. The fresh roots resemble in aroma of camphor.

The plant, *Inula racemosa* has been used as a traditional drug in India, China and Europe. The root of the plant *Inula racemosa* is widely used as indigenous medicine as an expectorant and in veterinary medicine as a tonic (Chopra *et al.*,1956). Plant extracts are prescribed for abdominal pain, acute enteritis and bacillary dysentery. Native Americans used the plant for treatment against tuberculosis (Moerman, 1986). *Inula racemosa* is hypoglycemic but at the same time it blocks Adrenaline-induced hyperglycemia (Tripathi and Chaturvedi, 1995).

III. CHEMICAL CONSTITUENTS OF *INULA*

Plants of the Asteraceae family produce a wide array of sesquiterpenoid compounds, especially sesquiterpene lactones (SLs), as their main secondary metabolites (Bohlmann *et al.*,1978; Muhammad *et al.,* 2003) and essential oil groups (Srivastava *et al.*,1971; Bohlmann and Zedero, 1977). Sesquiterpene lactones have been identified as the active constituents of several medicinal plants used in traditional medicine, with a wide

spectrum of biological activities including, anti-inflammatory and fungicidal properties (Hwang *et al.*,1996; Cohen *et al.*,2002).

Recent studies attempted to reveal the anticancer activity and the chemotherapeutic applications of sesquiterpene lactones (Zhang *et al.*,2005). The sesquiterpene lactone and essential oil groups (Srivastava *et al.*,1971; Bohlmann and Zedero, 1977) and some phenolic acids and flavonoids were evaluated as other constituents of this genus (Kowalewska and Lutomski, 1978).

Inula racemosa has been used as traditional medicine in East Asia and Europe (Okuda, 1986). The characteristic constituents of the *Inula racemosa* are sesquiterpene lactones especially eudesmanolides, guaianolides, and germacranolides (Guo and Yang, 2005). The phytochemical investigation of plant showed the presence of alantolactone, isoalantolactone, dihydroalantolactone, dihydroisoalantolactone, sitisterol, daucosterol, inunolide, aplotaxene, phenyllacetonitile and isoinunal (Wang *et al*., 2000).

Some of sesquiterpene lactones of *Inula recemosa* have the pharmcological activities (Tripathi *et al.*,., 1988). Alantolactone and isoalantolactone are the major constituent of Inula racemosa and possess anti-fungal and anithelmintic activities (Tan *et al.*,., 1998). Its roots are expectorant, seeds aphrodisiac. The roots of Inula racemosa find use in Indian System of Medicine for cardiac asthama cough, pulmonary infections and skin diseases (Jabeen *et al.*, 2007).

In-vitro cytotoxic activity of 95% ethanol extract of *I. racemosa* 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) (Pal *et al.*,2010).

Ma *et al.*, 2013,isolated racemosalactones A, alantolactone, isoalantolactone, alloalantolactone, 5-α-epoxyalantolactone, α-epoxyisoalantolactone and isotelekin from the methanol roots extract of *I. 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 antiproliferative 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 (Ma *et al.*, 2013)

Zhang *et al.*,2010,,isolated septuplinolide, 11-*α*-13-dihydro-2-*α*-hydroxy-alantolactone, 11,13-dihydroivalin and isoalantolactone from the ethanol roots extract of *I. racemosa*. All the isolated compounds were evaluated for their cytotoxic activities using human lung cancer (A-549), human liver cancer (BEL-7402), human stomach cancer (BGC-823), human colon cancer (HCT-8) and human ovarian cancer (A-2780) cell lines using MTT assays. All the tested compounds exhibited moderate anticancer activities (Zhang *et al.*,2010).

Macrophyllilactone E, isoalantolactone isolated from *I. racemosa* was evaluated for their anti-platelet activating factor against the release of *β*- glucuronidase in rat's polymorphonuclear leukocytes, whereas ginkgolide used as a positive control. For these two compounds, inhibition ratio was found to be 65.4% and 80.5% respectively at a concentration of 10 μM whereas ginkgolide produce 68.3% inhibition (Zhang *et al.,* 2010).

Ma *et al.,* 2013, isolated (4R, 5R, 10S)-5-hydroxy-11, 12, 13- trinoreudesm-6- en-8-one isolated from the methanol roots extract of *I. racemosa*. Isolated compound was evaluated for antiproliferative activity using human lung cancer (A-549), hepatocellular carcinoma (HepG-2) and human fibrosarcoma (HT-1080) cells lines using CCK-8 viability assay. The tested compound exhibited antiproliferative activities with IC50 values 3.71, 5.94 and 3.95 μgmL−1 respectively against human non-small-cell lung cancer (A-549), hepatocellular carcinoma (HepG-2), and human fibrosarcoma (HT-1080) cell lines respectively (Ma *et al.*,2013)

Zhang *et al.*,2012, isolated alantolactone, [1(10)E]-5-*β*-hydroxygermacra- 1(10),4(15),11-trien-8,12-olide, 2-α-hydroxyeudesma-4,11(13)-dien- 12,8-β-olide from the 95% ethanol roots extract of *I. racemosa* using MTT assay. Both isolated compounds evaluated for their inhibition of LPS-induced nitric oxide production in RAW264.7 macrophages.). IC50 values for all compounds were found to be 7.39 ± 0.36, 6.35 ± 0.26 and 5.39 ± 0.18 μM, respectively (Zhang *et al.*,2012)

IV. CONCLUSION

Cancer is becoming a high profile disease in developed and developing worlds, so the demand for a cure and the prevention of cancer is extremely high. Chemically-derived drugs have been developed and other cancer treatments pre-exist. However, current methods such as surgical interventions and chemotherapy have their limitations due to their toxic effects on non-targeted tissues furthering human health problems; therefore there is a demand for alternative treatments with naturally-derived anticancer agents with plants being the desired source. Although number of plants used for their therapeutic potential against cancer, but the one highly reputed medicinal plants *Inula racemosa* Hook. F. has been proved to be great success for the cure of this life taking disease. The secondary metabolites found in the plant have providing less toxic and less side-effect method for the safe management and treatment of cancer.

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