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Overview of Flaxseed Patent Applications for the prevention and treatment of human cancer

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ABSTRACT

Flaxseed, Linum usitatissimum, is a member of the genus Linum in the family Linaceae. It is a food and fiber crop cultivated in cooler regions of the world. The aim of this study is to overview its anti-cancer and anti-tumor effects. This review article was carried out by searching studies in PubMed, Medline, Web of Science, and IranMedex databases up to 2016.totally, of 108 found articles, 41 articles were included. The search terms were "Flaxseed. ", "therapeutic", "pharmacological", anticancer, anti-tumor. Various studies have shown that Flaxseed. Possess Anti-Breast Cancer properties, Anti-Breast tumors properties , Anti-Ovary cancer properties, Gut-associated diseases properties, Lung tumor properties, Inflammation properties, Anti-Skin Carcinogenesis properties, Pro-carcinogenic, Mastalgia properties, Aortic remodeling ,Anti-mammary Cancer effect ,Antioxidant and Antiproliferative ,Colon cancer properties, Esophagitis properties, Apoptosis properties. Flaxseed possess lots of therapeutic and pharmacological effects.in this study, its anticancer, anti-tumor effects was overviewed.

Keywords: Flaxseed, therapeutic, pharmacological, anticancer, anti-tumor.

INTRODUCTION

It is proved that herbal medicine is effective in the treatment of many diseases [1-10].Flax, *Linum usitatissimum*, is a member of the genus Linum in the family Linaceae. It is a food and fiber crop cultivated in cooler regions of the world. Flax was extensively cultivated in ancient Egypt, where the temple walls had paintings of flowering flax, and mummies were entombed in linen.

The textiles made from flax are known in the Western countries as linen, and traditionally used for bed sheets, underclothes, and table linen. The oil is known as linseed oil. In addition to referring to the plant itself, the word "flax" may refer to the unspun fibers of the flax plant. The plant species is known only as a cultivated plant, and appears to have been domesticated just once from the wild species Linumbienne, called pale flax[1-4].

Several other species in the genus Linum are similar in appearance to L. usitatissimum, cultivated flax, including some that have similar blue flowers, and others with white, yellow, or red flowers. Some of these are perennial plants, unlike L. usitatissimum, which is an annual plant[5].

Flax is grown for its oil, used as a nutritional supplement, and as an ingredient in many wood-finishing products. Flax is also grown as an ornamental plant in gardens. Flax fibers are used to make linen. The Latin species name usitatissimum means "most useful"[6,7].

Flax fibers are taken from the stem of the plant, and are two to three times as strong as those of cotton. Additionally, flax fibers are naturally smooth and straight. Europe and North America depended on flax for vegetable-based cloth until the 19th century, when cotton overtook flax as the most common plant used for making rag-based paper. Flax is grown on the Canadian prairies for linseed oil, which is used as a drying oil in paints and varnishes and in products such as linoleum and printing inks[8-10].

Breast Cancer prevention

The effect of the phenolic extract from FS oil has been evaluated on two human breast cancer cell lines and on the human non-cancerous breast cell line. The extract shows anti-proliferative activity on MCF7 cells by inducing cellular apoptosis, increase of the percentage of cells in G0/G1 phase and of lipid peroxidation, activation of the H2AX signaling pathway, and upregulation of a six gene signature. The data suggest that the extract has both cytotoxic and pro-oxidant effects only on MCF7 cells, and can act as a metabolic probe, inducing differences in the gene expression. [11].

The association between intake of flaxseed-the richest source of dietary lignans [a class of phytoestrogens]-and breast cancer risk was investigated. It has found that flaxseed intake is associated with a reduction in breast cancer risk. As dietary intake of flaxseed is modifiable, this finding may be of public health importance with respect to breast cancer prevention [12].

By using microdialysis in a model of human breast cancers in nude mice, species-specific analyses of released proteins in the microenvironment was carried out. It showed that tumors treated with tamoxifen and fed Flax or ENL exhibited decreased in vivo release of IL-1β derived from the murine stroma and decreased microvessel density whereas dietary GEN had no effects. It conclude that the release of IL-1s both by cancer cells and the stroma, where macrophages are a key component, may offer feasible targets for antiestrogen therapy and dietary interventions against breast cancer[13].

In an animal study, combining dietary FO (8%) compared with TRAS treatment (2.5 or 5mg/kg body weight) on established human breast tumors overexpressing HER2 (BT-474). Combined TRAS2.5 treatment with FO caused a significantly lower tumor cell proliferation and higher apoptosis compared to TRAS2.5 treatment alone and showed similar effect to TRAS5 treatment with or without FO. Thus, FO did not interfere with TRAS but rather enhanced its tumor-reducing effects and combined FO and low dose TRAS was as effective as high dose TRAS treatment [14].

An extraction procedure for lignans from flaxseed was investigated. The ability of these two compounds and that of secoisolariciresinol diglucoside to modulate the growth of human breast cancer MCF-7 and MDA-MB-231 cell lines was assessed. Results show that lignans modulate development of breast cancer cells. The most intense effect was observed for anhydrous ecoisolariciresinol, which significantly decreased cell growth at 50 and 100 microM [15].

Mammary and ovarian cancer progression were induced using local ovarian DMBA treatment and subcutaneous sustained release 17β-estradiol administered starting at 7 weeks of age. Treatment with SDG normalized several biomarkers in mammary gland tissue (dysplasia, cell number, and expression of several genes) that had been altered by carcinogen. There is no indication that SDG promotes preneoplastic progression in the ovarian epithelium [21].

The efficacy of tamoxifen, anti-estrogen treatments for breast cancer affected some of the most important endogenous angiogenesis regulators was evaluated. Results showed that one of the mechanisms of tamoxifen in normal breast tissue include tipping of the angiogenic balance into an anti-angiogenic state and that flaxseed has limited effects on the pro-angiogenic factors whereas the anti-angiogenic endostatin may be modified by diet. Further studies of diet modifications for breast cancer prevention are warranted [23].

In vitro, co-culture of breast cancer cells and primary human adipocytes was used. The levels of leptin decreased and adiponectin increased after a dietary addition of 25 g of flaxseed/day for one menstrual cycle. We conclude that VEGF and leptin correlate significantly in normal human breast tissue in vivo and that dietary addition of flaxseed affect adipokine levels in the breast [24].

Breast tumor prevention

the effects of SDG and SES on established human estrogen receptor-positive breast tumors (MCF-7) was differentiate in athymic mice with high serum estrogen to help explain the different effects. At high serum estrogen levels, SDG may not account for the tumor reducing effect of FS. SES was more effective than SDG in reducing breast tumor growth, but its effect may have been lost when consumed as a component of SS [27].

Flaxseed (FS) reduces breast tumor genesis and human epidermal growth factor receptor 2 (HER2) expression in postmenopausal patients and animal models. TRAS reduces tumor growth by influencing HER2 signaling. Dietary FS has minimal tumor-reducing effect, does not interfere with TRAS action, but improves overall survival in athymic mice [28].

the effect of 4% FSO alone and combined with TRAS on HER2-overexpressing tumor (BT-474) growth and to explore potential mechanisms with a specific focus on HER2, mitogen-activated protein kinase (MAPK) and Akt signaling and fatty acid profile was determined. Dietary FSO alone does not affect BT-474 tumor growth but enhances the tumor-reducing effect of TRAS (2.5 mg/kg). FSO alters tumor fatty acid profile that likely contributes to effects on signaling pathways. This supports FSO as a complementary treatment for HER2+ breast cancer treated with TRAS [29].

The in vitro effects of flaxseed sprouts on cell growth and apoptosis of human breast cancer cells was investigated. The results suggest that flaxseed sprouts induce apoptosis and inhibit cancer cell growth, thereby demonstrating their anti-proliferative effects in breast cancer cells. This study may provide important information for devising dietary strategies to reduce breast cancer risk [31].

The phytoestrogen properties of the components of flaxseed Linum Usitatissimum L., especially lignans and products of their biotransformation in humans and animals enterodiol (END) and enterolactone (ENL) are presented. The antioxidant activity of SIR, END, ENL and SIR-DG is higher than that of vitamin E and the antioxidant activity of SIR, END and ENL higher than SIR-DG. Finally, in epidemiological studies have proved the anticarcinogenic activity of the components of the flaxseed and validity of recommendations for preventive and curative use in hormone-dependent tumors [32].

Flaxseed, a rich source of dietary lignans, may be a potentially effective treatment of hot flashes. A phase III, randomized, placebo, controlled trial was conducted to evaluate the efficacy of flaxseed in reducing hot flashes. The results of this trial do not support the use of 410 mg of lignans for the reduction of hot flashes. The bars were fairly well tolerated, with both groups reporting gastrointestinal effects, probably due to the fiber content [33].

The effects of SDG and FO, alone or in combination, on BMC, BMD, and biomechanical bone strength in ovariectomized athymic mice with established human breast tumors (MCF-7) treated with or without TAM were studied. FS components did not significantly attenuate the positive effects on bone induced by TAM in this model system, indicating no apparent adverse effects on bone health [34].

n-3 fatty acid-rich cotyledon fraction of FS (FC), alone or in combination with TAM, has a similar effect and thus can substitute for FS. FC reduced the growth of ER+ human breast tumours at low circulating E2, alone and combined with TAM, in part through modulation of ER- and growth factor-mediated signalling pathways; it may substitute for FS in increasing the effectiveness of TAM [36].

Anti-Ovary cancer

The independent effects of the two flaxseed components on estrogen signaling and metabolism was examined. Some targets involved in the IGF/insulin signaling pathway (IRS1, IGFBP4, IGFBP5) were downregulated by flaxseed and its components. Flaxseed diet also downregulated AKT expression. The weak anti-estrogens, enterolactone, enterodiol and 2-methoxyestradiol, might be working synergistically to generate a protective effect on the ovaries from hens on whole flaxseed diet by altering the estrogen signaling and metabolism [16].

Gut-associated diseases

The efficacy of FS on altering critical aspects of gut health in healthy unchallenged mice was evaluated. muciniphila abundance by FS was also demonstrated in the colon tissue-associated microbiota (quantitative PCR). Furthermore, fecal branched chain fatty acids were increased by FS, indicative of increased microbial-derived putrefactive

compounds. In conclusion, consumption of a FS-supplemented diet alters the baseline colonic microenvironment of healthy mice which may modify subsequent mucosal microbial defense and injury-repair responses leading to altered susceptibility to different gut-associated diseases [17].

Lung tumor
cultured metastatic tumor cells were injected into the C57BL/6 mice through tail-vein injection (TVI) and the anti-metastatic properties of flax seed oil (FSO) were evaluated. These results support the protective role of FSO against lung cancer metastasis [18].

Inflammation
The ability of flaxseed lignan component (FLC) to prevent acute asbestos-induced inflammation in MM-prone Nf2 (+/mu) mice was tested. Results showed that FLC reduces acute asbestos-induced peritoneal inflammation, nitrosative and oxidative stress and may thus prove to be a promising agent in the chemoprevention of MM [19].

Anti-Skin Carcinogenesis
The potential of flaxseed oil to prevent chemically induced skin cancer in mice was evaluated. The results of the present study demonstrate that the oral administration of FSO has the potential to modulate the levels of LPO, antioxidants, and detoxification enzymes in the DMBA-croton oil-induced skin carcinogenesis in mice [20].

Pro-carcinogenic
The optimum dose of flaxseed that would decrease PG and alter oestrogen pathway endpoints implicated in ovarian cancer was found. The findings showed that Flaxseed decreased the expression of ERα in the ovaries. The ratio of 2-OHE1:16-OHE1 in the serum increased significantly in the 15% flaxseed diet, and there was a corresponding increase in CYP1A1 in the liver and decrease in CYP3A4 in the ovaries. CYP1B1 mRNA also decreased with flaxseed diet in the ovaries. The 15% flaxseed-supplemented diet significantly decreased inflammatory PGE2, ERα, CYP3A4, CYP1B1 and 16-OHE1, but it increased CYP1A1 and 2-OHE1, which thus reduced the inflammatory and pro-carcinogenic micro-environment of the ovaries [22].

Mastalgia
The efficacy of V. agnus and Flaxseed on cyclical mastalgia. This randomized controlled trial was conducted on 159 women referred to health centers of Tabriz, Iran. Subjects were allocated into three groups (n=53 per group) using block randomization was assessed. Flaxseed and V. agnus are effective in short-term period in decreasing cyclical mastalgia. However, further studies are needed to examine the long-term effectiveness and sustainability of the effects after stopping the treatment in order to decide whether these alternative treatments are suitable to treat mastalgia or not [25].

Aortic remodeling
The influence of flaxseed flour and oil on cardiovascular biochemical parameters was evaluated and the histoarchitecture of the aorta in adult rats which were offspring of diabetic mothers. The data suggest that the use of both flaxseed flour and its oil reduces the remodeling of the aorta; however; it has not been possible to modify the cardiovascular biochemical parameters [26].

Anti-mammary Cancer effect
Low flaxseed doses relevant to human dietary exposure can prevent mammary tumors in transgenic Tg was investigated. The number of tumor-bearing mice and multiplicity of tumors at necropsy were not statistically significantly lower compared to the controls. Thus, the effect of small dietary doses of flaxseed on mammary tumor development in Tg. NK mice remains to be established [35].

Antioxidant and antiproliferative
Lignan biosynthesis and potential health benefits in flaxseeds during 10-day germination was examined. Results showed that the highest antioxidant and antiproliferative activities were found on day 10. These findings suggest that germination for 8-10days leads to optimal lignan production and potential health benefits if incorporated into the human diet [37].

The effect of Tocopherols, the main oilseeds natural antioxidants on cell membranes was investigated. The results clearly showed that utilization of polar solvent enable extraction of significant amounts of phenolics and flavonoids.

Those components were the most potent antioxidants present in those extracts. Content of these compounds correlated well with results from applied methods for antioxidant assessment [40].

Colon cancer

The influence of flaxseed (Linum usitatissimum L.) and its total non-digestible fraction (TNDF) on the expression of genes involved in azoxymethane (AOM)-induced colon cancer in Sprague Dawley rats was analyzed. Finding suggests that both of these treatments induced cell cycle arrest. In addition, TNDF induced mitochondrial apoptosis because the TNDF + AOM group exhibited the expression of caspase-3, decreased bcl-2 expression and increased bax expression. These results suggest that the expression of the analyzed genes is associated with the presence of dietary antioxidants linked to the cell wall of flaxseed [38].

Esophagitis

The present study was undertaken to elucidate the effect of Linum usitatissimum fixed oil on experimental esophagitis in albino rats. The lipoxygenase inhibitory, histamine antagonistic, antisecretory (anticholinergic) and antioxidant activity of the oil was attributed for its effect in reflux esophagitis [39].

Apoptosis

Antioxidant and antiapoptotic effects of flax seed oil (FSO) on rats exposed to ultraviolet C (UVC)was determined. This investigation demonstrated that UVC exposure led to oxidative stress and apoptosis in rats as reflected by increased MDA, PC contents and decreased enzymatic and no enzymatic antioxidant levels, FSO may be useful for preventing photo reactive damage [41].

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