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Genistein- A Potential Boon for Cancer Therapy

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Abstract
'Cancer' is one of the leading causes of morbidity and mortality all over the world. In today's scenario, diet and various dietary supplements have been seen as the efficient and potential adjuvant to prevent the different types of cancers. Soy isoflavones are one of the most potent types of natural compounds that are consumed in high amount in Asian countries. *Genistein* is a type of small and biologically active isoflavonoid which is found in soy foods and its products. It possesses various types of biological activities, but best known for its ability to cure and inhibit the progression of cancer. It is an inhibitor of cancer metastasis, cell cycle arrest, cancer cell growth and induction of apoptosis. Various in vivo and as well as in vitro studies have proved that genistein is a promising agent for prevention and therapy of cancer. In this review, we attempt to provide a sneak peak of genistein and its mechanism and therapeutic effects in various types of cancers like breast cancer, prostate cancer, colon cancer, lung cancer, liver cancer, gastric cancer etc. The main aim is to highlight the potential effects of genistein in cancer therapy.

Keywords: Genistein, Cancer, isoflavones, soy-food, phytoestrogen.

Introduction
The International Agency for Research on Cancer reviewed that around 14.1 millions of people were diagnosed with cancer out of which 8.2 million deaths were reported [1]. Most commonly types of cancers diagnosed worldwide are colorectal, lung, breast etc. Dietary habits play an important role which has a great impact on the various types of chronic diseases such as cancers [2]. The foods derived from plant have their protective effects due to the presence of various phytochemicals [3]. Micronutrient content of plants such as vitamins, minerals etc. and as well as secondary metabolites like polyphenols, terpenes, alkaloids etc. has various biological and functional activities [4]. Amongst all the micronutrients and secondary metabolites polyphenols are the most studied which have been examined for its potential and protective effects on human health [5]. Polyphenols are characterized into two types of groups namely flavonoids and non-flavonoids [6]. Isoflavones are one of the most potent types of flavonoids. Genistein and daidazein are one of the most important types of isoflavones. Intake of soybean and soy products has been allocated to the lower incidence of cancers like breast cancer and prostate cancer in Asian population due to the presence of an isoflavone called Genistein. Genistein has low toxicity and has significant biological efficacy. Due to these properties, it is tested as a potential therapeutic and protective agent for various disorders which mainly includes cancers [7], cardiovascular diseases [8] and menopausal symptoms [10]. Genistein is an isoflavone which is derived from leguminous plant. It is amongst the well-known phytoestrogens which are biologically active phenolic compounds that are derived from plants and have similar structures to the principal mammalian estrogen i.e. 17β-estradiol (E2) [11]. Genistein was first derived from dyer's broom, *Genista tinctoria* in 1899. It is a flowering plant species that belongs to family Fabaceae. Soy is one of the most exuberant sources of genistein. Since 1990, due to genistein's chemopreventive efficacy enormous amount of scientific research has been conducted on it using various types of experimental tools [12]. There are various types of tumors which are affected by genistein like breast, liver, colon, ovarian, brain, prostate etc. [13]. In soy foods, genistein is present at a concentrations range from 1.9 to 229 mg/g. That's why; it is reported to be a major type of anticancer component of soybean [14].

History
Genistein is a natural compound that belongs to class of isoflavones. It was originally isolated by Perkin and Newbury [15] in 1899 from the dyer's broom or dyer's greenweed, *Genista tinctoria. Genista tinctoria* is a species of flowering plant belonging to family Fabaceae which

is native to meadows and pastures in Europe and Turkey. Its other common names are dyer's whin, waxen wood and waxen woad. This naturally derived component is a member of isoflavones belongs to family flavonoid [15]. The compound structure was established in the year 1926. After that, it was chemically synthesized in 1928. The concentration of genistein in soy foods ranges from 0.2-1 mg/g [16]. It is also present in Trifolium species and can be isolated from fermentation broth of various types of microorganisms like pseudomonas, streptomyces etc. [17]. In 1931, Waltz discovered genistein to be a major phytoestrogen in soybean. In the year 1989, Markovits *et al*. reviewed genistein to be a topoisomerase II inhibitor [18].

Structural Characteristics

The structural backbone of isoflavones consists of 3-phenylchromen-4one in which two benzene rings are linked to a heterocyclic pyran ring. Genistein and other types of isoflavones are polyphenols in which they consist of several types of hydroxyl groups which are attached to phenyl rings. These phenyl rings lend significant amount of antioxidant activity to genistein also to other types of flavonoids like epigallocatechin 3 [21]. The structural characteristics of genistein impart genistein with the ability to act as an estrogenic compound. Due to this reason, it leads to its classification as a phytoestrogen. Genistein has both, identical molecular weight and as well as kind of similar hydroxylation pattern as compared to 17-β-estradiol. It has two main phenolic groups present at C7 and C4′ positions [22]. The hydroxyl group present at C7 position is important for genistein to bind to the estrogen receptor so that it can mimic the steroidal estrogen core.

Mechanism of Action (51)

Genistein has its action on both, molecular level and cellular level.

On the molecular level, genistein has its mechanism of action on the following:

S.No.	Molecular Level	Action
1.	Acts as a potential protein tyrosine kinase inhibitor	Protein tyrosine kinases (PTK) help in growth and differentiation of cells. In 1987, Genistein was evidenced as a potential inhibitor of PTK. At high concentrations, genistein acts a potent inhibitor of purified PTKs in whole cells.
2.	Acts as a topoisomerase II inhibitor	Topoisomerase II is a type of a nuclear enzyme that helps in the replication and transcription of DNA, responsible for regulating topology of DNA, condensation or decondensation of chromatin, separation of chromosome and maintaining proper DNA structure. Genistein is a topo-II inhibitor. It induces DNA strand breakage.
3.	Acts as an inhibitor of phosphatidyl inositol turnover	Inositol-1, 4, 5-triphosphate (IP3) is a molecule that is active in cellular pathways of signal transduction. Genistein has the ability to block both PI kinase and as well as PIP kinase, therefore inhibiting and reducing the concentration of IP3.
4.	Acts via ER (estrogen receptor)-mediated pathways	The structure of genistein resembles estrogenic steroids that are how it exhibits a quite significant estrogen like activity. Genistein binds to estrogen receptor with a relative affinity about 100-1000 fold lower than that of estradiol. It attenuates the action of estradiol-activated receptors.
5.	Acts as an inhibitor of proteins that are involved in multidrug resistance of cancer cells	Multidrug resistance (MDR) in cancer cells is most often associated with over expression of P-glycoprotein or multidrug resistance protein cellular pumps catalyzing cytotoxic drug efflux from the cells. Genistein inhibits the functions of multidrug resistant proteins. It is specific against multidrug resistance protein activity and also blocks Pgp - mediated drug efflux [27].

On the **Cellular level**, genistein acts by:

S.No.	Cellular Level	Action
1.	Apoptosis	Genistein results in induction of apoptosis. When rapidly proliferating cancer cells get treated with genistein, they undergo apoptosis.
2.	Cellular proliferation	Genistein attack different signal transduction enzymes which results in the decreased rate of cell proliferation. Genistein has better inhibitory effects in leukemic cell lines and compared to cell lines derived from tumors [33].
3.	Cellular differentiation	Genistein inhibits cell differentiation. When various cancer cell lines treated with genistein undergo differentiation followed by apoptotic cell death.
4.	Alterations in cell cycle progression	Cell cycle is a sequence of various events in cellular life which leads to cell division and proliferation. It is controlled by various enzymes and some of them are affected directly or indirectly by genistein. As genistein is both topo II and PTKs inhibitor, it can modulate or alter cell cycling.
5.	Antioxidants	Reactive oxygen species (ROS) promotes mutagenesis, carcinogenesis and tumors. Genistein can inhibit primary events necessary for increase level ROS production or it can directly inhibit production of ROS.
6.	Anti-angiogenic	Angiogenesis is the generation of new capillaries is a physiologically important process, involved in production of cardiac arrest. Genistein is one of the most potent plant derived inhibitor in preventing angiogenesis.
7.	Multidrug-resistance	Multidrug resistance is resistance to various types of commonly used anti-neoplastic agents. Genistein is the inhibitor of MRP and is used to inhibit molecular pathways of MDR.
8.	Estrogenic property	One of the most remarkable properties of genistein is its estrogenic activity. Numerous cancer cell lines that possess functional estrogenic receptor system increase proliferation rate in response to estradiol treatment. In these cells genistein at low concentrations can imitate the action of estradiol and stimulate cell growth.
9.	Osteoclastic function	Osteoclasts are macrophage derivatives which mediate physiological and pathological degradation of bone which results when the rate of osteoclastic bone resorption exceeds bone formation. Osteoclasts treated with genistein in a bone tissue culture lose their bone degradation potency.

Genistein in Cancer

Introduction

Genistein has been reported to be a natural anti-cancer agent. It is a major isoflavonoid which is isolated from dietary soybean and its products. It suppresses the growth of various types of cancers like breast, colon, prostate, lung, liver cancer. Various types of epidemiological studies have shown that there is a relation between the soy-diet and cancer prevention.

Breast cancer

Breast cancer is one of the most common type of cancer that

occurring in women all around the world. It has been estimated that around 1.4 million women were diagnosed with breast cancer in 2012 out of which 521,000 died [34]. Breast cancer corresponds to various types of prognosis and treatments that affects various essential pathways like cellular pathway that regulates cellular proliferation, signaling pathway that regulates tyrosine kinase receptors and DNA repair [35]. Genistein induces apoptosis in the estrogen receptor positive MCF-7 breast cancer cell line and in the estrogen receptor negative MDA-MB-231 breast cancer cell lines [36].

LING ZHANG et al. [37] reviewed in their study about the potential therapeutic mechanism of genistein in breast cancer. Genistein helps in preventing tumorigenesis. The main aim of their study was to find out genistein's mechanism in breast cancer and also to determine whether genistein bring forth therapeutic effect or it induces the development of breast cancer. It was found that the most signifying function and pathway of differentially expressed genes involves the cell cycle which includes several genes like CDC20, BUB1, MCM2 etc. Thus, it was concluded that genistein stimulates the change in gene expression in breast cancer cell lines which increases with increase in doses of genistein.

Genistein when combined with docetaxel and adriamycin in MDA-MB-231 cancer cell line. It leads to synergistic pro-apoptotic effect [40].

Prostate cancer

Prostate cancer begs the second position amongst the most common type of malignancy and leading cause of cancer diagnosed in men in the year 2012 [41]. Death rate increases at metastatic stage of prostate cancer. *Davis et al*. [43] studied the mechanism of action of genistein in various androgens sensitive and insensitive prostate cancer cell lines. Genistein blocked the nuclear translocation of NF-κB and also reduced the NF-κB DNA binding that leads to apoptotic pathway activation. *Janet M Pavese et al*. [44] reviewed in their study as how genistein inhibits the cell detachment, invasion and metastasis in case of prostate cancer. Abeer *M. Mahmoud et al.* [42] reviewed in their study about the various benefits of soy isoflavones in prevention and treatment of prostate cancer. Soy isoflavones stimulate growth arrest and apoptosis of prostate cancer cells. *Li et al.* [45] reviewed that when prostate cancer cell lines got treated with genistein it leads to the alteration of genes. Some genes got up-regulated and some down regulated.

Colon cancer

According to the survey done by WHO, it was found that there were approx 694,000 deaths occurred in the year 2012 due to colorectal cancer. It is the second most common type of cancer diagnosed amongst women and men [34]. There are mainly two reasons which are responsible for the growth and progression of cancer of colon. First is increase in the cell proliferation and second is loss of normal cell cycle regulation [46].

.*Jian Qina et al.* [47] demonstrated as how genistein helps in inhibiting the growth of human colorectal cancer and suppression of MiR-95, Akt and SGK1. HCT-116 cells were used to evaluate the effects of genistein on the proliferation of cell using MTT assay.

Lung cancer

According to the survey done by WHO in the year 2012, it was found that lung cancer caused approx 1.59 million deaths. [34]. Lung cancer is caused mainly by various types of carcinogens like tobacco, smoke effluents etc. [51]. Various inhibitors of epidermal growth factor receptor (EGFR) like Gefitinib and Erlotinib has a beneficial effect on non-small cell lung cancer. Genistein has the ability to enhance the activity of various EGFR inhibitors. When EGFR inhibitors got combined with genistein they lead to the increase in inhibition of growth and as well as induced apoptosis in various non-small lung cancer cell lines like H3225, H1650, H1781 etc. [52]. Genistein has anti-cancer effect on molecule induced cell cycle arrest and as well as on apoptosis also [53].

Liver cancer

In the year 2012, there were approx 7, 45,000 deaths were reported that were caused due to liver cancer. It is also known as hepatocellular carcinoma. The final stage of chronic liver disease is Cirrhosis which ultimately leads to hepatocellular carcinoma [59]. Genistein is a promising agent which has been shown to induce apoptosis in various hepatocellular carcinoma cell lines. Some of them are HuH-7, HepG2, Bel 7402 etc. Various in vivo studies have shown that when BALB/C nu/nu mice injected with Bel 7402 cells and got treated with genistein it leads to tumor growth retardation. Genistein inhibited the invasion of Bel 7402 cancer cells and also altered the apoptosis, angiogenesis and cell cycle [1].

Gu et al. [62] used MHCC97-H, a HCC model cell line to evaluate the anti-metastatic activity of genistein. When cell line got treated with genistein, it showed induced cell cycle arrest at G2/M phase. Genistein has the ability to induce apoptosis in MHCC97-H cells. It targets various cell adhesion molecules like integrin that reduces the adhesion of MHCC97-H cells.

Ovarian cancer

Cancer of ovary is one of the malignant tumors which are related to various reproductive and hormonal events. According to a study, reviewed by *Choi et al*. genistein has the ability to inhibit proliferation in the ovarian cancer cell line SK-OV-3. In this, it caused cell cycle arrest at G2/M phase [63].

Lee et al. reviewed that protective and efficient mechanism of genistein depends on the concentration. At high concentrations, it causes cell death and induces apoptosis in ovarian cancer cells. At low concentrations, it shows antioxidant activity without showing any cytotoxic effect [66].

Bladder cancer

Bladder cancer comes in the category of occupational cancers. It is caused mainly by external environmental factors like UV radiation, air pollution etc. In various in vivo and in vitro studies genistein have shown to induce apoptosis and cell cycle arrest of cancerous cells in bladder [13].

According to an in vitro study, genistein showed inhibition of growth of cancer cells in 253J B-V human bladder cancer cell line. It caused the cell cycle arrest at G2-M phase and induced apoptosis.

Brain tumor

According to the survey done by The American Cancer Society, around 22,000 malignancies related to brain were diagnosed in 2015. Around 15,000 deaths were caused in the United States in 2015 [68]. *Khaw AK et al*. [69] demonstrated that genistein induces the growth of cell cycle and inhibits telomerase activity in brain tumor cells. In this study, it was shown that genistein inhibits the growth of medulloblastoma cells and glioblastoma multiforme. Genistein treatment caused the induction of cell cycle arrest which showed that genistein is effective in radiosensitive cells.

According to *Jagadeesh et al.* [70] telomerase enzyme inhibition is mainly targeted for the treatment of brain tumor. This is because of the reason that telomerase enzymes are present in the tumor cells and are absent in normal somatic cells.

Conclusion

We reviewed the promising role of genistein in cancer prevention and therapy. It is a phytoestrogen that inhibits the growth of cancerous cell by various mechanisms like inhibition of metastasis, induction of apoptosis etc. Genistein is a potent anti-cancer agent which helps in retarding, preventing and blocking carcinogens. Various types of experiments and clinical studies suggest a therapeutic role of genistein on different types of cancers. Drug resistance, unavailability of therapies and risk of relapse are some of the negative cases in cancer treatment which are well known. Therefore; in recent years more stress has been emphasized on the natural remedies for cancer treatment so as to lower the adverse effects.

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