REVIEW ARTICLE

Genistein: A multipurpose isoflavone

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Genistein is a soya isoflavone, mainly found in legumes, such as soybeans. Isoflavones may prove multipurpose biochemicals that have several functions such contribute colour to plant, protect the plant against bacterial and fungal infections, and serve a hormone-like role (as a phytooestrogen) in plant cell regulation. Scientists are discovering that when people eat soy products, such as tofu and soymilk, isoflavones and their derivatives produce health benefits in addition to nutritional values. Among various soya isoflavones, genistein has been shown to have a wide range of activities in animal models and experimental studies. On account of its tyrosine kinase inhibiting, antioxidant and oestrogenic or antioestrogenic activities as well as its p53 regulatory properties, researchers have been making endeavours in studying its effects against oxidative stress and related disorders. Convincing studies on its anticancer, lipid lowering, anti-diabetic, antiradiation, against eye diseases, against photodamage, against obesity and as well as immune system enhancers or stimulants have been heeded upon in the scientific world. This review reports some of the activities of genistein.

Key words: Genistein, soya isoflavone, soyabeans, antioxidants

INTRODUCTION

Isoflavones are types of flavonoids found in plants. Isoflavones [Figure 1] are multipurpose biochemicals that have several functions in plants. Soya isoflavones are also known as phytooestrogens and received a great deal of attention over the last few years because of their potentially preventive roles against chronic diseases, such as cardiovascular diseases and cancers. Among various soya isoflavones, genistein has shown a wide range of activities in animal models and experimental studies. Genistein [Figure 2] is found naturally as the glycoside genistin and as the glycosides 6"-O-malonylgenistin and 6"-O-acetylgenistin. Genistein is the aglycone (aglucon) of genistin. Genistein and its glycosides are mainly found in legumes, such as soybeans and chickpeas.

SOURCES OF GENISTEIN

Genistein is found in higher concentrations in the fermented soybean products miso and natto.[1] One metabolite of genistein (Genistein 7-sulfate) and two metabolites of biochanin-A (genistein and genistein 7-sulfate) were detected by high performance liquid chromatography (HPLC).[2] The breast cancer protection in Asian women is due to consuming a traditional soy-containing diet which contains genistein.[3] Genistein injected at 8 mg/kg per day produced serum levels comparable to those reported in soy-fed human infants, and this dose caused significant thymic and immune changes in mice.[4] One study was conducted to check the bioavailability of genistein after a single dose of orally administered soy beverage and soy extract capsules in postmenopausal Thai women.[5]

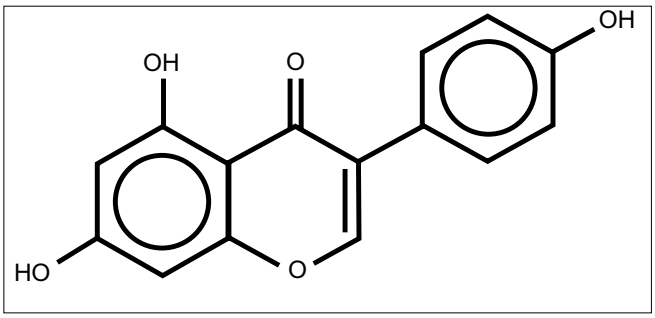

Figure 1: Structure of isoflavones

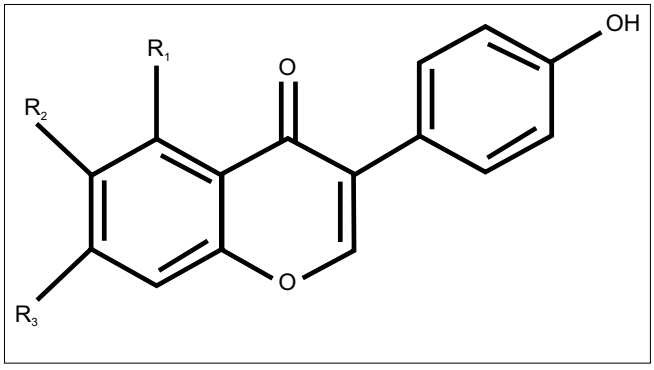

Figure 2: Structure of genistein

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Following are the activities of genistein:

1. Tyrosine Kinase Inhibiting Activity of Genistein

Tyrosine kinases (TKs) are enzymes that catalyze the phosphorylation of tyrosine residues. TKs play a key role in the regulation of cell proliferation, differentiation, metabolism, migration, and survival. As shown in Figure 3, the binding of a ligand to the extracellular region of TKs causes a series of structural rearrangements in the TKs that lead to its enzymatic activation. In particular, movement of some parts of the kinase domain gives free access to ATP and the substrate to the active site. This triggers a cascade of events through (http://web.virginia.edu/Heidi/chapter34/chp34.htm) phosphorylation of intracellular proteins that ultimately transmits the extracellular signal to the nucleus, causing changes in gene expression.

Autophosphorylation of a TKs receptor or phosphorylation of a receptor-associated adapter such as Shc allows Grb2 to bind to these proteins via its SH2 domain. The SH3 domain of Grb2 then binds to the proline-rich C-terminal tail of Sos and recruits Sos to the membrane-bound complex. Sos, a GTP/GDP exchange factor, activates Ras by exchanging GTP for GDP on the Ras molecule. The GTP-bound form of Ras then binds to Raf protein kinase (a MAPK kinase, kinase) isoforms, including C-Raf-1, B-Raf, and A-Raf. This interaction results in targeting of Raf to the membrane where its protein kinase activity is increased by phosphorylation, thereby allowing it to activate other signalling molecules.[6]

TKs use ATP as a source of phosphate, but if genistein, a TK inhibitor, binds to the enzyme instead of ATP, then the kinase can not phosphorylate proteins and signalling halts and ultimately prevent transmission of the extracellular signal to the nucleus and prevent changes in gene expression. Genistein inhibits protein TK (PTK), which is involved in phosphorylation of tyrosyl residues of membrane-bound receptors leading to signal transduction, and also topoisomerase II, which participates in DNA replication, transcription, and repair. By blocking the activities of PTK, topoisomerase II, and matrix metalloprotein and by down-regulating the expression of ~11 genes, including that of vascular endothelial growth factor, genistein can arrest cell growth and proliferation, cell cycle at G2/M, invasion, and angiogenesis. Genistein can alter the expression of gangliosides and other carbohydrate antigens to facilitate their immune recognition.[7]

The DING protein binds to genistein with high affinity.[8] Genistein has a direct inhibitory effect on glycine receptors that is not mediated via inhibition of PTK.[9] The TK may influence force development in the intact swine carotid media by altering [Ca^{2+}] rather than modulating the Ca^{2+} sensitivity of MRLC phosphorylation.[10] Genistein reduced Bcl-2 phosphorylation triggered by paclitaxel and vincristine

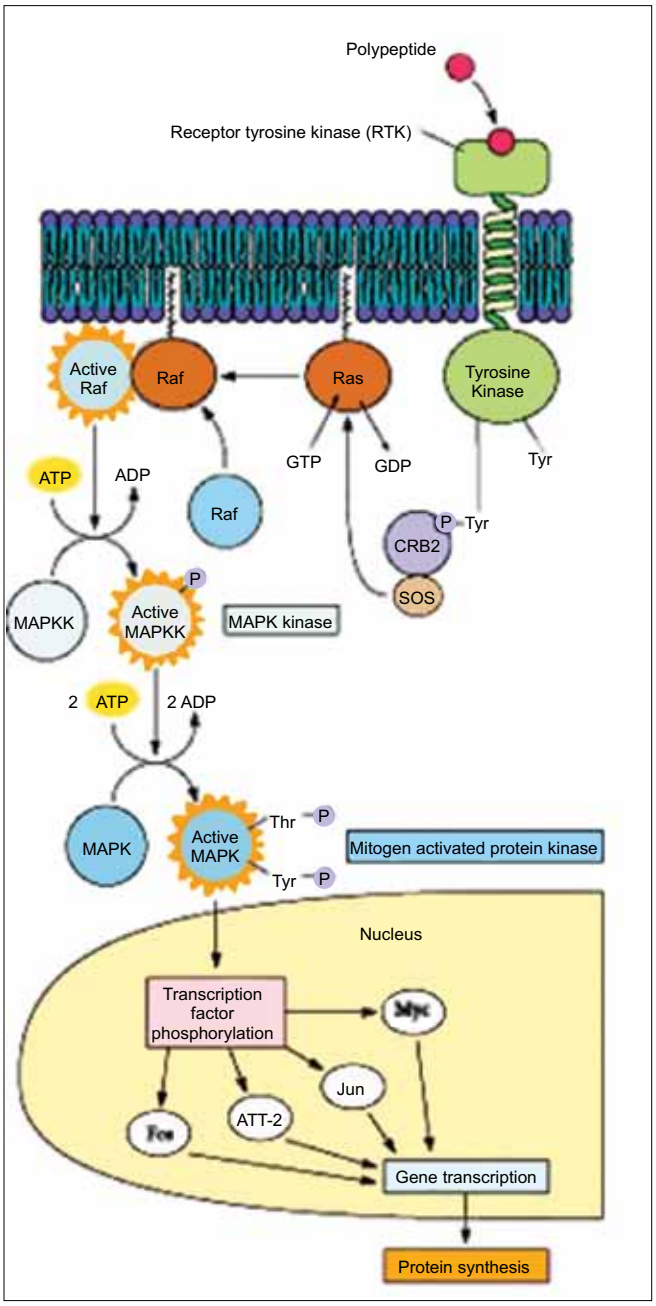

Figure 3: A complete signal transduction pathway that connects a tyrosine kinase receptor with transcription events in the nucleus (http://web.virginia.edu/Heidi/chapter34/chp34.htm)

without changing Bax protein expression and inversely affected tubulin-binding agent-induced apoptosis via down-regulation of cyclin B1/CDC2 kinase expression resulting in reduced Bcl-2 phosphorylation.[11] Genistein stimulates DDP accumulation by modulating the passive permeability of the plasma membrane, and the effect of TK inhibition on passive permeability is altered in C13 cells and pinocytosis contributes insignificantly to DDP accumulation.[12]

2. Antioxidant Activity of Genistein

Genistein has been found to have a number of antioxidant

activities. It is a scavenger of ROS and inhibits lipid peroxidation. It also inhibits superoxide anion generation by the enzyme xanthine oxidase. Genistein has been found to increase the activities of the antioxidant enzymes superoxide dismutase, glutathione peroxidase, catalase, and glutathione reductase.[13-15] Genistein oxidations with AMVN-derived peroxyl radicals yielded orobol, a hydroxylated derivative of genistein, and several stable adducts of 4'-oxo genistein with AMVN-derived radicals.[16] Genistein up-regulates expression of antioxidant genes, involving oestrogen receptors, ERK1/2, and NFKB[17].

3. Oestrogenic or Antiestrogenic Activity of Genistein

Genistein show oestrogenic effects in the uterus, mammary gland, and hypothalamic/pituitary axis[18]. Genistein show oestrogenic activity in rats.[19] Genistein acts as a classical antioestrogen, i.e., it competitively inhibits oestrogen's binding to the ER and transactivation of oestrogen-responsive genes and may inhibit oestrogen-metabolizing enzymes.[20,21]

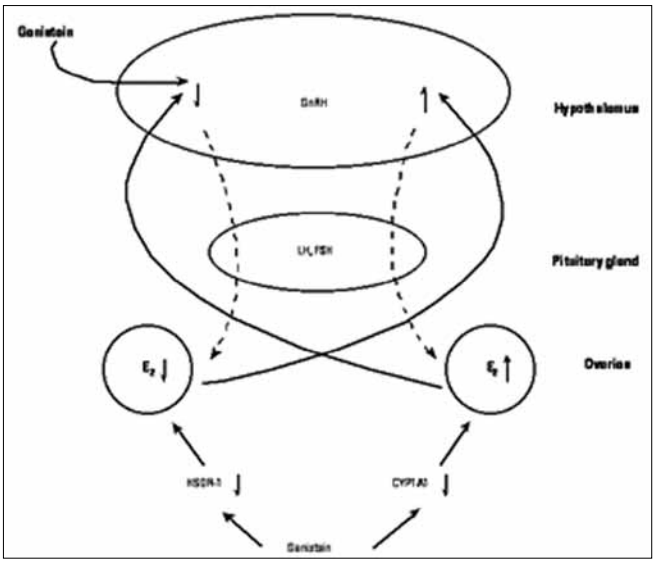

Figure 4: Estrogenic/antioestrogenic effects of genistein (Bouker and Clarke, 2000)

As shown in Figure 4, in the human breast cancer cell line T47D, *in vitro* studies show the ability of genistein to significantly inhibit the enzyme 17-ß-hydroxysteroid oxidoreductase type 1 (HSOR-1).[22] HSOR-1 belongs to the family of short-chain alcohol dehydrogenases, which are involved in the metabolism of steroids, antibiotics, and prostaglandins.[23] HSOR-1 is necessary for estradiol secretion from the ovaries in premenopausal women. Additionally, it may be essential for the reduction of estrone to estradiol that occurs in the adipose and other tissues.[24] Thus, inhibition of this enzyme could lead to decreased total estradiol. Some *in vitro* studies have also shown that isoflavones can inhibit the aromatase enzyme, which is responsible for the conversion of androgens to estrone in the peripheral (adipose) tissues, although this has not been shown with genistein specifically.[25] The idea of genistein leading to a decrease in oestrogenicity through the inhibition of these oestrogen-metabolizing enzymes is in contrast to the idea that genistein may increase oestrogenicity by inhibiting CYP1A1.

The inhibition of HSOR-1 could lead to decreased production of estradiol in peripheral tissues and ovarian release of estradiol, thus resulting in a decrease in total estradiol, whereas inhibition of CYP1A1 could result in the opposite, leading to a build up of total estradiol levels. It is not clear, therefore, what the net effect of genistein would be on overall oestrogenicity. Furthermore, in addition to genistein's ability to inhibit the enzymatic activity of HSOR-1 and CYP1A1, genistein may affect these oestrogen-metabolizing enzymes in another fashion. It is possible that the disruptive effects of genistein on the hypothalamic/pituitary/gonadal axis could lead to an upregulation of one or more of these enzymes, further complicating the issue of the overall oestrogenic effect of genistein. However, depending on which, if any, of these enzymes would be up-regulated in response to a perturbation of the hypothalamic/pituitary/gonadal axis, it is possible that the overall effect of genistein could be either lead to an increase or decrease in oestrogenicity.

Genistein-induced shifts in the coregulator status of ER alpha may be involved in transcriptional regulation and suggest that tamoxifen-mediated antagonism at ER-dependent genes is sensitive to attenuation by low levels of genistein.[26] The IFN-γ production level in NC mice that received genistein was significantly lower than that in control NC mice. The oral administration of genistein increased IFN-γ and IL-4 production from DO11.10$^+$ T cells in response to the ovalbumin $(OVA)_{323-339}$ peptide in female DO11.10 mice.[27]

4. Regulation of p53 by Genistein

In a normal cell, p53 is inactivated by its negative regulator, Mdm2. Upon DNA damage or other stress, various pathways will lead to the dissociation of the p53 and Mdm2 complex. Once activated, p53 will either induce a cell cycle arrest to allow repair and survival of the cell or apoptosis to discard the damage cell. How p53 make this choice is currently unknown. p53 is central to many of the cell's anti-cancer mechanisms. It can induce growth arrest, apoptosis and cell senescence. In normal cells, p53 is usually inactive, bound to the protein Mdm2 (Hdm2 in humans), which prevents its action and promotes its degradation by acting as ubiquitin ligase. Active p53 is induced after the effects of various cancer-causing agents such as UV radiation, oncogenes, and some DNA damaging drugs.[28]

As shown in Figure 5, the p53 becomes activated in response to a myriad of stress types, which include but is not limited to DNA damage (induced by either UV, IR or chemical agents, such as hydrogen peroxide), oxidative tress, osmotic shock, ribonucleotide depletion, and deregulated oncogene expression. This activation is marked by two major events. Firstly, the half-life of the p53 protein is increased drastically, leading to a quick accumulation of p53 in stressed cells. Secondly, a conformational change forces p53 to take on an active role as a transcription regulator in these cells. p53 activity, monitored by the reporter lacZ transgene, is the determinant of radiation and drug sensitivity. The accumulation of p53 protein following whole body irradiation of adult mice was detected in the hepatocytes of the irradiated mouse. The early expression of the p53 response is consistent with novel models of p53 function that suggest that it may have evolved principally as a defence against teratogenic insult that permits plasticity of development.[29] p53 activity, monitored by the reporter lacZ transgene, is the determinant of radiation and drug sensitivity *in vivo*; it indicates the importance of tissue and stage specificity of p53 regulation at the level of mRNA expression.[30]

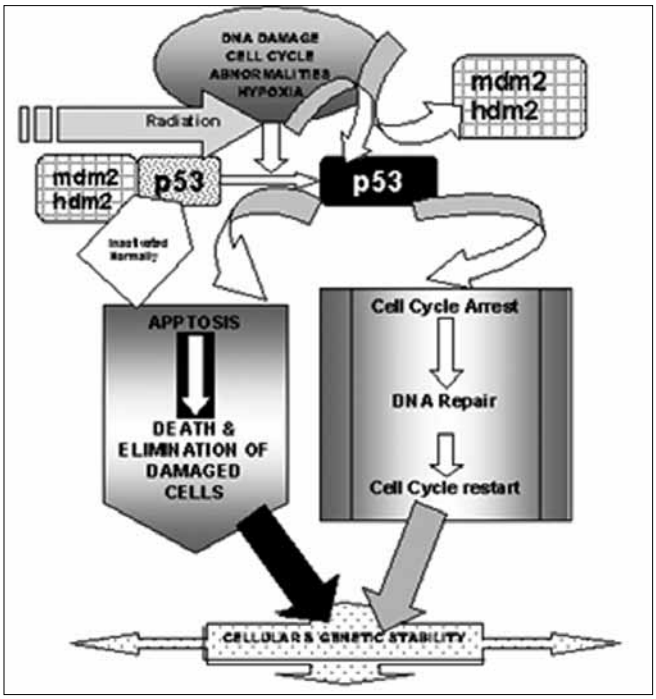

Figure 5: Regulation of p53 activities under stress of radiation (Bhatia, 2008)

Thus, the activation potential of p53 is tightly controlled *in vivo*, both spatially and temporally, and an important element in this control is the presence of limiting basal levels of p53.[31] Hence the antiradiation activity of genistein could be mediated through transcriptional level by activation of gene-like p53. Genistein induces the up-regulation of p53 protein, phosphorylation of p53 at serine 15, activation of the sequence-specific DNA binding properties of p53, and phosphorylation of the hCds1/Chk2 protein kinase at threonine 68. The phosphorylation and activation of p53 and phosphorylation of Chk2 were not observed in ATM-deficient cells.

In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 is complexed with cdk2, the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way and as a consequence, the p21 protein is not made available to act as the 'stop signal' for cell division. Thus, cells divide uncontrollably, and form tumours. The amount of information that exists on all aspects of p53 normal function and mutant expression in human cancers is now vast, reflecting its key role in the pathogenesis of human cancers. It is clear that p53 is just one component of a network of events that culminate in tumour formation.

It has been reported that the exposure of cells to ionizing radiation results in activation of ataxia telangiectasia mutated (ATM) protein-dependent signalling pathways that leads to the activation of p53 and the protein kinase Chk2.[32] Treatment of ATM-positive cells with genistein was found to dramatically increase the ability of p53 to bind to its specific DNA sequence. Binding of p53 to DNA was significantly reduced in A-T cells compared with normal cells, again indicating that the effect of genistein on p53 is very similar to that of ionizing radiation. The activation of the sequence-specific DNA binding properties of p53 suggests that genistein might activate the transcriptional activation activity of p53 and result in induction of downstream genes such as p21.[33]

5. Anticancer Activity of Genistein

Genistein, an isoflavone derivative related to coumarin, is found in soy products and holds great promise as a natural cancer preventative. There are a number of isoflavones in soy products, but research has shown that genistein is the most potent inhibitor of the growth and spread of cancerous cells. Coupled with epidemiological studies, which suggest a strong cancer preventative effect of high soy diets, genistein is being scrutinized as a potential anti-cancer drug.

Scientists point out that unlike mainstream traditional cancer treatments, genistein may target the malignancy while leaving healthy tissue unharmed. Genistein may not only inhibit cancer cell growth, but also encourage cell differentiation to help regulate proper cell growth. When cells become cancerous, they tend to become less specialized in their individual cellular functions, and thus become more harmful as they replicate. Undifferentiated

cells are particularly difficult to treat, and thus cell differentiation is vitally important. Genistein apparently reverse the process in which cancerous cells loose their individual identity.[34,35] Genistein acted in synergism with eicosapentaenoic acid, a fish oil component, on human breast cancer MCF-7 cells.[36] The Genistein derived from biochanin-A following metabolic processes in the intestinal microflora most likely acts as an inhibitor in breast carcinogenesis.[37] The genistein-induced alternations of gene expressions may be exploited for devising chemopreventive or therapeutic strategies, particularly for chemosensitization of metastatic prostate cancer to existing chemotherapeutic agents.[38] Genistein inhibited human prostate cancer (LNCaP and PC-3) cell lines in a dose-dependent manner and the up-regulation of gene expression levels accompanied elevation of GPx enzyme activities.[39] Genistein can up-regulate p21WAF1 expression in genistein-treated non-small lung cancer cells.[40] The addition of genistein to irradiated K562 cells provided the evidences of G1/S progression and G2-arrest, and their relationship with TK1 in cells treated with radiation and genistein.[41]

Genistein may induce apoptosis, programmed cell death in cancer, and also reduce the bioavailability of sex hormones that may stimulate tumour growth capacity in both men and women.[42,43] Genistein protects against mammary and prostate cancers by regulating specific sex steroid receptors and growth factor signalling pathways.[44] Both genistein and 1-alpha-25-dihydroxycholecalciferol induced a G(1/0) arrest either alone or in combination.[45] A prepubertal exposure to a low dose of genistein may protect the mammary gland from carcinogen-induced malignant transformation, possibly by increasing differentiation of the mammary epithelial tree.[46] The early prepubertal exposure of the mammary gland to genistein enhances cell proliferation and maturation making them less susceptible to chemically induced cancer of the mammary gland.[47] Analysis of the conditioned medium of human mammary epithelial cells exposed to genistein plus EGF showed increased levels of TGF-beta relative to those in the medium of cells exposed to EGF or genistein alone.[48] Genistein reduced proliferation and induced G2/M phase arrest, and apoptotic death in colon cancer HT-29 cells.[49] One study demonstrated an inhibitory effect of genistein on ovarian cancer cells.[50]

6. Genistein as Radiosensitizing Agent

Genistein results in variable and significant enhancement of the radiation effect that may be partially mediated by G_2M arrest, Mcl-1, and activation of the AKT gene.[51] Genistein appeared to promote oral submucosa stroma tumourigenesis in concert with DMBA in hamster cheek pouch.[52]

7. Genistein as a Lipid-lowering Agent

Some studies indicate that genistein may be responsible for up to three quarters of the measurable cholesterol lowering effect and indicate that the addition of genistein to the diet may lower blood cholesterol by as much as 35%.[53-55] One study had shown that genistein produce antilipogenic effects in mice.[56]

8. Genistein Against Cardiovascular Diseases

The 54 mg of genistein plus calcium, vitamin D_3, and a healthy diet were associated with favourable effects on both glycaemic control and some cardiovascular risk markers in a cohort of osteopenic, postmenopausal women.[57] Genistein inhibits the negative inotropic effect of ET-1 induced by crosstalk with NE through a PTK-unrelated mechanism.[58] Genistein has inhibitory effects on natural and PDGF-BB–induced SMC proliferation, thereby preventing atherosclerotic cardiovascular diseases.[59] Genistein supplementation improves endothelial dysfunction induced by oophorectomy in rats and reduces infarct size in an experimental model of myocardial ischaemia-reperfusion injury.[60]

9. Genistein as Anti-diabetic Agent

Genistein and daidzein exert anti-diabetic effect in type-2 diabetic conditions by enhancing the glucose and lipid metabolism.[61] Genistein may reduce glucose toxicity-induced cardiac mechanical dysfunction and thus possess therapeutic potential against diabetes-associated cardiac defects.[62]

10. Genistein Against Eye Diseases

Genistein inhibited the increase in tyrosine phosphorylation and protected the eyes from the induced ischaemic retinal degeneration.[63] Genistein significantly reduced ovalbumin-induced increases in total cell counts and eosinophils recovered in bronchoalveolar lavage fluid, airway eosinophilia, and eosinophil peroxidase activity.[64]

11. Genistein Against Photodamage

Genistein substantially inhibits skin carcinogenesis and cutaneous ageing induced by ultraviolet light in mice and photodamage in humans.[65] The UV irradiation elicits a series of oxidative events, which can be substantially inhibited by genistein through either direct quenching of ROS.[66]

12. Genistein Against Liver Diseases

Genistein did not change the liver cytochrome P-450 content.[67] One study had shown the major involvement of CYP1A2 in the hepatic metabolism of genistein.[68] Genistein increases the potential for hepatic and systemic exposure to hepatically generated glucuronides. Genistein has antifibrogenic potential and is useful for treating liver

disease.[69] Genistein has therapeutic potential against liver fibrosis.[70]

13. Genistein Against Obesity

Genistein may affect gene expression and alters susceptibility to obesity in adulthood by permanently altering the epigenome.[71]

14. Genistein as Immune Modulator

Genistein is an immune modulator that enhances systemic serum virus elimination and body growth in virally challenged pigs.[72] The neonatal genistein exposure altered mammary gland growth and development.[73]

15. Genistein Against Radiation

A single subcutaneous administration of genistein 24 hours before irradiation provides significant radioprotection to the hematopoietic progenitor cell compartment.[74] One study had shown the prophylactic action of genistein against radiation-induced damage in the hematopoietic system.[75] Genistein provides protection against radiation-induced lethality.[76-78] Intraperitonial administration of genistein increased the survival of mice against 8 Gy gamma irradiation. The 0.5 ml dose of genistein (200 mg/kg) was administered intraperitoneally to two different groups of mice, 15 minutes and 24 hours prior to gamma irradiation. In the mice treated with genistein with the optimum dose 24 hours before irradiation, a significant increase in 30-day survival has been recorded in contrast to the mice treated with genistein 15 minutes before the irradiation. The longer survivability (i.e., 20% for a period of more than 30 days) has been observed in the 24-hour group as compared to that of 15 minutes (i.e., 20% for 22 days). Although the radioprotective effect of genistein was evident in both groups, it was of greater magnitude in the group with a longer interval, indicating thereby demonstrating an efficacy with longer retention with the possible minimum toxicity, unlike hitherto other known radioprotective agents.[79,80]

CONCLUSION

Genistein, a soya isoflavone obtained naturally from legumes, has a wide range of activities like antioxidant, antioestrogenic, anticancer, and potent PTK inhibiting activities. Hence, it can be used as a nutraceutical in order to improve the defence system of body. Now there are evidences that genistein may be used as an antiradiation drug, as prophylactic and therapeutic medicine against radiation exposure in the event of nuclear leakage or high background in the vicinity of reactors. Nevertheless, as an adjuvant therapy in many chronic diseases like cancer, its use is almost established due to less or no side effects. Many studies on its lipid lowering, anti-diabetic roles, anti-photodamage effects, and against obesity are promising. Its convincing antiradiation effects as well as an immune system enhancers or stimulants are being heeded upon by the scientific world.

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