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# Genistein: A Multifaceted Flavonoid with Diverse Medicinal Applications

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*Abstract:* Phytochemicals and phytoalexins, comprising flavonoids, carotenoids, polyphenols, vitamins A, C, and E, are health-promoting compounds found in medicinal plants. Genistein, a prominent soy isoflavone predominantly present in leguminous crops like soybeans, is a multifunctional biochemical. Isoflavones are believed to serve diverse roles in plants, including pigmentation, protection against bacterial and fungal pathogens, and regulation of cellular processes akin to hormones. Numerous studies in animal models and experimental settings have unveiled the multifaceted actions of genistein. Its ability to inhibit tyrosine kinase, exhibit antioxidant properties, elicit estrogenic or antiestrogenic effects, and modulate p53 have garnered significant interest in exploring its potential for mitigating oxidative stress and related disorders. Compelling evidence has emerged on genistein's prospective benefits in cancer prevention, cholesterol reduction, diabetes management, radiation protection, eye disease prevention, photoprotection, obesity control, and immune system enhancement, drawing the attention of the scientific community. This review comprehensively examines the diverse mechanistic actions and therapeutic potentials of genistein.

*Index Terms* – Genistein, Isoflavone, Phytoestrogen, Antioxidant, Anticancer, Immunomodulatory, Soybean, Legumes, Phytochemicals, Phytoalexins, Disease prevention, Nutraceutical

## I. INTRODUCTION

Plants have long been used by humans as a food source and source of healing. Today, a sizable portion of the global population uses plants and plant-derived products—either as complementary supplements or as conventional medicines—to address their medical needs for overall health benefits. The main purpose of plants and plant-derived products is to provide nutrition (Ahn, K. 2017). The growing public interest in the use of plant-based products and herbal medicines has led to an expansion of scientific research on the therapeutic potential of important components of medicinal plants (Rates, S. M. K. 2001). The increase in life expectancy and to prevent the age related disorders is the main goal of researches that are based on today's scientific phenomena.

While lifestyle factors like food choices and physical activity have been shown to be crucial, genetics undoubtedly plays a significant role in the development of many illnesses (Brower, V. 2008). specifically, the latter one leads to the production of compounds derived from extracts of plants and the biologically active components that are extracted from them; these components have long-established medicinal properties that have been thoroughly studied (Bodeker *et al*., 2001). From a pharmaceutical standpoint, many compounds originating from plants are known to exhibit bio/pharmacological activity, and historically, plants have yielded a number of important human medications. Few decades in the past, many researches were conducted on the medicinal potential of phytochemicals. A lot of studies were conducted on the possible health advantages of antioxidant property of dietary plant polyphenols.

### 1.1 Flavonoids

Polyphenolic compounds called flavonoids are found naturally in fruits, vegetables, and soybeans (Panche et al., 2013). Animals or humans cannot synthesise the phytochemicals known as flavonoids. Flavonoids have gained popularity as dietary ingredients as attention has shifted to using natural compounds. According to Elliott et al., 2017 and Harborne et al., 2000, flavonoids are the cause of the colour that draws pollinators to flowers. These include substances with white or pale yellow coloration such as rutin, quercetin, and kaempferol, as well as compounds with red, purple, or blue anthocyanins. It is believed that these compounds in leaves aid in the physiological survival of plants by protecting them from UV-B rays and fungal infections (Harborne et al., 2000).

In addition, flavonoids influence respiration regulation, photosynthesis, morphogenesis, sex determination, photosensitization, energy transfer, and the activities of growth regulators and plant growth hormones. They function as unique UV filters and are crucial in protecting plants from a range of biotic and abiotic stressors. They also function as signal molecules, phytoalexins, detoxifying agents, allopathic compounds, and antimicrobial compounds that work in defence (Takahashi et al., 2004). They also significantly affect heat acclimation of plant, resistance in drought, tolerance in the freezing temperature and frost hardiness. Flavonoids, which act as protective antioxidants in plant tissues, are found in the nucleus of mesophyll cells and the centres of

ROS production sites. They are also crucial for symbiotic relationships because, through their chemoattractant properties, they attract microorganisms (Samanta et al., 2011).

Though some may exist as free aglycones, flavonoids are chemically speaking polyphenols that have been glycosylated and bound to a sugar. The common flavonoid structure, according to E. Corradini et al. (2011), is the flavan nucleus, which has a 15-carbon skeleton formed in two phenyl rings connected by a three-carbon bridge. It can be 4-phenylchromane (neoflavonoid), 3-phenylchromane (isoflavonoid) or 2-phenylchromane (flavonoid). As a result, the backbone of flavonoids is generally C6-C3-C6 (Harborne et al 1989; Raffa et al 2017). They are divided into six primary classes, according to Van Acker et al. (1996): isoflavones, flavonols, flavones, flavanones, and anthocyanins.

The location of the hydroxyl group, the presence or absence of carbonyl groups, and double bonds all affect further subclassification of flavonoids. Myricetin, Apigenin, Baicalein, Eriodictyol, Naringenin, Isorhamnetin, Quercetin, Luteolin, Chrysin, Kaempferol, Hesperetin, and Daidzein are a few prominent flavonoid examples. Flavonoids marked as one of the biggest class in phenolic compounds present in plant, encompasses many subclasses in which isoflavonoid is a distinct one with nearly 5000 members. Isoflavonoids, which have a molecular structure similar to that of the hormone oestrogen, are mostly found in soybeans. Daidzein and genistein are soybeans' two main isoflavonoids. Because of their similarities to oestrogen and their mode of interaction with the receptor of estrogen, phyto-estrogen is another name given to soybean isoflavonoids (Wuttke et al, 2003). The isoflavonoid studied among them is Genistein that we will be talking about in this chapter.

## II. GENISTEIN

Genistein (GEN) (4, 5, 7-trihydroxyisoflavone) is a soy dried naturally occurring isoflavone that exhibits multidirectional biological activity in plants and food products derived from them. According to Markovits et al. (1989), it exhibits anti-inflammatory, proapoptotic, antioxidant, and anti-estrogenic qualities. Genistein is created when sugar molecules are released during the breakdown of soybeans or soy compounds. As per the findings of Spaqnuolo et al. (2015), genistein possesses the capacity to influence various signalling pathways and molecular targets, thereby potentially influencing the response of cancer cells. The genistein pathway or mechanism of action is as follows. Genistein is released into the intestine and bound with glucuronic acid, a sugar acid made from glucose, when it passes through the intestinal epithelial cells. The glucuronide enters the liver, exits in the bile, and its re-entry occurs in the small intestine where it can be absorbed, added and metabolised once more, according to Steensma et al. (2006). Research has shown that one of the most studied isoflavones can be quite effective in treating some types of breast cancer, pancreatic cancer, liver cancer, and Alzheimer's disease.

### 2.1 Sources of Genistein

Genistein is found in plants belonging to the Leguminosae family, which includes soybeans (Glycine max). Many legume plants naturally contain it. The nutritional value of the leguminous family, which includes the genus Lupinus, or lupin, is comparable to that of soybeans. Consequently, it has genistein as well, albeit in trace amounts. Soy-based foods and beverages, including soy cheese, are among the primary sources of genistein that have been identified to date. The genistein content of the soy seeds comes in the range of 5.6 to 276 mg/100 g. Apart from genistein, products of soy also carry daidzein, a isoflavone produced via the phenylalanine pathway (Liggins et al., 2000). Due to their high genistein content, chick peas and broad beans are also important legumes but not in the similar amount as in soybeans. Genistein's estimated range available in vegetables, fruits and nuts is 0.03 to 0.2 mg/100 g (Lauteir et al., 2004).

Additionally, certain lichens, such as Amycolatopsis sp. YIM130642, can yield genistein. Lichen is a symbiotic relationship between fungi and algae that yields genistein for use in a variety of metabolic processes. Additionally, Streptomyces sp. bacteria are the source of it. However, very little genistein is produced by sources other than soy.

**Table 1:** Showing sources from which genistein is obtained and their part used.

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| Sr. No. | Compound Obtained | Source | Source Name | Plant Part |
|---|---|---|---|---|
| 1 | Genistein | Plant | *Genista tinctora* | Seed/Fruit |
| 2 | Prunetin/Genistein | Lichen | *Amycolatopsis sp.YIM 130642* | No particular part involved |
| 3 | Genistein/Daidzein | Plant | Soy Plant | Seed /Fruit |
| 4 | Daidzein/Genistein | Actinomycete (bacteria) | *Streptomyces sp. tpu1401a* | No particular part involved |
| 5 | Genistein | Plant | Alfalfa | Vegetable |

### 2.2 BIOSYNTHESIS OF GENISTEIN

Legumes and non-legumes share multiple branches of the phenylpropanoid pathway, which produces lignins, anthocyanins, and specific classes of phytoalexins that are important for normal development and act as defences against various environmental stressors (Dixon et al., 1995). PAL (Phenylalanine Ammonia Lyase) facilitates the conversion of phenylalanine into cinnamonate. Isoflavonoids are an important class of secondary metabolites that arise from the phenylpropanoid pathway (Dixon & R.A 2001).

Additionally, C4H facilitates the transformation of cinnamonate into p-coumarate. P-CoumaroylCOA, derived from p-coumarate, is the product. These p-CoumaroylCOA are then converted to naringenin chalcone and genistein. This suggests that genistein comes from phenylalanine. Phenylalanine is an amino acid and a component of protein.

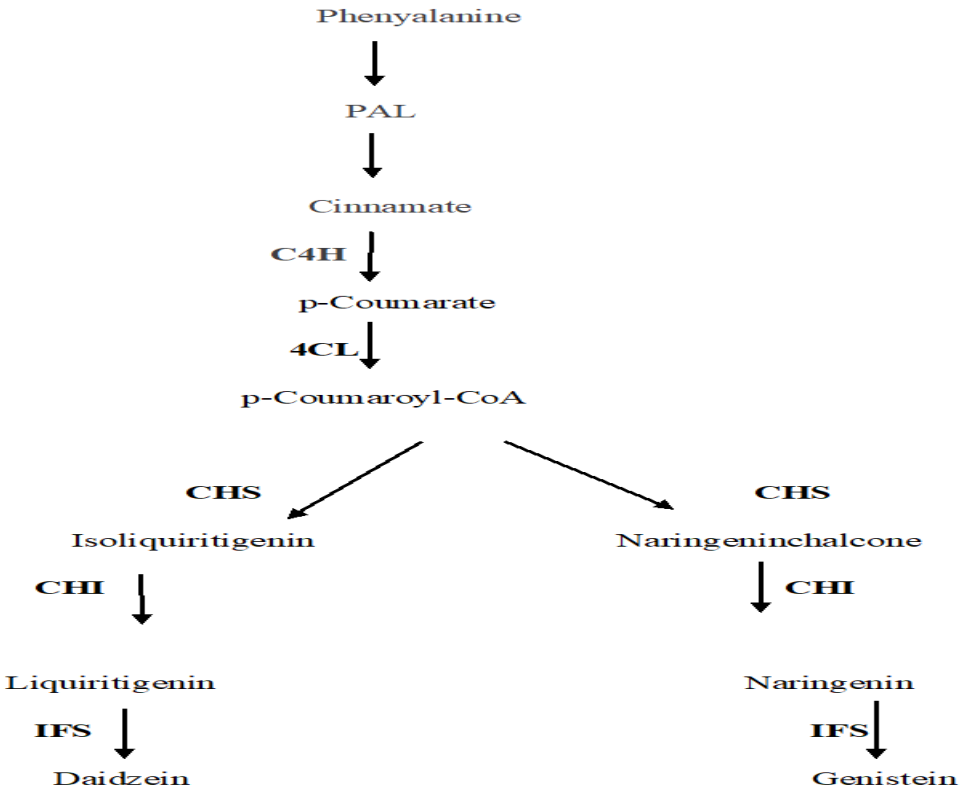


Figure1. Simplified scheme showing genistein as final product by the phenylpropanoid pathway (Yu *et al.*, 2000)

**2.3 Chemistry of Genistein**

Genistein (C15H10O5) is a multifunctional natural isoflavonoids belonging to the flavonoid class. Its skeleton has 15 carbons. Like other plant components that have an estrogenic effect, such as lignans, it depicts phytoestrogenic compound example. It was given the genus name of this plant and it was derived from Genista tinctoria L. in 1899 (Polwoski et al., 2000). Due to its selective regulation of oestrogen receptors, this phytoestrogen shows the properties of anti-inflammation by Borras et al. (2006), Duan et al. (2003), and Valsecchi et al. (2011). (ERs) represent a class of intracellular proteins. The hormone oestrogen (17β-estradiol) activates these receptors. It might have a roughly 20-fold higher binding capacity and higher affinity for ERβ than ERα. Whether oestrogen acts through the ER-beta or ER-alpha receptor is one aspect of its unknown mode of action (Kuiper et al., 1995).

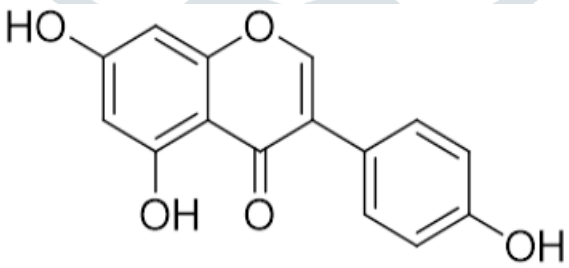


Figure 2. Structure of Genistein

**2.4 Metabolic Pathways**

**2.4.1 Protein kinases specific to tyrosine are inhibited by genistein**

The enzymes that mediate transfer of phosphate groups from the ATP molecule to specific cell-resistant protein's tyrosine residues. Genistein inhibits these enzymes as part of its function. It functions as a "ON" or "OFF" switch for several biological processes, for example MAPK pathway canonical receptor that depicts receptor of mitogen activated protein kinase (MAPK) and plays a role in the retardation of transducing extracellular signals (kim et al., 1998). Genestein has a pleiotrophic effect, which means that it stimulates cell differentiation and apoptosis while inhibiting the growth of various cancer cells. Genistein increases G2/M arrest in cases of lung, prostate, and breast cancer. Coward and colleagues (1996) have linked this to an upregulated p21 structure.

G1 checkpoint protein P21 functions as a Cdk inhibitor to prevent the cell cycle from continuing into S phase. Furthermore, the growth of cancer cells can be inhibited by genistein, a naturally occurring PTK inhibitor, by blocking the signalling networks that PTKs mediate. The renal function is measured by estimated glomerular filtration rate, or EGFR. In vitro, genistein has shown

to retard the specific-tyrosine kinase protein activity of EGFR. Furthermore, pro-oncogene HER2 is retarted by genistein, a protein that promotes growth on the outside of all breast cells, and stopped the growth of tumours in transgenic mice. Moreover significance of genistein was shown in the reduction of the expression of PTK-controlled proteins IGF1R (Insulin Like Growth Factor1 Receptor) and EGFR and also the substrates that are present in downstream ERK1/2 (Extracellular Signal Regulated Protein Kinase). Mitogen-activated protein kinases, Tyrosine kinases and other enzymes involved in the transfer of phosphate from ATP to the receptor are thus primarily inhibited by genistein. As a result, genistein disassembles the ligand that is accountable for the carcinogenic activity and blocks the entire pathway.

## III. APPLICATIONS IN HEALTH INDUSTRY

Genistein is used extensively in the medical field to treat a wide range of illnesses. They treat heart conditions by decreasing myocardial necrosis, which is the term for cardiomyocyte cell death. It also aids in the treatment of diabetes by inhibiting the insulin-mediated GLUT pathway, which lowers blood glucose levels. It also functions in the stress response by keeping the activity of monoamine oxidase (MAO) stable. It also improves 5-HT (5-hydroxytryptophan) metabolism and reduces stress.

**Table: 2.** Showing Genistein's effect on curing diseases.

| Sr. No. | Symptoms/Disease | Effects of Genistein | References |
|---|---|---|---|
| 1. | Cardiovascular | Reduction of myocardial necrosis, Severity of atherosclerosis. | Guo *et al.*, 2019 |
| 2. | Diabetes | Decrease in the glucose concentration during fasting. | Mareti *et al.*, 2019 |
| 3. | Stress response | Stabilizes MAO activity, Improves 5-HT metabolism. | Kageyama *et al.*, 2020 |
| 4. | Induction of apoptosis | Squamous cell cancer in the head and neck, breast cancer experience apoptosis in response to genistein. | Davis *et al.*, 1998 |
| 5. | Antiinflamatory effect | Genistein has distinct effects on the NF-κB-intermediate signalling cascade of activated macrophages as well as the signal transducer and activator of transcription 1. | Hamalainen et al., 2007 |
| 6. | Antiangiogenic effect | Inhibiting c-src activity, genistein stops hypoxia-induced overexpression of VEGF. | Mukhopadhyay *et al.*, 1995 |
| 7. | Cancer | lowers the risk of stomach, hepatocellular, and breast cancer. | Pons *et al.*, 2020 |
| 8. | Neuroblastoma cancer- | It has been shown that GST causes apoptosis and cell cycle arrest in neuroblastoma, at G2/M phase it inhibit SK-N-MC cells. | Ismail *et al.*, 2007 |
| 9. | Pancreatic cancer- | By increasing both autophagy and apoptosis, 5-FU and genistein together dramatically decreased the tumour of xenograft and its final volume. | Suzuki *et al.*, 2014 |
| 10. | Liver cancer | When HCC cells are cured with gelatin, the markers of mesenchyme that is N-cadherin and vimentin are upregulated at the mRNA and protein levels as well as in-vivo, while the epithelial markers α-catenin and e-cadherin are downregulated. | Sun *et al.*, 2004 |
| 11. | Genistein impact on Fibroblast | Genistein decreased CTGF mRNA and keloid fibroblast protein expression in a manner that is dependent on concentration. | Cao *et al.*, 2009 |
| 12. | Genestein for UV protection | Genistein dramatically lowers the risk of photodamage, UV-induced cutaneous ageing in humans, and skin cancer in mice. | Wei *et al.*, 2003 |

### 3.1 Antiinflamatory and Antioxidant Effect

Behavior of inflammation and cancer's beginning possess strong relatedness as it is a well-known fact. Structures that are inflammatory like cytokines and chemokines are contained by Cancer cells. It has previously been demonstrated that anticancer medications are useful in treating inflammatory reactions. It has been demonstrated that genistein is a multifunctional substance that supports the anti-inflammatory response as well as the antioxidant defence system (Palanisami et al., 2008). Genistein is known to activate the transducer signal as well as transcription 1 and NF-κB-intermediate signalling pathway by macrophage activation differently (Hamalainen et al., 2007). The defensive effect of genistein on dysfunction of kidney in rats fed a high-fructose diet by altering insulin resistance-induced pathological pathways shown by a study. Because traditional Japanese diets contain pigments from soybean plants called isoflavones, they are believed to have health benefits. The idea that isoflavonoids, flavonoids, or lignans can inhibit tumour growth has been confirmed by experiments on bladder cancer, both in vivo and in-vitro (Fotsis et al., 1997).

### 3.2 Induction of Apoptosis

Numerous cancer cell lines, such as those from pancreatic cancer, breast cancer, neck and head squamous cell cancer, undergo apoptosis when exposed to genistein (Davis et al., 1998). Recent research indicates that genistein shields oestrogen-expressing human pancreatic cells from the deleterious effects of elevated blood sugar, including apoptosis and the suppression of cell division via the Bcl-2 and estrogen-receptor ways. Programmed cell death that is also called as Apoptosis, is distinguished by distinct structures of the cell such as the production of new genistein via trihydroxybenzoin. Cell adhesion, cytoplasmic

contraction, DNA fragmentation, and other biochemical alterations that activate caspase via intrinsic and/or extrinsic mitochondrial pathways are among the anticancer pharmacology of genistein. Human cervical cancer cells (HeLa cells) may undergo apoptosis when genistein increases the movement of caspase-3, caspase-9 or both (Dhandayuthapani et al., 2013). However, it has been proposed that upregulating CCAAT/enhancer-binding protein and protein that is glucose-regulated 78 (GRP78) can cause genistein-mediated apoptosis in human cervical cancer cells (Yang et al., 2016).

**3.3 Inflammatory Mediated Inhibition**

Inflammation serves as the immune system's line of defence against injury or infection. Inflammation aims to remove foreign and toxic stimuli and restore tissue integrity and physiological function (Friere et al., 2013). Furthermore, genistein regulates the manner in which Akt and NF-κB are triggered during inflammation. Animals may have higher levels of neuronal nitric oxide synthase (nNOS) due to improvements in intracellular nNOS expression or an increase in the number of cells expressing nNOS (Kitaura et al., 2000). Moreover, an increase in nNOS in the genistein-treated animals may be the consequence of enchanced number of cells expressing nNOS, since genistein can enhance the amount of neurons in the DGlbarea (Sakla et al., 2007).

**3.4 Antiangiogenic Effects**

Indeed, genistein lowers inflammation by affecting lymphocytes, monocytes, and granulocytes. According to Dixon et al. (2002), this effect could provide a fresh supply of phytotherapeutic agents for anti-inflammatory therapies. Furthermore, genistein decreased the VRVPL-V-induced oedema in the mouse paws in a manner that is dependent on concentration. At an amount of 21 lM Genistein effectively retarded the oedema-inducing effect after the injection of VRV-PL-V. Angiogenesis is the process of creating new blood capillaries, is one of the most significant physiological processes. The larger-than-one-millimeter solid tumours will promote the formation of new blood vessels because they provide full access to glucose and oxygen. Angiogenesis is closely associated with the point at which tumour cells enter the vasculature and the site at which they ultimately metastasize (Harlozinska, A. 2005). This is why substances with antiangiogenic properties deserve more research. Bagheri et al. (2012) state that genistein is the most important plant-derived inhibitor for decreasing vascular endothelial cells and preventing angiogenesis. Moreover, genistein, an isoflavone found in soybeans, has antiangiogenic qualities (Fotsis et al., 1995). Moreover, mukhopadhyay et al. 1995 report that genistein inhibits c-src activity to stop hypoxia-induced VEGF overexpression.

Whether this inhibits angiogenesis in RCC by controlling angiogenic factor expression is still unknown. The key aim in the cancer treatment is thought to be angiogenesis, because it is a process by which pre-existing vasculature gives rise to new vessels. Since angiogenesis provides oxygen and nutrients, which cancer cells need to proliferate, blocking the vasculature can be an extremely effective cancer treatment approach. Strong antiangiogenic effects of genistein have been demonstrated by earlier research. For instance, downregulating the expression of MMP-9, matrix metalloprotease-2 (MMP-2), E6 and five human bladder cancer cell lines, platelet-derived growth factor, vascular endothelial growth factor (VEGF) and urokinase plasminogen activator when treated by genistein they demonstrated an anti-angiogenic effect.

**3.5 Genestein for UV Protection**

UV radiation from the sun is one of the primary causes of photoaging, or premature skin ageing. Among its clinical features are rough skin textures, blotchy dyspigmentation, and fine and coarse wrinkles (Weiss et al., 1988; Schatrffetter-Kochanek, K. 1996). Genistein has shown promising results in cosmetic antiaging preparations by promoting skin elasticity, preventing photoaging, and preventing skin cancer. Cosmetic creams containing genistein have been used to lessen skin dryness and wrinkles (Ehlers et al., 2001). Genistein suppressed both the stimulated expression of cyclooxygenase-2 and basal, when tested for safety against UV light exposure, indicating that it may have anti-inflammatory qualities. Cells of human skin fibroblast -BJ-5ta cells that have been preserved through hTERT—are exposed to UVB radiation. In these cells, genistein reduced COX-2 expression while upregulating the gene expression of Gadd45, which activates the repair of DNA pathway. In another study, genistein significantly reduced the carcinogenesis of skin and photodamage of hairless mice by UVB-induction. The scavenging of reactive oxygen species, retardation in the tyrosine protein kinase, prevention of oxidative and photodynamic damage to DNA, MAPK activation, EGFR phosphorylation downregulation and oncoprotein expression suppression are some of the mechanisms possible for the action of anticarcinogenic factors that the writers have proposed.

**3.6 Genestein's Impact on Fibroblasts**

The complex environment of systemic and local influences plays a multifaceted role in the dynamic biological processes of wound healing and scar formation, involving multiple interactions between cells and matrixes. Chin et al. (2000) identified dysregulated tyrosine kinase signalling, malfunctioning receptors, and altered growth factor expression as the root causes of fibroblasts that are abnormal hyper-proliferating that comes from scars that are hypertrophic. Phosphorylated ERK molecules' nuclear translocation was changed by genistein, which reduced cell activity and proliferation. While ERK primarily controls growth, cell proliferation and differentiation, primarily P38 is linked to inflammatory responses and stress. Because of the interconnection of these pathways genistein could prevent cell division by interfering with them (Cao et al., 2009). Genistein decreased CTGF protein and mRNA expression in keloid fibroblasts in a concentration-dependent manner. Genistein retarded cell activity and its growth by altering the translocation of nuclear phosphorylated molecules of ERK. While ERK primarily controls cell growth and its proliferation, and its differentiation also, so P38 is primarily linked to inflammatory responses and stress.

Due to the interconnection of these pathways, genistein's suppressive effects on cell proliferation may be achieved by impeding these pathways (Cao et al., 2009). Fibroblast’s Collagen synthesis is needed for homeostasis of skin and healing of wound. The genistein’s effects on biosynthesis of collgen and the signalling cascades that control it were verified using fibroblasts of human dermal cells in the context of conditions that are due to oxidative stress brought on by t-BHP (t-butylhydroperoxide) (Miltyk et al., 2008).

### 3.7 Genistein and the process of wound healing

It promotes collagen synthesis, which is essential for preserving the equilibrium of the skin and speeding up the healing of wounds (Kumaran et al., 2017). According to Emerson et al. (2010), genistein directly affects the signalling pathways that regulate the synthesis of collagen in human dermal fibroblasts. Genistein was shown to be necessary for wound healing in both excisional and incisional wound models. After two weeks of a genistein-enriched diet (containing 0.01 and 0.025 percent genistein), ICR mice showed a higher rate of wound healing, generation of Reactive oxygen species (ROS), which further decreased TNF-α and NF-κB activity in the first 72 hours following wounding, was most likely the cause of this.

Ovariectomised, a mouse which is Ten-week-old with skin incisional wounds of full thickness were given systemic administration of genistein (50 mg/kg/day) or 17-estradiol (0.05 mg, subcutaneously implanted, 17-estradiol pellet slow release, 21 days). Not only did genistein lower inflammation, but it also aided in wound healing. In particular, prolonged or persistent inflammation may cause dysregulation of the activation and differentiation of fibroblasts and keratinocytes, which may interfere with the healing process of wounds frequently resulting in an excess of scar formation (Landen et al., 2016). Remarkably, despite an excessively elevated inflammatory response associated with age-related diseases (Ashcroft et al., 2003).

### 3.8 Characteristics of genistein that prevent cancer

Cancer is the primary reason of death that occur worldwide. It has been discovered that elevated MMP expression occurs during metastasis specific to cancer. Genistein demonstrated that the carcinoma cells of salivary adenoid cystic (ACC) could spread by preventing the expression of VEGF and MMP-9 in a research conducted on nude mice (Liu et al., 2007). Additional data demonstrated that genistein inhibited the migration of cancer cells of prostate region in rat (AT-2 and MAT-LyLu). Additional anti-cancer characteristics of genistein include:

#### 3.8.1 Liver cancer

The fifth most common tumor in the world is Hepatocellular carcinoma (HCC), is spreading throughout East Asia and the rest of the world and has responded favourably to a number of chemotherapeutic agents (Parkin et al., 1999; Bosch et al., 2004). Epidemiological research (Cohen et al., 2000) suggests that increased dietary isoflavonoids may protect against carcinogenesis, which raises the possibility of using isoflavonoids to prevent cancer. The most crucial course of treatment for individuals with HCC is surgery. A review of Genistein's work with HCC cells was completed recently.

Changes in cellular migration and mobility had made it clear. When HCC cells are cured with gelatin, the mesenchymal markers vimentin and N-cadherin are upregulated in vivo, as well as at the mRNA as well as in the protein levels, while the epithelial markers α-catenin and E-cadherin are downregulated. Additionally, it inhibits the TGF-β processed epithelial-mesenchymal transition (EMT), which has been connected to tumour metastasis, and reverses the EMT phenotype in SMMC-7721, Bel-7402 and HepG2 cells (Sun et al., 2009).

#### 3.8.2 Pancreatic cancer

Pancreatic cancer is one of the primary reason of cancer caused deaths in the US. According to a recently published five-year survival report on pancreatic cancer, five percent of cases have not shown any improvement over the previous thirty years (jemal et al., 2006). Elevated genistein amplifies the effects of 5-fluorouracil (5-FU-), which in turn promotes autophagy and cell death. Autophagy was reduced as a result of elevated Beclin 1 protein levels and decreased Bcl-2. Combining genistein with 5-FU boosts both autophagy and apoptosis, resulting in a significant reduction in the xenograft tumour final volume in comparison with 5-FU alone (Suzuki et al., 2014).

It has been demonstrated that the genistein scheme inhibits peripheral lymphocyte NF-nB switching in vivo in healthy individuals. Based on the experimental data that was gathered, both in vivo and in-vitro, our hypothesis was that genistein would lessen the inhibition of the EGFR/NF-nB/Akt signalling pathway on pancreatic cancer cells' ability to proliferate and survive when added to erlotinib. Our theory, which was based on the possibility that cancer cells treated with genistein and erlotinib had a multiblockade mechanism, has been applied to the data (Davis et al., 2001). In the US and other countries, pancreatic ductal adenocarcinoma (PDAC) remains an unresolved medical problem. Since 80% of PDAC patients have metastatic disease, chemotherapy is one of the main treatments for the condition (Sener et al., 1999).

#### 3.8.3 Neuroblastoma cancer

Neuroblastoma is a common extracranial solid tumour in children. An extracranial solid tumour typically manifests as the initial indication of this type of cancer. It has been shown that GST causes arrest of cell cycle and apoptosis at the G2/M phase in SK-N-MC cells of neuroblastoma (Ismail et al., 2007). Autophagy is increased in human malignant neuroblastoma IMR-32 and SK-N-BE2 cells by 200 nM rapamycin injection. Together, microtubule-associated protein light chain 3 short hairpin RNA (LC3 shRNA) plasmid transfection at a concentration of 50 nM and genistein at a concentration of 25 μM caused cell death that was programmed, decreased cell viability, and hindered the effects of autophagy promoted by rapamycin. Furthermore, both cell lines exhibit a decrease in markers that promote autophagy (Myd88, Beclin 1, LC3 II, and TLR4) and an increase in markers that inhibit autophagy (p62 and mTOR).

#### 3.8.4 Genistein regulates ovarian and breast cancer

Furthermore, research on the Genistein's anti-tumoricidal properties in vitro, in-vivo, and in silico has shown critical role that this molecule plays in a range of cancer types (Spagnuolo et al., 2015). It has been shown that genestein retards the growth of cells of cancer and the process of ovarian carcinogenesis through its pleiotropic mechanisms against ER, apoptosis, cell proliferation, metastasis, angiogenesis and oxidation. Genistein's hormonal effects are thought to give it anticancer properties (Andres et al., 2011). Since oestrogens' primary function is established by ER-β binding, many of the complications linked to

them are thought to arise from binding with ER-α. Phytoestrogens, like genistein, an isoflavone that is estrogenic with more than twenty times affinity for ER-β than α, do not exhibit this behaviour.

Since genestein can treat a variety of postmenopausal symptoms, including ovarian and breast cancer, it may prove to be a good choice as a therapy of hormone replacement (HRT). Genistein has been found to mimic the effects of oestrogens on several molecular pathways, but it has not been demonstrated to alter any potentially fatal side effects (Pintova et al 2019). Multiple studies' worth of epidemiologic data have shown a negative correlation between the risk of breast cancer and soy consumption. Breast cancer incidence was found to be 40% lower in Asian women and men who consumed a diet high in soy, while those who did not adhere to this traditional diet were not immune to the disease (Dia et al., 2001).

**IV Discussion and Conclusion**

The review highlights the numerous potential health benefits of the isoflavone genistein derived from soybeans and other legumes. Genistein exhibits antioxidant, anti-inflammatory, and anti-cancer properties through modulating various molecular signaling pathways. A key mechanism of action is genistein's ability to inhibit tyrosine kinases, which are enzymes that play critical roles in cell growth, proliferation, and survival pathways. By inhibiting tyrosine kinases like EGFR and IGF1R, genistein can induce cell cycle arrest and apoptosis in cancer cells. This makes it a promising compound for chemoprevention and adjuvant therapy for cancers like breast, pancreatic, liver, and neuroblastoma.

Genistein also displays anti-inflammatory effects by downregulating NF-κB signaling and inflammatory cytokines. This anti-inflammatory activity may contribute to its benefits for cardiovascular disease by reducing atherosclerosis severity. The antioxidant capabilities of genistein likely play a role in mitigating oxidative stress involved in inflammation and carcinogenesis as well. Beyond cancer and inflammation, genistein may provide protection against skin photoaging and cutaneous malignancies induced by UV radiation. It has also shown potential for enhancing wound healing and regulating fibroblast activity relevant to scarring. Other applications discussed include ameliorating diabetes and stress responses. While the in vitro and preclinical in vivo data are compelling, more robust clinical evidence is still needed to substantiate genistein's therapeutic efficacy in humans. Issues like bioavailability, metabolism, and optimal dosing also require further research consideration.

In summary, this review comprehensively covers the wide-ranging bioactivities and molecular mechanisms of the soy isoflavone genistein. The cumulative evidence highlights genistein as a promising nutraceutical and pharmaceutical lead compound worthy of continued investigation. Its pleiotropic effects position it as a potential preventative and therapeutic agent for an array of pathologies including cancer, inflammatory diseases, metabolic disorders, and skin conditions.

While promising, additional clinical validation is still required. Overall, genistein represents an exciting example of the therapeutic potential contained within plants and natural products. Further research expanding our understanding of its mechanisms and therapeutic applications is warranted given the initial compelling findings outlined in this review.

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