The Mechanisms of Anticancer Agents by Genistein and Synthetic Derivatives of Isoflavone

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Abstract: Genistein is the most abundant isoflavone in soybeans. It has exhibited diverse biological activities, among these, its anticancer effects is most noteworthy. Through regulating critical cell cycle genes, genistein can inhibit cancer cell growth *in vivo* and *in vitro*. It has been reported that genistein can inhibit activation of NF-κB and Akt signaling pathways to induce cell apopt1osis, both pathways are well known for their function to maintain a balance between cell survival and apoptosis. In order to find out more outstanding anticancer isoflavone agents, against cancers extended synthesis of genistein derivatives has been carried out. Some of these synthetic compounds demonstrated higher anti-cancer activity with lower doses. Based on these results, genistein and its synthetic derivatives may be an emerging new type of anticancer agents.

Keywords: Genistein, isoflavone, derivative, anticancer, molecular mechanisms, signaling pathways.

1. INTRODUCTION

Flavonoids are a class of plant secondary metabolites. Traditionally, they were considered to be phenylchromones derivatives. Nowadays, flavonoids refer to be compounds characterized by a C6-C3-C6 carbon skeleton, with a chroman (C6-C3) nucleus (the benzyl ring A and the heterocyclic ring C), and a phenyl (the aromatic ring B) substitution usually at the 2-position. Typically, different substitutions can occur in the A and B rings [1]. In different organisms, flavonoids have displayed to possess a variety of biological activities at nontoxic concentrations [2, 3], such as antitumor, antioxidant, anti-inflammatory, antiallergenic and hepatoprotective effect [4]. Based on variations in a heterocyclic C3 ring, flavonoids are classified into different subclasses, such as: flavones, flavonols, flavanones, isoflavones, catechins, anthocyanidins, proanthocyanidins flavans, and aurones.

Convincing evidence from epidemiological studies has shown that diet is implicated to play an important role in many diseases including cancers, dietary factors can regulate carcinogenesis processes, including: initiation, promotion and progression [5]. Soybean foods comprise a significant portion of the Asian diet, providing 10% of the total per capita protein intake in China and Japan, where the incidence of breast and prostate cancers is much less than that in the United States [6]. The mortality of the hormone-dependent neoplasm patients is also significantly lower in Asia than in Western populations. Research has shown that elevated levels of soy isoflavones are found in the serum, urine and prostatic fluid of Asian men who consume a soy rich diet. consequently These people are found to have lower incidence of prostate cancer. One survey involving 59 countries identified that soy products have a highly protective effect against prostate cancer [7]. consumption of soymilk has also been associated with reduced risk of prostate cancer [8].

A well know major secondary metabolite of soy is isoflavone family member genistein, also called 4, 5, 7-trihydroxyisoflavone. (Fig. **1**) Genistein is a secondary metabolite belonging to the isoflavone family, which evokes great interest because of its pleiotropic biological activity and possible applications in human cancer therapy and chemoprevention [10-13]. Although genistein and synthetic derivatives of isoflavone are not under clinical development at present, but previous studies have shown that genistein can inhibit the growth of various cancer cell lines, as well as block or reverse carcinogenesis, *in vitro* and *in vivo*, including: leukemia, lymphoma, prostate, breast, lung and head and neck cancer cells [14-20]. Genistein has also been identified as a protein tyrosine kinases (PTKs) inhibitor, and as a phytoestrogen that is capable of binding to the estrogen receptor [21]. Based on these interesting results, this review summarizes the molecular mechanisms of action of genistein, and the inhibitory effects of synthetic derivatives of genistein on prostate and breast cancer cells cancer cell growth in order to provide a comprehensive view on the role of and synthetic derivatives of isoflavone, especially in the inhibition of growth of growth of prostate and breast cancer cells.

2. MOLECULAR MECHANISMS OF GENISTEIN

2.1. Regulation of AR (Androgen Receptor) and ERβ (F Receptor) Pathway

The structure of genistein is very similar to that of estrogen, thus it has been known as phytoestrogens. Because of this structural similarity genistein was proposed to bind to estrogen receptors (ERs). The binding profile was illustrated in (Fig. **2**).

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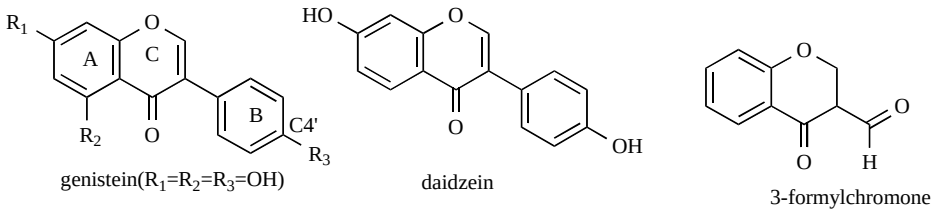

Fig. (1). Genistein and its derivatives.

Genistein effect on androgen receptor (AR) has also been investigated. AR signaling pathway is involved in the development and progression of prostate cancer through regulation of transcription of prostate specific antigen (PSA) [22, 23]. PSA is used to monitor treatment response, prognosis and progression in patients with prostate cancer as a clinically important androgen-responsive gene [26]. Research on androgens has shown that androgens were involved in the development and progression of prostate cancer [25], and play an important role in the proliferation, differentiation and function of the prostate [24]. transcriptional regulation of PSA occurs *via* androgen binding to the androgen responsive element (ARE) in the promoter region of PSA [27]. PSA expression is initially regulated by androgen, and undergoes a sharp decline after medical castration [28]. The prostate tumor becomes androgen-independent and PSA expression is constitutively up-regulated through an important mechanism, suggesting the importance of PSA in oncogenesis.

Because of the important of estrogen in cancer development and progression, researches have been focused on natural estrogen substitutes. Over years, soy isoflavones is called ‘‘weak estrogens’’, In fact, as one soy isoflavones member, genistein, has been shown to be a potent agonist for the recently characterized beta isoform of the estrogen receptor (ERβ) [29].

ERβ was expressed by human prostatic epithelium cell. ERβ activity has an antiproliferative impact on both healthy and cancer prostate [30]. Prostatic hypertrophy is common in aging ERβ-knockout mice [31, 32]. Furthermore, transfection of ERβ into human prostate cancer results in cancer apoptosis [33]. As prostate cancers progress, ERβ expression tends to decrease, consistent with the hypothesis that ER receptor exerts a restraining effect on cell proliferation [34, 35]. Meanwile, in ERβ rich expressed prostate cancer cells,, a variety of estrogens and anti-estrogens including genistein have displayed obvious antiproliferative andpro-apoptotic effect [36-39]. Genistein has been shown to down-regulate the expression of the androgen receptor in the human prostate cancer-derived LNCaP cell [40]. Moreover, soy phytochemical concentrates could substaintially slow down LNCaP growth in nude mice [41, 42]. Likewisely, genistein feeding down-regulates androgen receptor expression in rat prostate [43], and reduces the yield of prostate cancer in carcinogen-treated rats, as well as in transgenic ‘‘TRAMP’’ mice that have a high spontaneous incidence of this cancer [44, 45]. To evaluate the impact of oral genistein on early stage prostate cancer, clinical studies have achieved (indicated) a moderate reduction of PSA in a minority of patients, and an apparent reduction in cancer growth rate in others [46, 47]. Case control studies are consistent with the hypothesis that soy products rich diets are associated with lower risk of prostate cancer [48-50], with high soy intake being a diet marker.

2.2. Regulation of the Expression of Genes Related to Cell Cycle and Apoptosis

2.2.1. Effects on the Inhibition of Cancer Cell Growth

Genistein has been identified as a protein tyrosine kinases (PTKs) inhibitor [51]. PTKs are known to play key roles in carcinogenesis, cell growth and apoptosis [52, 53]. It has been reported that genistein is a potent inhibitor of cell proliferation, oncogenesis and clonogenic ability of animal and human cells [54, 55]. Experiments have shown that genistein inhibits growth of cancer cells including leukemia, lymphoma, neuroblastoma, breast and prostate cancer cells [56-61]. Fazlul H. [62] have experimentally studied the

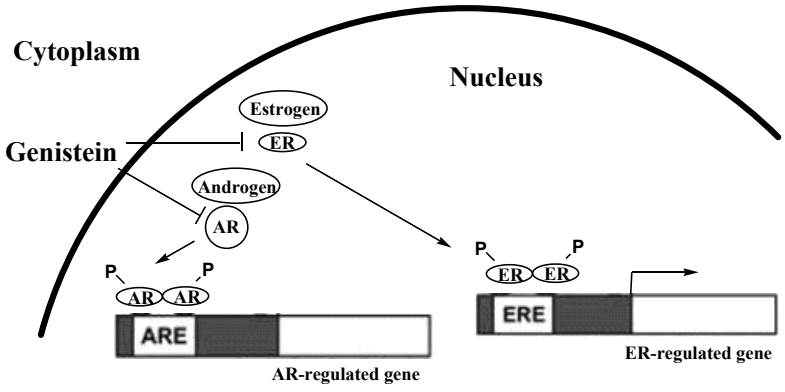

Fig. (2). The effect of genistein on AR pathway.

effects of genistein on cell growth of various cancer cells, including MDA-MB-231, MDA-MB-435 and MCF-7 breast cancer cells that are ER positive or negative; PC3 and LNCaP prostate cancer cells that are AR negative and positive, respectively; H460 and H322 non-small cell lung cancer cells with wild type or mutant p53, and HN4 head and neck squamous carcinoma cells. These cells when treated with 5–50 μM genistein for a period of 24–72 h showed cell growth inhibition, regardless of the status of ER, AR and p53. The inhibition of cell proliferation was also found to be dose- and time-dependent. These effects of genistein clearly indicate that it could be very useful for inhibiting the tumor cell growth of a variety of cells having heterogeneous molecular signature, a known hallmark of solid tumors.

2.2.2. Effects on cell cycle regulation

Perturbations in cell cycle progression may account for the anticarcinogenic effects of flavonoids. Mitogenic signals commit cells to entry into a series of regulated steps allowing traverse of the cell cycle. Synthesis of DNA (S phase) and separation of two daughter cells (M phase) are the main features of cell cycle progression. The time between the S and M phases is known as G2 phase. This phase is important to allow cells to repair errors that occur during DNA duplication, preventing the propagation of these errors to daughter cells. In contrast, the G1 phase represents the period of commitment to cell cycle progression that separates M and S phases as cells prepare for DNA duplication upon mitogenic signals. Cyclin-dependent kinases (CDKs) have been recognized as key regulators of cell cycle progression. Alteration and deregulation of CDK activity are pathogenic hallmarks of oncogenesis. A number of cancers are associated with hyperactivation of CDKs as a result of mutation of the CDK genes or CDK inhibitor genes. Therefore, inhibitors or modulators would be of interest to explore as novel therapeutic agents in cancer. Checkpoints at both G1/S and G2/M of the cell cycle in cultured cancer cell lines have been found to be perturbed by flavonoids such as silymarin, genistein, quercetin, daidzein, luteolin, kaempferol, apigenin, and epigallocatechin 3-gallate. Studies from different laboratories revealed that flavopiridol could induce cell cycle arrest during either G1 or G2/M by the inhibition of all CDKs thus far examined [63].

Cell cycle progression (Fig. **3**) is known to be tightly regulated by different cyclins, CDKs and cyclin dependent kinase inhibitors (CDKIs), in different phases of the cell cycle. However, Fazlul H. [62] found that compared to the control cells, the cancer cells treated with different concentrations of genistein showed a dose-dependent decrease in the expression of cyclin B, which plays important roles in the positive regulation of CDK activity and is necessary for forming cyclinB/CDK complex during the G2/M phase procession, and that this effect was a time-dependent phenomenon. These observations were correlated with the G2/M cell cycle arrest, suggesting that genistein-induced cell cycle arrest in cancer cells is partially due to the down-regulation of cyclin B [64].

Cyclins/CDKs complexes are negatively regulated by several CDKIs including $p21^{WAF1}$, p27 and p16. Fazlul H.'s lab examined whether genistein altered the expression of $p21^{WAF1}$ in MDA-MB-231, MDA-MB-435 and MCF-7 breast cancer cells; PC3 and LNCaP prostate cancer cells; H460 and H322 non-small cell lung cancer cells; and HN4 head and neck squamous carcinoma cells, by Western blot and/or Northern blot analysis. And the data revealed that a significant dose dependent up-regulation of $p21^{WAF1}$ expression in genistein treated cancer cells compared to control cells. This finding was consistent with the results on the inhibition of cancer cell growth, cell cycle arrest and down-regulated expression of cyclin B and all suggests that genistein can inhibit the growth of cancer cells by modulating the expression of genes that are involved in the regulation of cell growth and the cell cycle [62].

Aberrant cell cycle progression is an inherent characteristic of almost all types of cancer growth and progression. Some studies discussed suggest that there is a vast gap between the advances in basic research for cell cycle regulatory mechanisms and their investigation with many natural chemopreventive agents including flavonoids. The research efforts and the published data for the *in vivo* cell cycle regulatory effects of natural flavonoids are very limited. Hence, extensive pre-clinical studies are needed to determine the doses, efficacy and mechanisms of natural flavonoids against different types of cancer growth and progression. The investigation of integrated biochemical mechanisms including cell cycle progression would be helpful in the appropriate development of the test agent for cancer control [64].

2.2.3. Effects on the Induction of Apoptosis

Besides to cell cycle regulation, the overall cell growth inhibition induced by genistein could also be due to increased program cell death known as apoptosis. The data showed that genistein could induce apoptosis in many kinds of breast cancer cells, prostate cancer cells, non-small cell lung cancer cells and squamous carcinoma cells [64, 65]. Fragmentation of cellular DNA at the internucleosomal linker regions has been observed in cells undergoing apoptosis. This cleavage produces ladders of DNA fragments that are the sizes of integer multiples of a nucleosome length (180–200 bp). Because of their characteristic patterns revealed by agarose gel electrophoresis, these nucleosomal DNA ladders are widely used as biochemical markers of apoptosis [66-68]. DNA ladder formation and poly ADP-ribose polymerase (PARP) cleavage were observed in cancer cells treated with genistein for 48 h. Cysteine protease protein, 32kDa (CPP32) activation was also observed in the genistein-treated cancer cells. Flow cytometry revealed that the number of apoptotic cells increased up to 43–57% with longer genistein treatment. These results clearly suggest that genistein can induce apoptosis, and these observations are consistent with studies reported by other investigators [69, 70]. In order to exploit the molecular mechanism of action of genistein-induced apoptosis, the alternation of gene expression involved in the apoptotic pathway was investigated. Some results suggest that up-regulation of Bax and downregulation of Bcl-2 may be one of the molecular mechanisms by which genistein induces apoptosis (Fig. **4**). The p53 and p21 tumor suppressor genes are also known to be involved in apoptotic process. Functional p53 can down-regulate Bcl-2 which allows cells to survive a variety of fatal

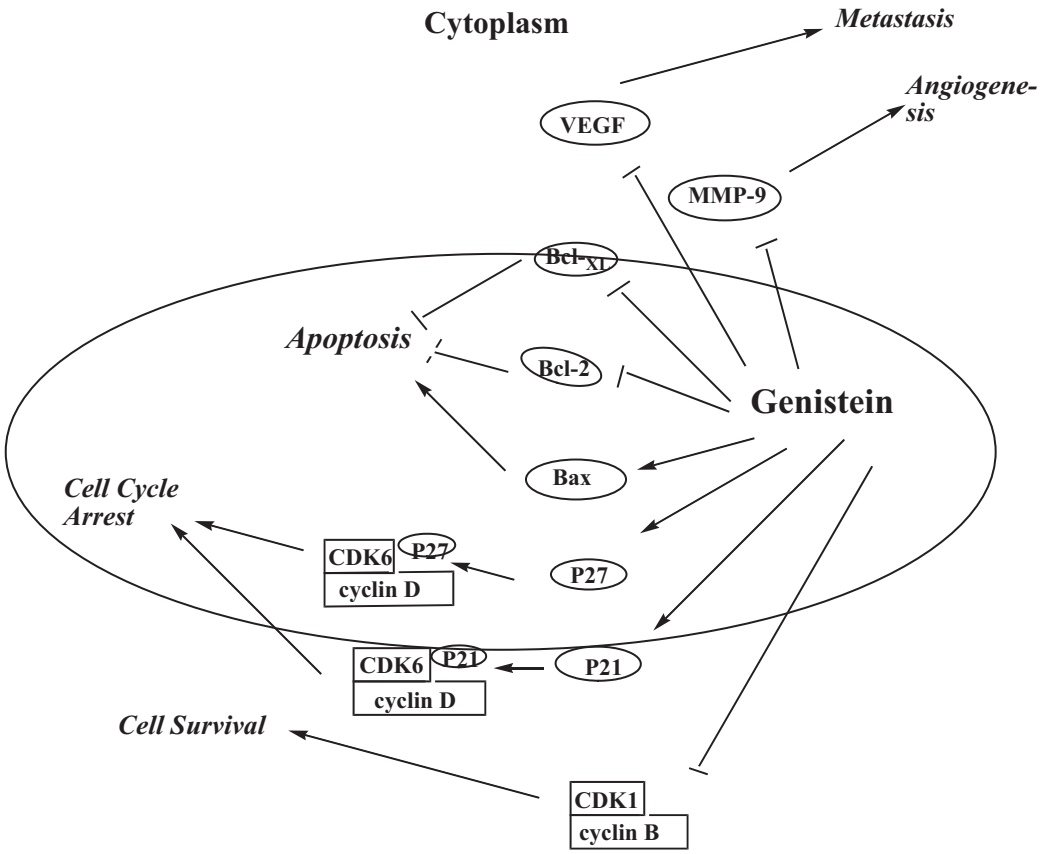

Fig. (3). The effects of genistein on cell cycle and apoptosis pathways.

cellular events and protects cells from apoptosis [71, 72]. Functional p53 can also induce $p21^{WAF1}$, and an increased level of $p21^{WAF1}$ can inhibit the activity of CDKs, resulting in growth arrest [73-77]. Cells that fail to progress through mitosis are eventually destined to apoptotic cell death.

It has been reported that genistein induces apoptosis in MCF-7 breast cancer cell which is ER-positive and harbors wild type p53 [78-80]. Fazlul's laboratory [62] detected the expression of p53 gene in MDA-MB-231 breast cancer cells, which are ER-negative and harbor mutant p53. The treatment of these cells with genistein down-regulated the expression of the dysfunctional p53 after treatment for 72 h, while $p21^{WAF1}$ was induced within 24 h [81]. These results suggest that the induction of $p21^{WAF1}$ and apoptosis induced by genistein is functionally operated through a p53-independent pathway. Above all, the results suggest that genistein may induce apoptosis in breast cancer cells through p53-dependent or independent pathway.

In addition to the conclusions mentioned above, expressions of genes that are critically involved in theapoptotic pathways after genistein treatment have been also examined [62]. The results showed that genistein treatment reduced Bcl-2 protein expression and significantly increased expression of Bax in all cancer cells tested [82-83]. Other investigators have also reported that soy isoflavone genistein could induce apoptosis in human hepatoma cells and breast cancer cells through caspase-3 activation and down-regulation of Bcl-2, Bcl-XL, and HER-2/neu [84-86]. Kazi *et al* showed that genistein induced apoptosis by inhibition of proteasome and induction of $p27^{KIP1}$, IκB-α, and Bax [87]. These results suggest that caspase activation, inhibition of proteasome, upregulationof Bax, and down-regulation of Bcl-2, Bcl-XL, and HER-2/neu may partly represent the molecular mechanisms by which genistein induces apoptosis and many of these molecules may also be regulated directlyor indirectly by the DNA-binding activity of NF-κB.

Genistein is cytotoxic to ovarian cancer cells. The mechanism of genistein-induced cell death includes both apoptosis and autophagy. Because autophagy is typically an adaptive response to nutrient starvation, we hypothesized that genistein could induce a starvation-like signaling response. Genistein treatment results in caspase-independent cell death with hallmarks of autophagy. Genistein treatment dramatically inhibits glucose uptake in ovarian cancer cells, and methyl pyruvate, a cell-permeable 3-carbon substrate for oxidative phosphorylation and fatty acid synthesis, rescues cells from genistein-induced autophagy. In addition, genistein treatment results in reduced levels of phosphorylated Akt, which may contribute towards a mechanism to limit glucose utilization [88, 89].

Genistein also has activity as an inhibitor of Topo II and protein tyrosine kinases. It induces Topo II-mediated DNA breaks in mammalian cells. It has been shown that genistein causes G_1 or G_2/M cell cycle arrest and apoptosis in human cells. Though it has been shown that genistein can induce

p53 phosphorylation, it has also been shown that genistein induces p53-independent $p21^{WAF1/Cip1}$ expression in human breast and prostate carcinoma cell lines. The exact mechanism underlying $p21^{WAF1/Cip1}$ expression induced by these agents is still unknown. Although both agents cause Topo II-mediated DNA strand breaks by inhibiting Topo II, it has been suggested that they may activate different DNA damage response pathways [90].

Based on the above mentioned research results, our conclusion is that most conventional chemotherapeutic agents induce cell death through apoptoticpathway. However, genistein can induce cell death through both apoptotic and autophagicpathways, As a result, it has the potential to circumvent chemoresistance due to alterations in apoptotic signaling [91].

2.3. Regulation of NF-κB Pathway

In the cell growth and proliferation, the initiation and regulation of gene transcription in cells is a complicated process in which transcription factors play important roles. Transcription factors interact with short consensus DNA sequence that is present in the enhancer and promoter regions of target genes. This sequence allows the binding of RNA polymerase and the initiation of gene transcription program [92]. Each of these transcription factors can regulate the expression of multiple genes. The transcription factor, NF-κB (Fig. **6** [62]) was first identified as a protein that binds to a specific DNA site in the intronic enhancer of the immunoglobulin κ light chain gene [93]. At present there are five known proteins that comprise the NF-κB family; RelA (p65), RelB, Rel, NF-κB1 (p50) and NF-κB2 (p52), each of which may form homo- or heterodimers [94-97]. In almost all cell types, NF-κB is sequestered in the cytoplasm through tight association with the inhibitory IκB protein. NF-κB can be activated by many types of stimuli including TNF, IL-1, UV radiation, free radicals, etc [98]. The activation of NF-κB typically occurs through site-specific phosphorylation and ubiquitination of a complexed IκB protein, promoting its subsequent degradation by the 26S proteasome degradation pathway. This allows the translocation of NF-κB into the nucleus to bind to NF-κB-specific DNA-binding sites or interact with other transcription factors and regulate gene transcription [99-102]. NF-κB controls the expression of numerous genes involved in the immune and inflammatory responses, cell adhesion, and growth control [103,104]. There is growing evidence to suggest the role of NF-κB in the protection against apoptosis. It has been reported that over expression of NF-κB protects cells from apoptosis, while inhibition or absence of NF-κB, induces apoptosis or sensitize cells to apoptosis-inducing agents including: TNF-α, ionizing radiation and other anti-cancer agents [105,106]. An *in vivo* study showed that mice lacking NF-κB p65/RelA died embryonically from extensive apoptosis in the liver, suggesting anti-apoptotic role of NF-κB [107].

Some chemotherapeutic agents such as cisplatin and docetaxel induce the activation of NF-κB in cancer cells, and this may be responsible for drug resistance too [108-110]. By *in vitro* and *in vivo* studies, it has shown that pre-treatment with genistein followed by treatment with lower doses of docetaxel or cisplatin elicited significantly greater inhibition of cell growth and induction of apoptosis compared to either agent alone [111]. By EMSA, people found that NF-κB activity was significantly increased by docetaxel or cisplatin treatment, and the NF-κB inducing activity of these agents was completely abrogated in cells pre-treated with genistein. These *in vitro* results were also recapitulated the *in vivo* studies [112]. The results suggest that genistein pre-treatment, which inactivates NF-κB activity, together with other cellular effects of genistein, may contribute to increased cell growth inhibition and apoptosis with non-toxic doses of docetaxel or cisplatin. Hwang *et al* also reported that combination of genistein with 5-fluorouracil induced apoptosis synergistically in chemoresistant colon cancer cells [113]. Other investigators also found that genistein in combination with EGCG or vitamin D could exert enhanced anti-tumor activity through synergic action or compensation of inverse properties [114,115], suggesting that administration of combined agents with distinct molecular mechanisms could be a more effective factor for cancer prevention and therapy.

In addition to the above mentioned statements, the molecular mechanism for soy isoflavones preventive effect against radiation remains to be clarified. NF-κB and APE1/Ref-1 were identified as soy isoflavones two potential molecular targets, the cross-talk between each other could be involved in increased PC-3 cell killing [6, 9], both signaling molecules closely involved in cell death or survival pathways. In response to cellular stress, including radiation, NF-κBs activation is responsible fortumor progression, and is the major transcription factor involved in critical cell survival proteinbiosynthesis i, [116-118]. Vinita Singh-Gupta have further investigated soy isoflavones effect on cell survival pathway, and determined two major isoflavones activity : genistein and daidzein. radiation activated Src/STAT3/HIF-1a and nuclear translocation of HIF-1a could be inhibited by isoflavones pretreatment . These correlated with decreased APE1/Ref-1 expression and DNA binding activity of HIF-1a and NF-κB. In APE1/Ref-1 cDNA transfected cells, increased HIF-1a and NF-κB activities was inhibited by pretreatment with soy prior to radiation [119].

2.4. Regulation of Akt Pathway

Nuclear factor-κB (NF-κB) pathway plays important roles in the control of cell growth, differentiation, apoptosis, and stress response. Akt signaling pathway (Fig. **5**) is another important transduction pathway in cells. Akt, also referred to as protein kinase B (PKB), plays a critical role in controlling the balance between cell survival and apoptosis [120]. Akt contains an aminoterminal pleckstrin homology (PH) domain that binds phosphorylated lipids at the membrane in response to activation of phosphatidylinositol-3 (PI3) kinases. Akt may be activated by insulin and various growth and survival factors through activation of PI3 kinase [121,122]. Akt is activated by phospholipid binding and phosphorylation at Thr308 by PDK1 [123], and also by phosphorylation within the C-terminus at Ser473 by PDK2. Akt functions to promote cell survival by inhibiting apoptosis by its ability to phosphorylate and inactivate several targets including; Bad, Forkhead transcription factors and caspase-9, all of which are involved in apoptotic

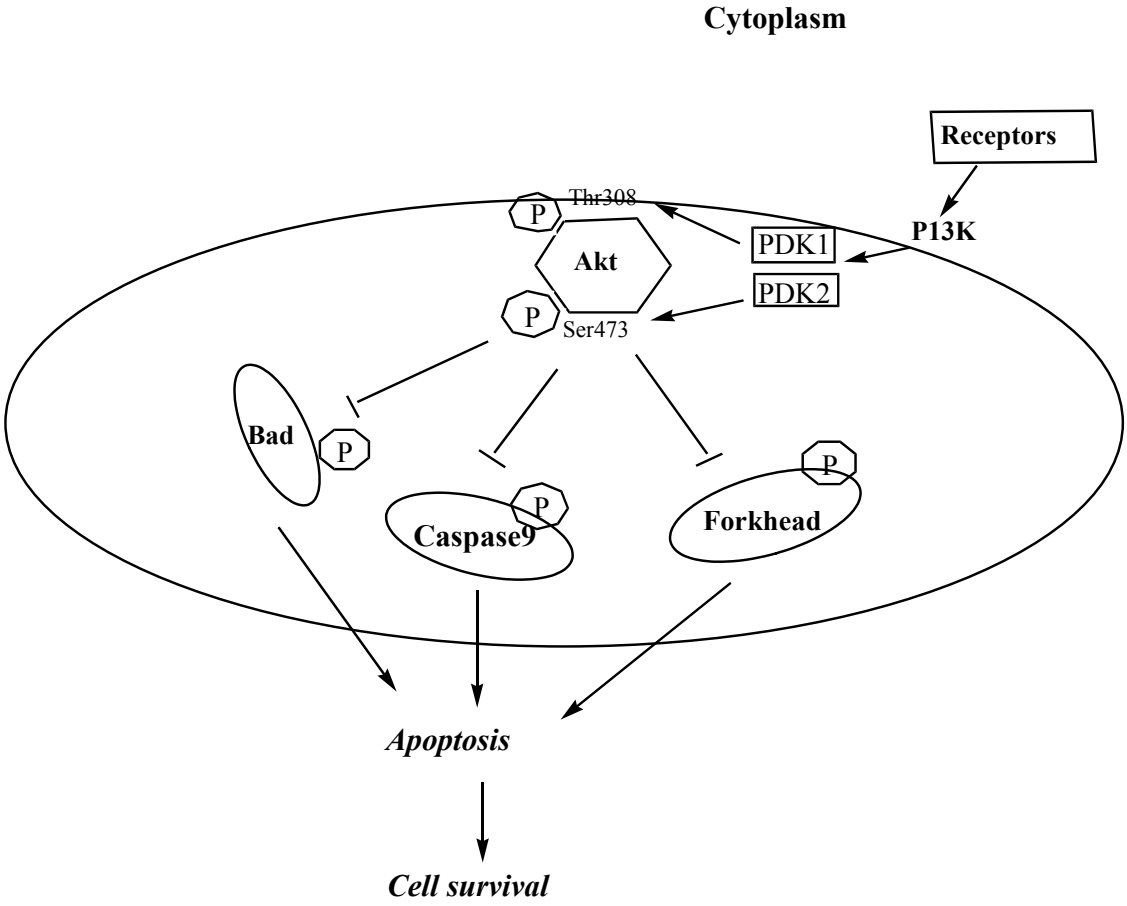

Fig. (4). Akt signaling pathway in cell.

pathway (Fig. **4**) [124]. Recent reports showed that Akt also regulates the NF-κB pathway *via* phosphorylation and activation of molecules in the NF-κB pathway (Fig. **5**) [125]. Furthermore, genistein treatment induced mitochondrial membrane potential change, caspase-3 activation and PARP cleavage. From these results, it was concluded that inhibition of the Akt signaling pathway and induction of apoptosis by genistein could be used as a new treatment modality for the prevention [126].

Anaplastic large-cell lymphoma (ALCL) is a distinct subgroup of non-Hodgkin's lymphoma usually composed of large pleomorphic tumor cells that express the membrane antigen CD30 [127]. Despite variations in histological features, ALCL is commonly associated with a t (2; 5) (p23; q35) translocation that results in the fusion of the nucleophosmin (NPM) gene at 5q35 with the tyrosine kinase gene anaplastic lymphoma kinase (ALK) at 2p23 [128,129]. Fusion of NPM to ALK results in the dimerization and constitutive activation of the NPM-ALK oncoprotein that is capable of transforming fibroblasts and inducing a lymphoma-like disease in mice [130,131]. Also NPM-ALK recruits the C-terminal SH2 domain of the antiapoptotic PI3-kinase, which activates the serine/ threonine kinase Akt, as likely contributes to the molecular pathogenesis of ALCL [132].

Two t (2; 5) ALCL cell lines, SUDHL-1 and Karpas299, with genistein induced apoptosis in a time- and dose-dependent manner. Concurrently, these cells exhibited a decrease in Akt protein levels and subsequent downregulation of Akt activity (Akt phosphorylation). Furthermore, genistein treatment induced mitochondrial membrane potential change, caspase-3 activation and PARP cleavage. From these results, it was concluded that inhibition of the Akt signaling pathway and induction of apoptosis by genistein could be used as a new treatment modality for the prevention and/or treatment of t (2; 5) ALCL and otherhematopoietic malignancies [132].

2.5. Regulation of the Expression of Genes Related to Angiogenesis and Metastasis

Angiogenesis is a strictly controlled process in the healthy adult human body, which is regulated by a variety of endogenous angiogenic and angiostatic factors. However, pathological angiogenesis can occur in cancer. When deprived of proper vascularization, the high proliferation rate in the tumor would be balanced by cell death due to the lack of diffusion of nutrients and oxygen. Flavonoids are known as angiogenesis inhibitors derived from natural sources. The abilities of particular flavonoids to block solid tumor growth may be due to their inhibition of the neoangiogenic process. Angiogenesis inhibitors are able to interfere with various steps of angiogenesis, like basement destruction of blood vessels, proliferation and migration of endothelial cells, or the lumen formation. Therefore, these compounds may have potential for the treatment of solid tumors [133,134].

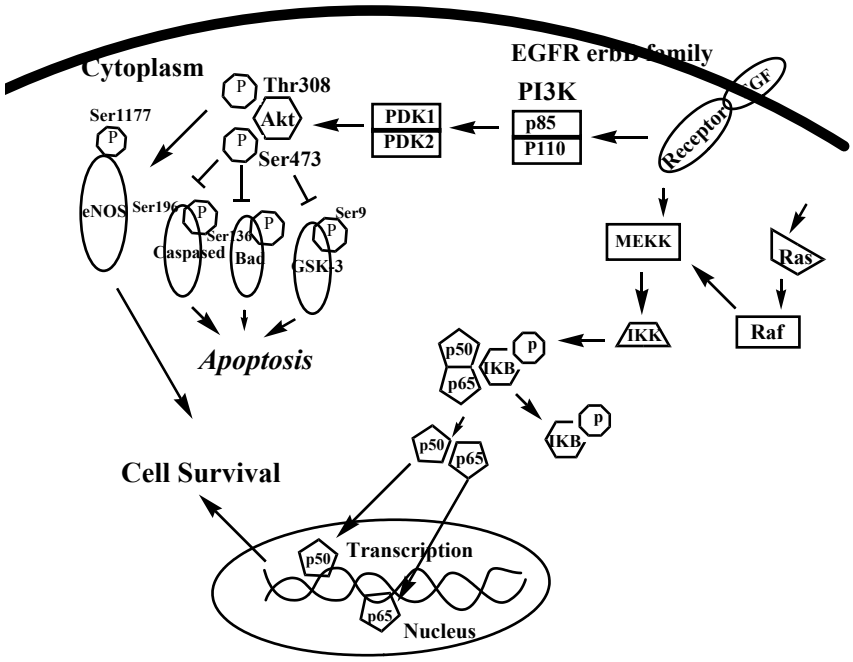

Fig. (5). NF-κB and Akt signaling pathway in cell [62].

The formation of new blood vessels is called angiogenesis. It is essential for normal reproductive function, development and wound repair processes. However, angiogenesis in solid tumors are believed to promote cancer cell proliferation, invasion and metastasis. It has been found that genistein inhibits vessel endothelial cell proliferation and *in vitro* angiogenesis at half maximal concentration of 5 and 150 *μ*M, respectively, suggesting that genistein is a potent inhibitor of vascularization and cancer cell growth [135]. Transforming growth factor-β (TGF-β) is the known major factor to regulate cell proliferation[136], TGF-β signaling is an virtue feature in angiogenesis regulation of [137]. Genistein was known to inhibit angiogenesis through TGF-β signaling[138]. we hypothesize that genistein is a potent anti-angiogenic agent and its application on tumor therapy awaits further investigation.

Genistein has been shown to reduce the angiogenic and metastatic potential of cancers. Genistein could prostate cancer cell growth and down-regulated the transcription and translation of genes critically involved in tumor cell invasion and metastasis *in vitro* and *in vivo*. Other investigators have also found that isoflavones inhibited bone metastasis of human breast cancer cells in a nude mouse model, androgen-sensitive human prostate tumors metastasis [139,140]. Although genistein could induce pleiotropic effect on cancer cells; it appears that genistein itself may not be an attractive agent for cancertreatment. In order to alleviate this problem, synthetic derivatives of isoflavone with robust biological activity should be investigated..

In this regards, genistein was observed to shown angiogenesis and *in vitro* invasion in an OSCC model. Oral squamous cell carcinoma (OSCC) is one of the most common head and neck cancers, due to its local invasion and subsequent metastasis, OSCC generally has a poor prognosistendency , After treating HSC-3 cells with genistein (27.3 *μ*g/ml),. a down-regulation in VEGF mRNA expression, but not in bFGF and MMP-2 mRNA expression were observed through northern blot analysis. Genistein reduced *in vitro* invasion through the artificial basement membrane, and gelatin enzymography analysis also suggesteda reduced gelatinolytic activity in the genistein-treated group. However, the tumor growth and metastatic behavior in the experimental group and the control group were similar. However, it appears that genistein alone as anti-angiogenic agentmay not provide a satisfactory outcome for OSCC treatment. As a result, further research is recommended to confirm genistein as an adjunct drug for OSCC

In summary, genistein exerts its inhibitory effects on carcinogenesis, cancer cell growth, and cancer progression. These effects of genistein have been known to mediated by molecular mechanisms through regulation of cell cycle, apoptosis, cell signaling pathways and transcription factors (Fig. **6**).

3. SYNTHETIC DERIVATIVES OF ISOFLAVONE IN CANCER PREVENTION AND THERAPY

Like natural anticancer isoflavone, many synthetic isoflavone derivatives also exhibited significant anticancer activities. It has been shown that the anticancer properties of isoflavonoids are in part due to some structural motifs that include a benzopyran motif with a double bond between C2-C3 positions and a side chain containing a phenyl ring having metal chelating ability [142-144]. More importantly, these compounds are capable of forming metal conjugates with therapeutically important metal ions, among which copper is particularly effective in yielding moieties with potent radical scavenging properties [145]. In recent years, many derivatives of isoflavone have been synthesized. Recent reports show that investigators are interested in

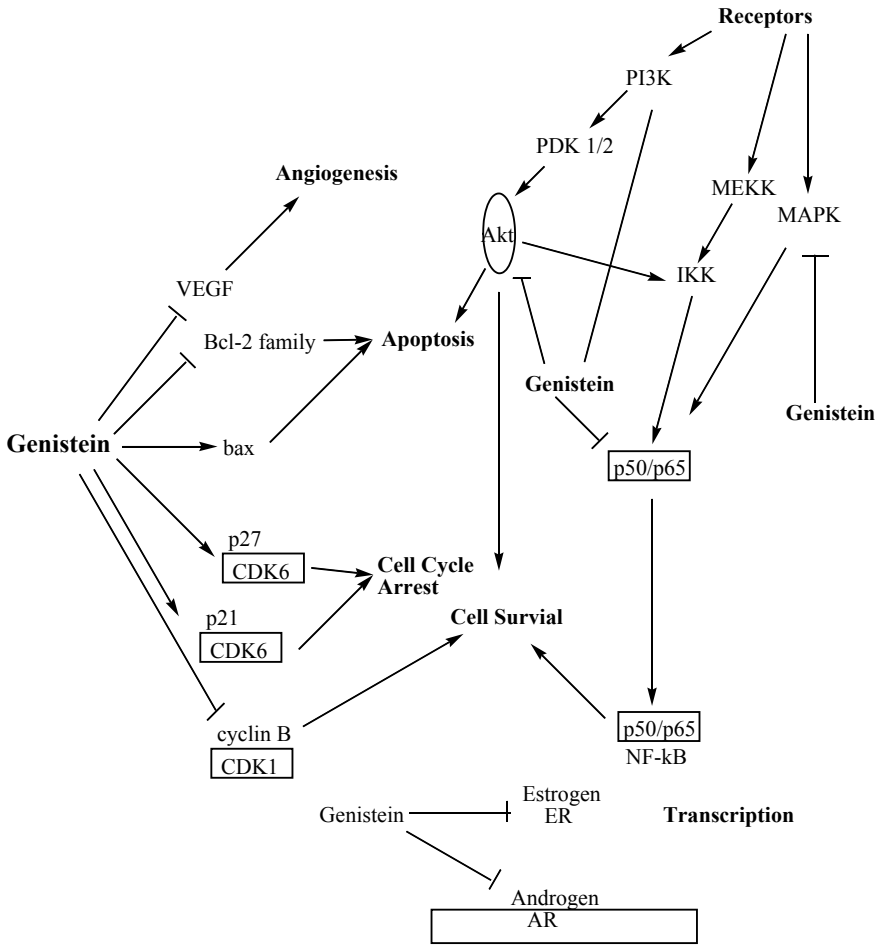

Fig. (6). The effect of genistein's activity in relation with kinases and transcription factors [141].

designing derivatives of isoflavone [146-150], which provide confidence in our recent synthetic derivatives of isoflavone for their anti-tumor activity. Fazlul H. Sarkar have tested the effects of synthetic derivatives of isoflavone on the growth of hormone independent breast (BT20) and prostate (PC-3) cancer cells and K-ras positive(Colo357) and negative (BxPC-3) pancreatic cancer cells. They found that the synthetic derivatives of isoflavone inhibited cell proliferation in all cancer cell lines tested [62].

Now, we focus on the anticancer activity of several synthetic derivatives of isoflavone, together with the design of target compounds and the exploration of SAR to improve the anticancer activity of the derivatives.

3.1. Biological Activity of Novel Synthetic Derivatives of Chromen-4-one in Human Cancer Cells

Genistein can inhibit the growth of various cancer cell lines, including leukemia, lymphoma, prostate, breast, lung, and head and neck, both *in vitro* and *in vivo*. These structural requirements can be easily built into the compound 3-formylchromone, which is a versatile synthon in heterocyclic chemistry, having antiinflammatory and anticancer activities. Corresponding Schiff bases can be synthesized by condensing it with various amines in alcoholic medium. Such compounds are capable of forming metal complexes with several transition metal ions among which copper is particularly effective in yielding moieties with potent radical scavenging properties [19].

The synthesis and characterization of Schiff base derivatives of 3-formylchromone, the minimal biologically active structural motif of soy isoflavone, genistein, and their copper complexes have been once reported [158]. These copper complexes possess distorted squareplanar geometries capable of stabilizing Cu^{2+}/Cu+ redox forms. The molecular modeling study revealed that the key interaction of the metal complexes was with amino acids in the pleckstrin homology (PH) and the kinase domain of the PKB (Akt) protein. In this article, one type of copper complex significantly forms stronger charge interactions in the kinase domain than genistein, leading to better stabilization in the active pocket. ELISA apoptosis assay of genistein copper complexes against hormone-independent and metastatic breast (BT20) and prostate (PC-3) cancer cells revealed that that these isoflavone derivatives significantly induced apoptotic cell death in BT20 breast and PC-3 prostate cancer cells. Since all copper compounds were redox active metal conjugates, it is concluded that the regulation of oxidative stress may be involved in the molecular mechanisms by which copper conjugates derivitives of isoflavone induce apoptotic cell death in breast and prostate cancers [141, 151].

Through the research, an inverse relationship was observed between IC_{50} values of the anti-proliferative

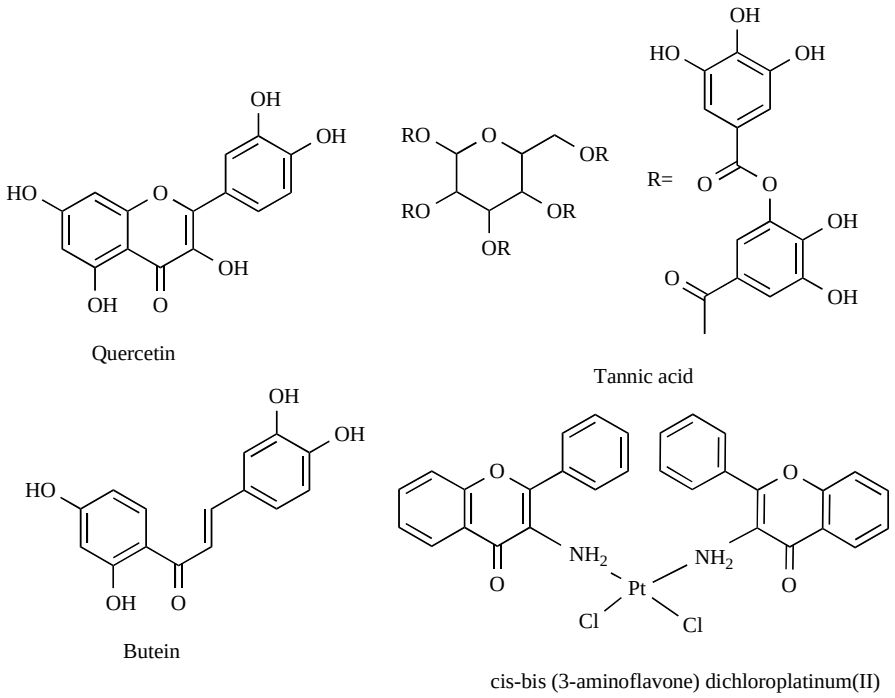

Fig. (7). Chemical structure of flavonoid compounds interacting with cis-DDP for synergistic interactions.

activities and the Cu2+/Cu+ redox couple for these compounds, which may provide a rapid screen for evaluating the efficacy of active metallodrugs affecting redox-senstitive transcription factors such as NF-B and its upstream target, the PKB (Akt) pathway and cell life cycle modulation in multiple cancers.

3.2. Isoflavone Derivatives Interactions with cis-DDP

Diamminedichloroplatinum (cis-DDP) (Peyrone's chloride; Fig. **7**) was first synthesized in 1845, and its structure was only determined in 1893. The cytostatic properties of cis-DDP were first observed in L1210 cells and murine solid sarcoma-180 [35], and by 1971 its anticancer properties were confirmed in the clinic in germinal testicular cancer. In 1978, it was approved as an anticancer drug for chemotherapy of testicular and ovarian cancer. cis-DDP is one of the most popular compounds used in the chemotherapy of both small- and nonsmall-cell lung, cervical, endometrial, bladder, and esophageal cancers, in squamous cell carcinoma of the head and neck, as well as in osteosarcoma. It is also a therapeutic option in several other solid neoplasms including liver and gastric cancer, brain tumors, melanoma, and soft-tissue sarcomas. However, cis-DDP has many side effects that limit its use that include nephrotoxicity, myelotoxicity, ototoxicity, peripheral neuropathy, hypomagnesemia, hematological toxicity (leukopenia, thrombocytopenia, and anemia), anaphylactic reactions, and gastrointestinal side effects(severe nausea, vomiting, and diarrhea).

Here, we mainly discuss anticancer activity of cis-DDP interacted flavonoid compounds. According to previous studies, flavonoid compounds, especially quercetin and genistein, have antitumor activity. These compounds are cytotoxic to cancer cells but have no or insignificant activity in normal cells. These beneficial properties prompted synthesis of flavonoid synthetic derivatives, e.g., flavopiridol; B43-genistein and EGF-genistein .cis-DDP is one of the most effective drugs used for chemotherapy, but its actions are limited by many side effects. Beneficial synergistic effects of flavonoids (e.g., quercetin, genistein, butein, tannic acid) and cis-DDP were found in cis-DDP-sensitive and resistant cancer cells that resulted in a lower toxicity for cis-DDP. Further studies focused on the synthesis of complexes of compounds belonging to different groups, e.g., cis-bis (3-aminoflavone) dichloroplatinum(II) where introduction of the flavone ligand altered the DNA-binding properties of the complex as compared to cis-DDP alone. The beneficial anticancer and antioxidant properties of flavonoids and their synthetic derivatives have prompted further research on the synergistic interactions of these compounds with routinely applied chemotherapeutic drugs, e.g. cis-DDP [52].

4. CONCLUSIONS

In conclusion, numerous studies have revealed that genistein ingested from natural food exerts inhibitory effects on carcinogenesis, cancer cell growth and progression. These activities are mediated through actions on: AR (androgen receptor), cell cycle, cell growth, angiogenesis, invasion, angiogenesis and metastasis processes. And these effects may be primarily due to specific effects of genistein on Akt, NF-κB, MMPs and Bax/Bcl-2 signaling pathways. The synthetic derivatives such as the cis-DDP interacted isoflavone derivatives, and the aboved mentioned chromen-4-one derivatives demostratedeven stronger inhibitory effects on cancer cell growth at much lower doses.

However, further basic and clinical research along with animal and clinical trials are awaited to prove the value of

genistein and the synthetic derivatives of isoflavone against human cancers with utmost confidence.

CONFLICT OF INTEREST

Declared none.

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