Genistein for Breast Cancer

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Breast cancer (BC) is one of the most common malignancies in women. Genistein (GNT) is a soy-based phytoestrogen and is consumed regularly by Asian populations. This phytoestrogen may be one of the leading compounds as its safe and anticancer activities have already been tested in several in vitro and preclinical models. GNT has a structural similarity to 17 β-estradiol, and it binds to estrogen receptor ER-β with higher affinity compared to ER-α. Several studies suggested that GNT exerts pleiotropic effects, including inhibiting the cell cycle, inducing the cellular apoptosis process, suppressing metastasis and angiogenesis, modulating oxidative stress, and mammosphere formation in in vitro BC models. Furthermore, this phytoestrogen exerts several synergistic activities, as it can enhance the efficacy of conventional drugs against BC and reduce chemotherapeutic drug resistance. Moreover, many in vivo and clinical trials also support that GNT can be considered a promising chemopreventive agent for treating different types of BC.

Keywords: genistein ; breast cancer ; molecular pharmacology

1. An Overview of Genistein (GNT)

Genistein (GNT) (IUPAC: 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is a phytoestrogen isoflavone that is widely available in soybean, mature seeds, and raw soy-related food (5.6–276 mg/100 g) [1] and legumes (0.2–0.6 mg/100 g) [2]. It possesses lower oral bioavailability, perhaps due to its high solubility in several polar solvents such as acetone, dimethylsulfoxide, and ethanol, and its poor solubility in water [3]. The oral administration of GNT results in high absorption with a t_{max} (transport maximum) of 5–6 h and t1/2 of 8 h [4][5]. GNT is rapidly distributed throughout the body by crossing the placental and blood–brain barriers. GNT is most abundant in the gastrointestinal tract and liver tissue distribution, consistent with its enterohepatic recycling [6]. GNT is absorbed rapidly and nearly completely in vivo. It showed high permeability in Caco-2 (3×10^{-5} cm/s) and Madin–Darby canine kidney (MDCKII) cells, where passive diffusion is the major transport mechanism, but breast cancer resistance protein (BCRP) may play a role in limiting its intestinal absorption [7][8][9]. In vivo, GNT undergoes a complex and extensive metabolic process that includes oxidation, reduction, conjugation, glucuronidation, sulfation, and limited CYP reaction [10][11][12][13][14][15]. Coldham et al. found that GNT has the highest concentrations in the gut (18.5 µg/g), followed by the liver (0.98 µg/g), plasma (0.79 µg/g), and reproductive tissues (uterus, ovary, vagina, and prostate, ranging from 0.12 to 0.28 µg/g) in rats [16]. The excretion of GNT depends on the activity of conjugating enzymes and relies on the efflux transporters' capacity [17]. In vivo, ADME studies revealed that GNT metabolites are excreted via the intestinal, biliary, and renal tracts [18][19]. Although there is limited evidence that consuming large amounts of GNT in the diet causes a deleterious effect in humans, the toxicity of GNT on fertility and fetal development has been extensively studied in recent years. Several studies have demonstrated that therapeutically relevant doses of GNT have a harmful effect on BC differentiation, the estrous cycle, and fertility in rodent models [20][21]. This natural phytochemical can exhibit a wide range of important therapeutic activities, including antioxidant [22], anti-inflammatory [23], antibacterial [24], antiviral [25], antidiabetic [26], and anticancer activities [27]. GNT has proven its ability against various types of human cancers such as lung [28], liver [29], prostate [30], pancreatic [31], skin [32], cervical [33], uterine [34], colon [35], kidney [36], bladder [37], neuroblastoma [38], gastric [39], esophageal [40], pituitary [41], salivary gland [42], testicular [43], ovarian [44], and finally, breast cancer [45].

2. Cell-Specific Molecular Mechanisms of Genistein-Mediated Anti-Breast Cancer Activity In Vitro

Cancerous cell lines derived from humans are critical models for in vitro cancer research to determine the therapeutic advantage of anticancer agents [46]. Anticancer activity of phytochemicals is cell-specific, where one phytochemical is effective in one or more cell lines, and this may be the difference in the cell components system

2.1. The Effects of Genistein on MCF-7 BC Cells

According to Prietsch et al., GNT (0.01–100 μM) promoted apoptosis via mediating the autophagy-dependent mechanism and increasing the ratio of Bax/Bcl-2 and inhibiting the oxidative stress of cancer progression through changing the expression of antioxidant enzymes [47]. Liu et al. summarized that GNT (5–20 μM) induced apoptosis through the mitochondrial-dependent pathway by decreasing the Bcl-2/Bax ratio and increasing tumor suppressor gene p73 expression and ATM phosphorylation with G2/M phase arrest permanently [48]. Similarly, GNT (50–200 μM) halted cellular growth and induced apoptosis by following the downregulation of Bcl-2 protein, upregulation of Bax, and decreasing cyclin D1 expression in the MCF-7 BC cell line [49]. At a low concentration, GNT (1 μM) stimulates cell proliferation, but a higher concentration (25 μM) induces apoptosis pathways by upregulating the CDKN1A and p53 responsive genes and downregulating CCNG1 GADD45A, NF-κB, Bcl-2, TNFR, ESR1, NCOA2, and NCOA3 [50]. Another study investigated that GNT (50 μM) induced apoptosis by upregulating poly-(ADP-ribose)-polymerase and p53, and downregulating the Bcl-2/Bax protein ratio [51]. An in vitro study by Lemos investigated that GNT (10 μM) induced apoptosis by breaking the plasma membrane, nuclear membrane, and upregulating pS2 expression [52]. A later study reported that GNT (100 μM) mediated programmed cell death and suppressed cell growth by upregulating caspase 7, apoptosis signaling kinase-1, ADP ribose, and p38-dependent mitogen protein kinase [53]. Inhibition of metastasis and angiogenesis processes is a common mechanism in BC treatment. In vitro study demonstrated that GNT (3.125–12.5μM) decreased tumorigenic processes by increasing GSTP1 and RARβ2 gene expression and activity [54]. Shon et al. concluded that GNT suppressed angiogenesis by downregulating COX, TPA, and EROD proteins [55], while at 1–10 μg/mL, it inhibited angiogenesis by decreasing tyrosine kinase and ribosomal S6 kinases [56]. In an in vitro study, GNT lowered cell proliferation via mitochondrial-dependent pathways by reducing Fis1 (mitochondrial fission) and Opa1 (mitochondrial fusion) mRNA expression [57] at 10 nm–10 μM, while 4–10 mol/L of GNT inhibited cell proliferation by downregulating cyclin D1 and arresting the cell cycle in the G0/G1 phase, resulting in the blockage of cell survival, according to H. Jiang et al. [58].

Chen et al. reported that GNT (5–100 μM) inhibited the proliferation of cells by inducing apoptosis through IGF-1R-PI3 K/Akt-mediated pathway inactivation and upregulating the Bax/Bcl-2 ratio [59]. Furthermore, it has been shown that GNT (5–30 μM) inhibited BC cell growth, proliferation, and promoted apoptosis by following the downregulation of the Hedgehog–Gli1 signaling pathway and decreasing the mRNA level of Smo and Gli1 [60]. Marik et al. also found similar results, that GNT at a low concentration (0.1 μM) stimulates cancer progression, but GNT (20 μM) at a high concentration inhibits cell proliferation by downregulating mRNA expression of ER-α protein and arresting the cell cycle at the G2/M phase [61]. Furthermore, Chinni et al. reported that GNT (100 μM) inhibits cell proliferation by downregulating Akt-mediated signaling pathways, decreasing telomere length, and overexpression of cyclin-dependent kinase inhibitor p21WAF1 [62]. An early study demonstrated that GNT (50 μM) inhibited tumor growth with apoptosis inductions by increasing Ca^{2+}-dependent pro-apoptotic protease, mμ-calpain, and caspase-12 [63]. On the other hand, Liao et al. showed that GNT (100 μM) inhibited cell growth alongside decreasing paclitaxel-induced tubulin polymerization, Bcl-2, cyclin B1, and CDK2 kinase, leading to cell cycle arrest at the G2/M phase [64]. Chen et al. showed that GNT (50–100 μM) suppressed cell division through uplifting heat shock protein (HSP) activity and reducing SRF mRNA, RAG-1, and DOC 2 expression [65]. GNT (40 nm–2 μM) inhibits mammosphere formation in BC stem cells by suppressing PI3K/Akt signaling through upregulating the PTEN expression [66]. A similar result found by Y. Liu et al. confirmed that GNT (40 nm–2 μM) inhibited mammosphere formation and induced stem cell differentiation by activating PI3K/Akt and MEK/ERK signaling in a paracrine manner, increasing E-cadherin mRNA expression by reducing the ratio of CD44+/CD24-/ESA in MCF-7 BC cells [67]. GNT (1 μM) induces an anticancer effect through upregulating pro-inflammatory genes, i.e., pS2 and COX2, and downregulating anti-inflammatory gene expression, i.e., TFGβ and PPARγ in MCF-7 BC cells [68]. Furthermore, Kazi et al. reported that GNT (50–200 μM) halts cancer progression by upregulating IκB-α and p27 (Kip1) levels, and downregulating proteasomal chymotrypsin-like activity and CDKs [69]. Epigenetics regulation by GNT (60–100 μM) is mediated by diminishing DNA methylation levels, DNMT1 expression, and DNA methyltransferase enzyme activity. However, this reduction in DNA methylation occurs in the promoter region of multiple tumor suppressor genes (TSGs) such as adenomatous polyposis coil (APC), ataxia telangiectasia mutated (ATM), phosphatase and tensin homolog (PTEN), and mammary serpin peptidase inhibitor (SERPINB5) [70].

2.2. The Effects of Genistein on MDA-MB-231 BC Cells

Recently, an experiment conducted by Liu et al. GNT (5–20 μM) induced apoptosis through the mitochondrial-dependent pathway by reducing the Bcl-2/Bax ratio and inhibiting cell growth and increasing the expression of p73, leading to the activation of G2/M phase arrest and the ATM/Cdc25C/Chk2/Cdc2 checkpoint pathway [48]. GNT prompted the apoptotic pathway and directly inhibited the growth of cells through the prevention of NF-κB signaling by the Notch-1 pathway and by downregulating cyclin B1 and Bcl-2 expression, resulting in the arrest of the cell cycle at the G2/M phase at 5–20 μM

[71], while at 5–50 µM, this phytochemical induced apoptosis by targeting the endogenous copper ion, reducing Cu(II) to Cu(I) through the production of reactive oxygen species (ROS) [72]. Before that, an in vitro study by Dampier et al. reported that GNT (10 µM) induced apoptosis and inhibited cell proliferation and cell cycle arrest at the G2 phase, degrading proto-oncogene *c-Fos* and prohibiting protein-1 (AP-1), and also ERK activity [73]. Another study by Yang et al. demonstrated that GNT (50 µM) exerted apoptosis by upregulating poly-(ADP-ribose)-polymerase, activating p53, and downregulating Bcl-2/Bax protein [51].

In the case of angiogenesis, Mukund et al. explained that GNT (100 µM) reduced angiogenesis by blocking the transactivation of downstream HIF-1α effectors, e.g., VEGF, leading to the reduction in hypoxia-inducible factor-1α expression in MDA-MB-231 BC cells [74]. Furthermore, 1–10 µg/mL of GNT suppressed angiogenesis and cell mutation by decreasing tyrosine kinase, ribosomal S6 kinases, and DNA topoisomerases I and II [56], while at a 50 µM concentration, it decreased angiogenesis and inhibited cell division through the underlying mechanism of downregulating COX, topoisomerase II enzyme TPA, and EROD protein activity [55]. Followed by angiogenesis, GNT (15–30 µM) [75] and (5–20 µM) [76] obstructed cancer cell migration and invasion, respectively, by lowering levels of CDKs, tyrosine kinase, and paracrine stimulation and decreasing MEK5, ERK5, phospho-ERK5, NF-κB/p65, and Bcl-2/Bax.

Another study conducted by Kousidou et al. reported that GNT (35–100 µM) progresses slowdown invasiveness by decreasing MMP gene expression, PTK activity, and glucose uptake rate, leading to phagocytosis of cancerous cells [77]. Apart from this, it reduces cell viability by decreasing the DNA methyltransferase activity and DNMT1 expression and affecting the expression of TSGs, i.e., APC, ATM, PTEN, and SERPINB5 at 60–100 µM of GNT [70]. Another recent study by Pons et al. summarized that GNT (1 µM) causes a considerable decrease in cell viability through the mitogen-dependent protein kinase pathway and by promoting apoptosis mechanisms [68].

In MDA-MB-231 BC cells, cell growth control is a significant target for GNT. Gong et al. stated that GNT (5–50 µM) inhibited cell growth by partly inducing apoptosis via downregulation of the Akt and NF-*κ*B cascade pathways [78]. In another in vitro analysis, the cell growth inhibitory activity was evidenced by GNT (2.5–400 µM) through the upregulation of two crucial TSGs, p21WAF1 (p21) and p16INK4a (p16), and the downregulation of two tumor-promoting genes, c-MYC and BMI1, ultimately inhibiting cancer progression [79]. Y. Fang et al. concluded that GNT (40 µM) inhibited cellular growth by following the activation of DNA-dependent damage response and the ATR signaling pathway and activating the BRCA-1 complex, inhibiting the cohesion complex, and increasing phosphatide, which is distributed among CDK1, CDK2, and CDK3 [80]. Recently, it was established that GNT (1000 ppm) suppressed tumor growth by cell cycle regulation via maintaining the expression level of the cyclin D1 protein, leading to G0/G1 phase arrest, which causes cell cycle blockage [58]. Subsequently, Rajah et al. summarized that GNT (10–100 µM) inhibited tumor growth by downregulating MEK5, pERK5, and NF-κB proteins [81]. In the case of cell proliferation, a low dose of GNT (10 µM) slightly inhibited cell proliferation by reducing the P-STAT3/STAT-5 ratio [57]. In comparison, at a double dose, i.e., 20–40 µM, it significantly prevented cell proliferation by inducing apoptosis and suppressing Skp2 expression by upregulating the tumor suppressor genes, i.e., p21 and p27, resulting in G2/M phase arrest [82]. Li et al. investigated that GNT (5–20 µM) inhibited cell differentiation with cell cycle arrest at the G2/M phase by decreasing CDK1, cyclin B1, Cdc25C, c-Jun, and c-Fos levels [83]. GNT can also play a role in MDA-MB-231 by inhibiting mammosphere formation. A lower dose of GNT (2 µM) prevents mammosphere formation through PI3K/Akt signaling by increasing the PTEN expression [66], while at a higher dose, GNT (40 nm–2 µM) prevents the formation of mammosphere cells and promotes differentiation through the PI3K/Akt and MEK/ERK signaling pathway by reducing the CD44+/CD24-/ESA ratio and increasing E-cadherin mRNA expression [67]. Finally, GNT (50 µM) impedes primary tumor formation by downregulating chelator neocuproine and Bcl-2/Bax and by upregulating the caspase-3 pathway [72].

2.3. The Effects of Genistein on T-47D Breast Cancer Cells

Mukund et al. summarize that GNT (50 µM) lowered angiogenesis by preventing the transactivation of downstream HIF-1α effectors such as VEGF, reducing the expression of hypoxia-inducible factor-1α in the T-47D BC cell line [74]. Cell proliferation efficacy was evident by GNT (10 nm) with apoptosis induction through the mitochondrial-dependent pathway via upregulating the cyt-C and oxidase activity, and downregulating the ATP synthase/cytochrome c oxidase ratio [57]. GNT at 1 nm–100 µM inhibits cell proliferation through ERK1/2-mediated signaling by the downregulation of phosphorylated p90RSK [84], while 10 µM of GNT induces apoptosis and inhibits cell proliferation through degrading proto-oncogene c-Fos levels and prohibiting protein 1 (AP-1) and ERK expression [73]. Another in vitro study by Rajah revealed that GNT (10–100 µM) inhibits cell proliferation and tumor growth by downregulating MEK5, pERK5, and NF-κB proteins [81]. Additionally, a high GNT (20 M) concentration inhibits cell proliferation by reducing ER-messenger RNA transcription and arresting the cell cycle at the G2/M phase [61]. According to Sotoca et al., GNT (500 nm) inhibited cell growth and induced apoptosis by activating cytoskeleton restructuring that results in interaction among integrins, focalized adhesion kinase,

and CDC42 that leads to cell cycle arrest in the T-47D BC cell line [85], while according to Pons et al., GNT (1 μM) caused a significant decrease in cell viability by increasing Sirt1, TGFβ, and PRARγ and decreasing IL-1β expression in T-47D BC cells [68].

2.4. The Effects of Genistein on HCC1395 Breast Cancer Cells

Lee et al. demonstrated that GNT (1–200 μM) inhibited HCC1395 cell invasion and metastasis through the upregulation of TFPI-2, ATF3, DNMT1, and MTCBP-1 gene expression and the downregulation of MMP-2, MMP-7, CXCL12 genes, leading to cell cycle arrest at the G2/M phase, therefore reducing cell viability [86].

2.5. The Effects of Genistein on HCC38 Breast Cancer Cells

Donovan stated that GNT (4–10 ppm) inhibited cell growth by increasing the BRCA1 protein level and reducing CpG methylation, consequently decreasing the aryl hydrocarbon receptor (AhR) binding at BRCA1 in the HCC38 cell line [87].

2.6. The Effects of Genistein on Hs578t Breast Cancer Cells

According to Parra et al., GNT (1–50 μM) inhibits cell viability and induces apoptosis through the downregulation of mir-155, resulting in the upregulation of casein kinase, FOXO3a, p27, and PTEN expression, and the reduction of β-catenin in the Hs578t cell line [88].

2.7. The Effects of Genistein on DD-762 and Sm-MTC Breast Cancer Cells

Nakagawa et al. appraised that GNT (7–274.2 μM) inhibited cell proliferation by upregulating caspase-3 protein activity in DD-762 and Sm-MTC BC cell lines [89].

2.8. The Effects of Genistein on BT-474 Breast Cancer Cells

GNT at a low concentration (1 μM) could promote cancer but at a high concentration (50 μM), it inhibits cell division by downregulating tyrosine kinase, HER2 activation, and the MAPK pathway [90]. GNT (3.125–25 M) inhibits cell replication and arrests the cell cycle in the G2/M phase, and inhibits the expression of EGFR, HER2, and ER-alpha [91].

2.9. The Effects of Genistein on BT20 Breast Cancer Cells

Cappelletti et al. revealed that GNT (15–30 μM) inhibits metastasis by lowering levels of CDKs, tyrosine kinase, DNA topoisomerase II, and paracrine stimulation in the BT20 cell line [75].

2.10. The Effects of Genistein on 21PT Breast Cancer Cells

Marik et al. demonstrated that GNT at a 0.1 M concentration stimulated cancer progression, while 20 M of GNT inhibited cell proliferation by decreasing ER-messenger RNA expression and arresting the cell cycle at the G2/M phase in the 21PT cell line [61].

2.11. The Effects of Genistein on 184-B5/HER Breast Cancer Cells

Katdare et al. showed that GNT (2.5–10 μM) impeded the cell cycle and induced apoptosis by increasing the P16INK4a gene and decreasing HER-2/neu and tyrosine kinase [92].

2.12. The Effects of Genistein on MCF-10A, MCF-ANeoT, and MCF-T63B Breast Cancer Cells

An early study showed that GNT (1–10 μg/mL) obstructed angiogenesis and cell mutation by decreasing the expression of ribosomal S6 kinases and tyrosine kinase [56].

3. Clinical Trials

Human clinical trials have confirmed the in vitro research findings. In some cases, when consumed at a consistent dose, pure GNT had no estrogenic effect on breast tissue [93][94], although in other cases, dietary soy supplementation had pro-estrogenic effects on breast tissue [95][96][97]. Several secondary endpoints were evaluated in a recently published clinical study to determine whether purified GNT affects endometrial thickness, vaginal cytology, and breast density [93][54][55]. Following the implementation of safety measures, it was possible to identify the potential estrogenic effects of 54 mg/day of purified GNT as indicators of BC risk in the research participants. Indeed, while the placebo group maintained a constant endometrial thickness, the GNT group demonstrated a time-dependent reduction that reached statistical

significance during the 36-month follow-up (approximately 12% reduction, $p < 0.01$). Moreover, levels of gene expression of BRCA-1 and 2 breast tumor suppressor genes [98][99] have been preserved for three years in the GNT-administered group, while levels of both BRCA-1 and 2 have decreased in the placebo group [93][94]. GNT also significantly reduced sister chromatid exchanges, implying that it may prevent genotoxicity and subsequent mutagenesis [94]. In this regard, based on the use of GNT in BC, two clinical trials—a phase II study entitled “Gemcitabine Hydrochloride and GNT in Treating Women with Stage IV BC” (NCT00244933) and a phase I study entitled “GNT in Preventing Breast or Endometrial Cancer in Healthy Postmenopausal Women” (NCT00099008)—have been completed, but the results are not yet published.

4. Nano-Formulation of Genistein for Breast Cancer Treatment

GNT research for cancer treatment has been extended in recent years due to evidence of lower disease risk associated with its administration and a quest for pharmacological medicines that impact growth factor signaling pathways in cells. A significant drawback of GNT as a natural substance is its low water solubility. This may necessitate modifying its chemical structure to increase solubility and boost bioavailability [100].

However, the advancement of nanomedicines has the potential to overcome phytochemical limitations and allied health concerns, such as improved solubility, increased bioavailability, targeted treatment of tumor cells or tissues while avoiding healthy cell damage, and increased cell take-up. Nanomedicines could provide new avenues for circumventing these concerns. Additional advantages may include improved blood stability, multifunctional nanomedicine design, minimal interaction with synthetic medications, and improved anticancer activity [101]. Furthermore, multidrug resistance (MDR) is one of the most important variables contributing to the failure of phytochemical therapy in cancer. MDR can be circumvented using a new technique including nanocarriers and phytochemical delivery. Modifying the biophysical interaction between the nanomedicines and cancer cell membrane lipids can increase phytochemical delivery and overcome drug resistance. This is accomplished by improving the transport of phytochemicals to target tissues through surface modification of nanomedicines [102][103]. Currently, advancements in treatment efficiency through nanomedicines have received much attention because of the increased delivery of phytochemicals to tumors and cancer cells. Numerous highly successful nanomedicines have been employed to enhance phytochemicals’ physicochemical qualities and anticancer activity [104]. BC treatment with doxorubicin and GNT is improved by using multifunctional hybrid nano-constructs that enable intracellular localization of the drugs [105]. A research study by Jimmy Pham and his colleagues demonstrated that mitochondriotropic nano-emulsified genistein-loaded vehicles showed more effective potential against hepatic and colon carcinomas than the control drugs [106].In one study, cervical cancers were treated with bioflavonoid genistein-loaded chitosan nanoparticles targeted to the folate receptor, which had a significant anticancer effect. The naturally derived chitosan nanoparticles exhibited potent biodegradability and biocompatibility when coated with the GNT [107]. Additionally, genistein-loaded biodegradable TPGS-b-PCL nanoparticles possessed enhanced therapeutic effects in cervical cancer cells [108]. Moreover, the nanoformulation of GNT promoted selective apoptosis in the cell line of oral squamous cancer by suppressing the expression of a 3PK-EZH2 signaling pathway [109].

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