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REVIEW

Genistein: a promising modulator of apoptosis and survival signaling in cancer

Hemant Joshi[1] · Dhruv Sanjay Gupta[2] · Nosheen Kamruddin Abjani[2] · Ginpreet Kaur[2] · Chakrabhavi Dhananjaya Mohan[3] · Jagjit Kaur[4] · Diwakar Aggarwal[5] · Isha Rani[6] · Seema Ramniwas[7] · Hadi Sajid Abdulabbas[8] · Madhu Gupta[9] · Hardeep Singh Tuli[5]

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Abstract
Genistein, a commonly occurring isoflavone, has recently gained popularity owing to its ever-expanding spectrum of pharmacological benefits. In addition to health benefits such as improved bone health and reduced postmenopausal complications owing to its phytoestrogen properties, it has been widely evaluated for its anti-cancer potential. Several studies have established the potential for its usage in the management of breast, lung, and prostate cancers, and its usage has significantly evolved from early applications in traditional systems of medicine. This review offers an insight into its current status of usage, the chemistry, and pharmacokinetics of the molecule, an exploration of its apoptotic mechanisms in cancer management, and opportunities for synergism to improve therapeutic outcomes. In addition to this, the authors have presented an overview of recent clinical trials, to offer an understanding of contemporary studies and explore prospects for a greater number of focused trials, moving forward. Advancements in the application of nanotechnology as a strategy to improve safety and efficacy have also been highlighted, with a brief discussion of results from safety and toxicology studies.

Keywords Isoflavones, Phytotherapy · Phytoestrogen · Nanoformulations · Chemoprevention

Introduction

Genistein is a widely abundant isoflavone that commonly exists in a variety of soy-based products. Popular in Chinese and Ayurvedic traditional systems of medicine, it is widely consumed in Asian diets and is slowly gaining popularity worldwide (Smeriglio et al. 2019). Its benefits have been studied in different diseases including diabetes, cardiovascular, and obesity-related conditions as well as age-related disorders, chiefly menopausal complications for women and prostate cancer for men (Islam et al. 2020). As the incidence of cancer continues to increase globally, there is a need to explore alternative treatment strategies (Hazafa and Rehman K-U-, Jahan N, Jabeen Z. 2020). Owing to the rising rates of cancer, there is an increased pressure on the healthcare system and a substantial decrease in the overall quality of life of patients. This has directed focus to phytoconstituents such as isoflavones, possessing a broad spectrum of therapeutic benefits. Soy isoflavones have been widely studied for their potential in regulating bone health and improved respiratory and cardiac functioning, as well as neurological actions (Kim et al. 2021). Regular supplementation has been linked with the exertion of a protective effect, and as research continues to grow, a variety of cancers and signaling pathways have been targeted using genistein.

Genistein has found extensive applications in the management of breast and prostate cancer and has been dubbed as one of the "big five" chemicals targeting stem cells (Naujokat and McKee 2021). This has been attributed to its ability to target various signaling cascades and control the expression of numerous biomarkers and genes, as discussed further in the review. Genistein has been observed to chiefly inhibit the expression of inflammation-promoting markers and reactive oxygen species (ROS) (Obinu et al. 2021), which are linked with oxidative damage and tumor proliferation (Křížová et al. 2019). By inducing apoptosis

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and controlling the migration and spread of neoplasms, it has found applications as a popular chemopreventive agent (Kim 2021). In addition to its clinical potential in isolation, genistein has been evaluated for its synergistic effects with a variety of natural and synthetic anti-cancer agents. The results from these studies have been promising, indicating opportunities for further research and expansion of the conditions that may be managed by its usage (Abdulridha et al. 2020). Another growing avenue is the usage of nanotechnological interventions to get rid of the issues involved with the delivery of phytoconstituents, such as poor aqueous solubility and propensity for metabolism, thereby reducing beneficial outcomes. Various nanoformulations of genistein, including nanosuspensions, liposomes, nanoparticles, and structured nanovesicles have been evaluated (Dutta et al. 2018). Besides the clinical efficacy of this agent, it is also essential to discuss its safety and toxicology profile, to determine optimum dosing and develop an understanding of adverse effects associated with its usage, if any. This review offers a holistic overview of the chemistry of this molecule, the key pathways targeted for cancer management, and recent updates on clinical trials and nanotechnological interventions, as well as future perspectives.

Chemistry and pharmacokinetics of genistein

Chemistry of genistein

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one), a well-studied isoflavone, has its place in the class of aglycones. Soy products contain this isoflavone, which is a metabolite of soybeans. Also known by its chemical name, 4′,5,7-trihydroxyisoflavone, genistein was first isolated in 1899 from plants belonging to the family Fabaceae and represents 60% of the total soy isoflavone content (Tuli et al. 2019). It is a secondary metabolite consisting of 2 aromatic benzene rings and one non-aromatic heterocyclic pyran ring (Garbiec et al. 2022). Genistein's basic carbon skeleton also consists of a C_2–C_3 double bond and an oxo group at the C4 position of the C ring. Figure 1 showcases the skeleton structure of genistein, with the three cyclic rings (A, B, C) highlighted. In addition to this, it shows the presence of three OH groups at the C5, C7, and C4′ positions of rings A and B, respectively. Isoflavones in their natural sources exist in glycosylated forms, but they become physiologically active only in aglycone form. In mammals, isoflavones may show effects similar to estrogen. Genistein too potentiates an estrogen-like effect owing to C4 and C7 on the phenol ring that is comparable functionally and structurally to the phenol groups in E2, allowing both estrogen receptor isoforms to bind with equal potential (Sharifi-Rad et al. 2021). Several derivatives of genistein are being made to improve its anticancerous potential such as 2-alkyl substituted fluorinated genistein derivatives are developed to selectively inhibit breast cancer cells, whereas genistein-1,3,5-triazine analogs have shown anti-proliferative activities against various cancer cell lines including breast, cervical, prostate, and liver (Zhu et al. 2022; Zou et al. 2023).

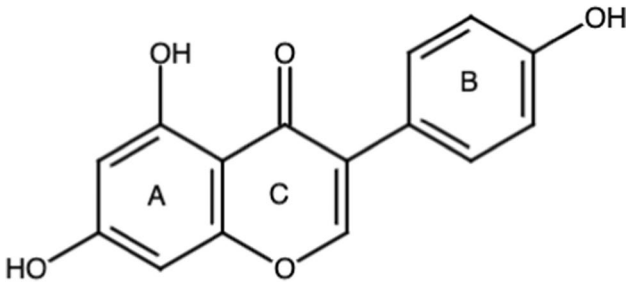

Fig. 1 Structure of genistein

Pharmacokinetic profile

Genistein shows poor aqueous solubility; hence, a study has suggested that increasing the dose has no significant effect on its bioavailability. Genistein is cleaved by phlorizin hydrolase in the brush border cells or by enteric microflora into its biologically active aglycone form. Its oral bioavailability is roughly 10%, has a low absorption potential, and is therefore transported passively through the intestinal membrane, undergoing post-absorption metabolism. (Yu et al. 2021) Retinal distribution was observed to be higher in diabetic rats, due to increased blood–retinal barrier permeability (Hakami et al. 2021). Owing to its poor bioavailability, an array of advanced nano-based drug carriers are being explored to improve its water solubility and stability and make its bioavailability more efficient (Rasheed et al. 2022). An example of this is the formulation of solid lipid nanosuspensions, aiding the bypassing of the first-pass metabolism and preferentially reaching the lymphatic system of the intestine, thereby improving bioavailability (Obinu et al. 2021). Genistein is observed to undergo phase II biotransformation reactions, encompassing methylation, glycosylation, glucuronidation, acetylation, and sulphonation reactions in rats. The main metabolic products observed in human plasma following ingestion were genistein-7-glucuronide, 4′-glucuronide, 7-sulfate, 4′-sulfate, 4′,7-diglucuronide, and 7-glucuronide-4′-sulfate. The malonyl glucoside conjugation pathway is a conserved pathway for isoflavones. Malonyl genistein is also a metabolic product observed wherein the malonyl group replaces the hydroxy group; however, it is not a major metabolic pathway. Genistein is also reported to undergo enterohepatic circulation (Yang and Tsai 2019).

Genistein is known to be excreted into breast milk in very minute quantities and not in significant amounts. It is excreted by urine within 1 day of intake (Yu et al. 2021). Developing an understanding of the pharmacokinetic profile of phytoconstituents is essential, as it enables the detection of any potential interactions, as well as aids the designing of suitable carriers for optimal delivery.

Apoptotic mechanisms of genistein in cancer

The Fas-FasL pathway

The apoptotic effect in the cells is generated via the cross-talk between the intrinsic and extrinsic apoptotic pathways as depicted in Fig. 2 (Petak and Houghton 2001; Slee et al. 1999). The intrinsic apoptotic pathways are associated with intracellular cysteine protease or caspases (CASP) (Yeh et al. 2007) such as mitochondria-dependent pathways regulated by CASP-9. CASP-9 is activated by the conjugation of apoptotic protease-activating factor 1 (Apaf-1), an adaptor molecule with cytochrome c and procaspase-9 in the presence of ATP (Fig. 2) (Chen and Wang 2002; Budihardjo et al. 1999). Alternatively, the extrinsic apoptotic pathways are commenced by CASP-8 and regulated via death receptors (DR) like tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and Fas ligand (FasL) (Fig. 2) (Petak and Houghton 2001; Chen and Wang 2002; Budihardjo et al. 1999). In an experiment performed by Yeh et al. (Yeh et al. 2007), it was shown that genistein moderately increased the levels of procaspase-9 in human hepatocellular carcinoma (Hep3B cells). However, no apoptosis via extrinsic or intrinsic pathways was observed in Hep3B cells when the cells were exposed to 100 µM genistein for 24 h as there was no change in the expression of death receptors like DR4, DR5, and Fas and their associated ligands: Apo-2L/TRAIL, and FasL. Further, genistein-treated cells for 48 h altered the levels of various proteins including Bad and Mcl-1, leading to cell death. The apoptotic mechanisms of genistein in different cancers are described in detail in Table 1.

The TRAIL-DR pathway

TRAIL is a cytokine that specifically prompts cell death of tumor cells over healthy counterparts through interacting with DR4 and DR5 (Oishi et al. 2013; Dai et al. 2015). TRAIL belongs to the TNF family, and it can exist in both soluble form and on cytotoxic T-lymphocytes/natural killer

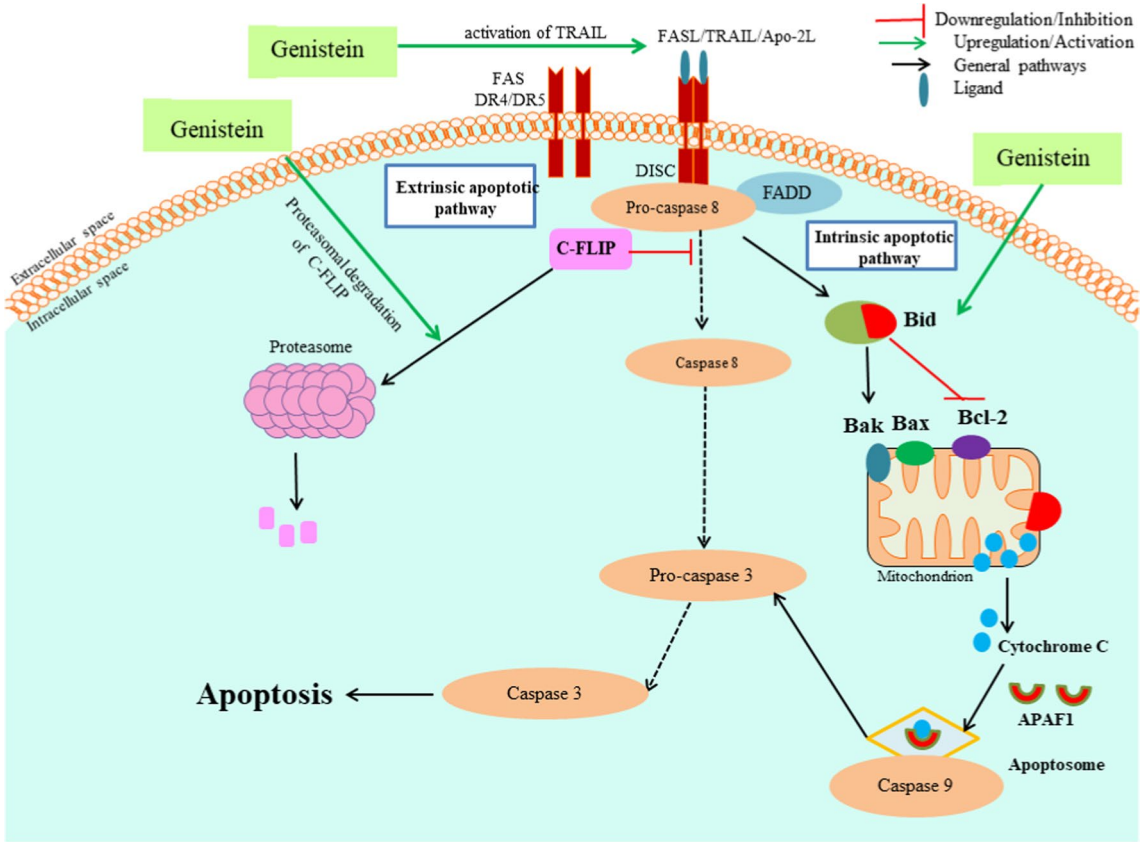

Fig. 2 The effect of genistein on both extrinsic and intrinsic apoptotic pathways

Table 1 Apoptotic (anti-cancer) activities of genistein based on in vitro experiments

Type of cancer	Cell lines	Mechanisms	Concentration	References
Leukemia	HL-60	↑ asparaginase activity, ↓ viability of cancer cells, ↑ G2/M phase seize, ↑ DNA damage, ↑ disruption of the mitochondrial membrane potential, ↓ Bcl-2, ↑ Bax,↑ Bak, ↑ CASP-3	Asp (0.3 or 0.5 U/ml), GEN (30 or 40 μM)	Hsiao et al. 2021)
	HL-60	↑ G2/M phase seize, ↓ Cells viability, ↑ DNA destruction and fragmentation, ↑ ROS, ↑ Ca^{2+}, ↓ ΔΨ m, ↑ IRE-1α, ↑ GRP78, ↑Calpain 1, ↑CASP-7, ↑GADD153, ↑CASP-4, ↓ Bid, ↑ ATF-6α, ↑ CASP-9 and 3,↑ Bax, ↓ Bcl-2, ↑ PARP cleavage	0, 20, 30, 40, and 50 μM	Hsiao et al. 2019)
Squamous cell	SK-MEL-28	↑ fragmented DNA (comet-shaped), ↓ cell migration and cell invasion, ↓ MMP-9, ↓ p-MEK, ↓ p-ERK, ↓ p-JNK	0, 12.5, 25, and 50 μM	Li et al. 2020)
Head and neck	HNC-TICs	↓ the proliferation of cancer cells, ↓ EMT, ↑ cytotoxicity mediated by three chemotherapeutic agents (cisplatin, doxorubicin, and 5-FU), ↑ ROS production, ↑ miR-34a, ↓ ALDH1 + and CD44 + , ↓ Snail, ↓ ZEB1, ↓ Slug, ↓ vimentin, ↑ E-cadherin	0, 20, and 40 μM	Hsieh et al. 2020)
Nasopharyngeal	CNE2 and HONE1	↓ size and number tumorspheres, ↓ EpCAM + cells, ↓ CD44, ↓ ALDH1, ↓OCT-4, ↓ NANOG, ↓ cell proliferation, ↓ Cyclin D1, ↓ c-MYC, ↓ PCNA, ↑Bax, ↑ CASP-8, ↑ cleaved CASP-9, ↑ cleaved CASP-3	0, 50, 75, & 100 μM	Zhang et al. 2019a)
Laryngeal	TU212 and Hep2	↑ miR-1469, ↑ Bcl-2 and Mcl1 downregulation, ↑ p53	100 μM	Ma et al. 2018)
Esophageal	CaES-17, EC9706, Het-1A, and Eca-109	↓ Cyclin D1, ↓ EsC cell proliferation, ↑ Bid, ↑ apoptosis frequency, ↓ CDK6, ↑ G0/G1 phase arrest, ↑ Bax, ↑ cleaved PARP, ↑ cleaved CASP-3, ↓ CDK4, ↓ Bcl-Xl, ↑ P53, ↓ Bcl-2, ↓ mitochondrial membrane potential, ↑ ROS, ↓ p- STAT3, ↓ p-JAK1, ↓ p-JAK2	0, 5, 10, 20, 40, & 80 μM	Gao et al. 2020)
Colon	HT29 and SW620	↓ cell viability, ↑ G2/M arrest, ↑ H_2O_2, ↑ cancer cell death, ↑ stress fibers, ↓ PPARGC1a, ↑ SOD2 and SOD1, ↓ ESRRA, ↑ filopodia, ↓ CXCL8, ↓ TFAM, ↑IL10, ↑ IL1B, ↑ SSBP1, ↑ CXCR2, ↑ TNF, ↑ HPSE	1, 5, 50, and 100 μM	Alorda-Clara et al. 2022)
	HT-29	↓ cell migration, ↑ E-cadherin, ↓ N-cadherin, ↓ Snail2/slug, ↓ ZEB1, ↓ZEB2, ↑ Bax/Bcl-2, ↓ FOXC1, ↓ FOXC2,↓ TWIST1, ↓ notch-1, ↓p-NF-κB, ↑ CASP-3	0, 25, 50, 100, 200, and 400 μM	Zhou et al. 2017)
	HT29	↓ viability, proliferation and migration of HT29 cells, ↑ caspase-3, ↓ p38 MAPK, ↓ MMP-2	0, 10, 30, 50, 70, and 90 μM	Shafiee et al. 2016)

Table 1 (continued)

Type of cancer	Cell lines	Mechanisms	Concentration	References
Breast	MDA-MB-231, MCF-4T1, MCF-10A, and MCF-7	↑ G2/M cell cycle phase arrest, ↓ Bcl-2, ↑ cleavage of CASP-3/7 & 9 and PARP, ↓ pPI3K/ NF-κB/Akt, ↓ cyclin B1, ↑ Bax, ↑ phospho-cdc2 expression, ↑ chromatin condensation, ↑ mitochondrial structural integrity disruption, ↑ nucleoli loss, ↑ ROS generation	10 μM centchroman and 50 μM genistein	Kaushik et al. 2019)
	MCF-7	↓ MCF-7 cells proliferation, ↑ nuclear condensation, and fragmentation, ↑ early apoptotic cells, ↑ Bax, ↓ IGF-1R & p-Akt, ↓ Bcl-2	0, 5, 10, 20, 30, 40, 60, 80, and 100 μM	Chen et al. 2015)
	MCF-7 and MDA-MB-231	↑ DNA damages, ↑ G2/M phase seize, ↓ Rad51 foci generation, ↑ cell death, ↓ homologous recombination repair, ↑ pATM, Cdc2, Cdc25c, and Chk2, ↑ Bax, ↑ p73, ↓ Bcl-2	5–20 μM	Liu et al. 2013)
	MDA-MB-231	↓ tumor cells proliferation, ↓ Bcl-2, ↓ proCASP-3, ↓ cleavage of CASP-3, ↓ MEK5, ↑ Bax, ↓ ERK5, ↓ phospho-ERK5, ↓ NF-κB/p65	0, 5, 10, or 20 μM	Li et al. 2008)
Lung	A549	↓ cancer cells viability, ↑ apoptosis rate ↑cleaved CASP-3, ↑ cleaved CASP-9, ↓ CASP-3, ↓ CASP-9, ↓ IMPDH2	0, 20, 40, 80 μM	Xu et al. 2022)
	A549 and 95D	↓ cell viability, ↑ cellular shrinkage and rounding, ↓ colony-forming ability, ↑ DAPI, and TUNEL fluorescence, ↑ levels of cytochrome c, ↑ Bax, ↓ Bcl-2, ↑ intracellular ROS formation, ↓ mitochondrial activity, ↓ mitochondrial membrane potential, ↑ FOXO3a, and PUMA	0, 25, 50, 100, 150, 200, and 250 μM	Chan et al. 2022)
	A549	↑ inhibition of A549 cells growth, ↑ apoptosis, ↑ CASP3/9, ↑ microRNA27a, ↓MET	0, 10, 25, 50, 100, and 200 μM	Yang et al. 2016a)
Cholangiocarcinoma	KKU055 (JCRB1551), KKU100 (JCRB1568), and KKU213A (JCRB1557)	↑ CCA cells susceptibility to natural killer (NK-92) cells, ↓procaspase-8 and -3, ↓ c-FLIP, ↑ death receptors, ↑ Fas, ↑ TRAIL, ↓ Bcl-2	0–400 μM	Chiawpanit et al. 2022)
Hepatocellular	Huh-7, Hep3B and Hep G2	↑ radiosensitivity, ↑ DNA damage, ↑ chromosomal aberrations, ↑ G2/ M phase arrest, ↓ phospho-Bad (Ser136), ↑phosphoChk2 (Thr68), ↑ phospho-ATM (Ser1981), ↑ c-H2AX, ↓ POU6F ↓ CCNE2 expression, ↑ FBXO32, ↑ cyclin B1 expression	0, 2.5, 5, 10, 20, and 40 + 8 Gy X-ray	Yan et al. 2020)
	HepG2	↓ survival of HepG2 tumor cells, ↓ colony-forming potential, ↑ Bax, ↑ G2/M seize, ↑ ROS generation, ↑ Cyt c, ↑cleaved CASP-3 & 9, ↓ Bcl-2	0, 6.2, 12.5, 25, 50, and 100 μM	Zhang et al. 2019b)
	Hep3B	↑ phospho-AMPKα, ↑Cleaved PARP, ↑ cleaved Cas-3 ↑ Bax, ↓ Bcl-2, -↓ Mdm2	0, 25, 50, and 100 μM	Lee et al. 2019b)
	Hep3B and HepG2	↑ ER stress mediating regulators, ↑ CASP-12, ↑ GADD153, ↑ GRP78, ↑ m-calpain, ↑ CASP-2	0, 20, 40, 60, 80, and 100 μM	(22)

Table 1 (continued)

Type of cancer	Cell lines	Mechanisms	Concentration	References
Bladder cancer	T24	↑ G2/M seize, ↑ CASP-3, CASP-8, and CASP-9, ↓ cyclin A, ↑ PARP cleavage, ↓ cyclin B1, ↑ p21WAF1/CIP1, ↑ Cyt c, ↑ destruction of mitochondria integrity, ↑ Bax/Bcl-2 ratio, ↑ ROS accumulation	0, 40, 80, 120, 160, and 200 μM	Park et al. 2019)
Kidney	CAKI-1, 769-P, CAKI-2, 786-O, HK-2, and HEK293	↓cell proliferation, ↑ CDKN2a, ↓ CDKN2a methylation	0, 25, 50, 100 μM	Ji et al. 2020)
Pancreatic	Mia-PaCa2 and PANC-1	↓ cancer cell viability, ↑ G0/G1 phase, ↑ ROS accumulation, ↓ MMP-2 and 9, ↑ Cyt c, ↑ cleaved CASP-3 and 9, ↑ Bax, ↓ Bcl-2, ↓ survivin, ↓ cyclin D1, ↓ ALDH1A1	0, 10, 20, and 40 μM	Bi et al. 2018)
Prostate	PC3	↓cell proliferation, ↓ migration, and metastasis, ↓ MMP-2, ↓ p38MAPK, ↑ caspase-3,	0, 10, 30, 50, 70, or 90 mM	Shafiee et al. 2022)
	PC-3 and LNCaP	↑ cell death of tumor cells, ↓ cellular GSH concentration, ↑ ROS formation, ↓Glut-1 receptors, ↓ COX-2 formation	A liposomal system containing celecoxib and GEN (100 μM celecoxib and 10 μM GEN)	Tian et al. 2019)
Colorectal	SW480 and SW620	↓ cell viability, ↑ ROS, ↑ oxidative stress, ↑ p53, ↑ DNA fragmentation, ↑ PARP cleavage, ↑ CASP-3, ↑ Cyt c, ↑ cytokines (GM-CSF, IL-1B, IL-1B-2, IL-1B-4, IL-1B-5, IL-1B-10, IL-1B-17A, IL-1B-18, and IL-1B-27)	5.52 mg genistein/1 g bacterial nanocellulose capsules)	Rendón et al. 2022)
	HCT-116 and LoVo	↑ apoptotic cells, ↑ Bax, ↑ p- Akt	0, 25, 50, and 100 μM	Qin et al. 2016)
Ovarian	HO-8910	↑ DNA destruction, ↑ G2/M seize, ↑ cell death, ↑ pATM, ↑p- Chk1, ↑ pATR, ↑ p53, and ↑ p-Chk2, ↓ phosphatases Cdc25C and Cdc25A, ↓ Bcl-2/Bax, and Bcl-xL/Bax ratio, ↓ p- Akt	0, 1, 5, 10, 25, 50, and 100 μM	Ouyang et al. 2009)
Cervical	HeLa	↓ migration rate, ↓ invasion of tumor cells, ↓ invasive cells, ↓ p- FAK,↓ paxillin, ↓ p38 and ↓ p42/44, ↓ Snail, ↓ twist	0, 12.5, 25, 50, and 100 μM	Chen et al. 2020)
	HeLa	↓ viability of HeLa cells, ↑ ER stress, ↑ GRP78 ↑ CHOP expression, ↑cleaved CASP-3, ↑ cleaved PARP	0, 25, 50, and 100 μM	Yang et al. 2016b)

(NK) cells, thereby provoking immune surveillance against tumor cells (Yang et al. 2019; Girisa et al. 2019). The interaction between TRAIL on the NK cells and DR on the target cells initiates the activation of cascade of proteins ultimately leading to the cleavage of CASP-8. Further, CASP-8 activates CASP-3 and Bid to commit the cell to apoptosis. Genistein has been known to potentiate the cytotoxic effects of TRAIL in various types of human malignancies. Szliszka and colleagues demonstrated that cervical tumor cells are resistant to TRAIL-associated cytotoxicity, whereas the combination of genistein and TRAIL showed additive cytotoxicity indicating that genistein may potentiate the cytotoxic effects of apoptosis-inducing agents (Szliszka et al. 2008). Similarly, the combinational treatment of indole-3-carbinol, genistein, and TRAIL upregulated the level of DR4 and DR5 and thereby significantly promoted cell death of endometrial tumor cells (Parajuli et al. 2013). The combination of genistein and TRAIL substantially regressed cancerous growth in orthotopic pancreatic mice models with caspase-3 activation (Nozawa et al. 2004). Interestingly, dexamethasone was found to potentiate cell death of pancreatic β-cells by upregulating the levels of TRAIL and DR5, whereas the combination of dexamethasone and genistein decreased the levels of TRAIL and DR5 and rescued the β-cells from undergoing apoptosis indicating that genistein can serve as a cytoprotective agent in normal cells (Suksri et al. 2022).

Activation of anti-apoptotic mechanisms is the primary means by which cancer cells escape from cell death, and therefore, reversal of anti-apoptosis is crucial to promote cell death of tumor cells. Interestingly, pre-treatment of cholangiocarcinoma cells with genistein led to a substantial elevation in the ability of NK cells to induce apoptosis which was evidenced by upregulation in the level of FasR, DR4, and DR5 in cholangiocarcinoma cells upon treatment with genistein (Chiawpanit et al. 2022). Genistein also sensitized hepatocellular carcinoma (HCC) cells to TRAIL, promoted the cleavage of Bid, and reverted resistance to TRAIL (Jin et al. 2009a). Genistein enhanced TRAIL-driven cell death of advanced glioma cells by promoting the proteasomal degradation of the short isoform of c-FLIP (FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein) without affecting the viability of normal astrocytes (Siegelin et al. 2009). C-FLIP is a prominent apoptosis-inhibiting protein offering resistance against drug/cytokine-driven apoptosis in cancer cells (Safa 2013). The p38-MAPK pathway drives cell proliferation and anti-apoptosis, and inhibition of p38-MAPK could be a good strategy to counteract cell proliferation and induce apoptosis. Genistein inhibited the p38-MAPK pathway in HCC cells and upregulated the TRAIL-driven apoptosis (Jin et al. 2009b). Similarly, TRAIL-mediated apoptosis potentiating effects of genistein were found in diverse cancerous cell lines, including HCC, lung cancer, and gastric cancer cells (Jin et al. 2011, 2007; Nazim and Park 2015).

The TNF-α-TNFR1 pathway

There is no doubt that cancer causes inflammation of the cells (Tuli et al. 2019). Genistein is known to induce inflammation inhibitory effect by reducing the release of IL-8, IL-6, and IL-1β from MH7A cells elicited by TNF-α. It also inhibited the cell viability and proliferation by suppressing the TNF-α-induced AMPK inhibition, phosphorylation of IκB kinase-α/β and IκBα, and translocation of TNF-α-induced NF-κB into the nucleus (Fig. 3) (Li et al. 2014). Further, genistein inhibited the levels of TNF-α and IL-1β in lipopolysaccharide-stimulated BV2 microglia by inactivating toll-like receptor-4 and NF-κB (Jeong et al. 2014). In another study, 1.04 or 1.3 mg/day of genistein abrogated inflammation by lowering the level of IL-6 and TNF-α in a murine model of peritoneal endometriosis (Sutrisno et al. 2018). The anti-cancer and inflammation inhibitory effects have been also reported in diethylnitrosamine-mediated HCC in mice when they were treated with genistein for longer periods (Lee et al. 2019a).

Modulating Bcl_2-Bax pathway

The apoptotic activity of genistein in oral squamous cell carcinoma (OSCC) was demonstrated in a study using genistein-loaded lactalbumin nanoparticles (GLNPs). The GLNPs destroyed the mitochondrial membrane in OSCC by the accumulation of ROS making it permeable to proapoptotic proteins, such as Bcl_2-Bax and CASP-3. The increased expression of these proapoptotic proteins causes cytochrome c translocation to the cytosol from the mitochondria leading to apoptosis (Fig. 3) (Dev et al. 2021). Similar results were seen in different studies where genistein was administered orally for the in vitro treatment of colorectal cancer on SW620 and SW480 cell lines (Rendón et al. 2022) and HT29 and LoVo colon cancer cell lines (Luo et al. 2014). Another study found that 50 μM of genistein causes ER-α-dependent cell death in MCF-7 BC cells by increased of Bcl_2–Bax ratio and cyclin D1 down-regulation (Jiang et al. 2018). Genistein (0.01–100 μM) changes the antioxidant enzyme expression to impede oxidative stress and increase the Bcl_2–Bax ratio, promoting autophagy-dependent apoptosis in MCF-7 breast cancerous cells (Lavigne et al. 2008). In other studies, genistein potentiated cell death in tumor cells by reducing the Bcl_2–Bax ratio and increasing the ATM phosphorylation and expression of tumor suppressor gene p73 (Xu and Loo 2001) and upregulating the p53 and poly-(ADP-ribose)-polymerase (Shim et al. 2007; Sohel et al. 2022).

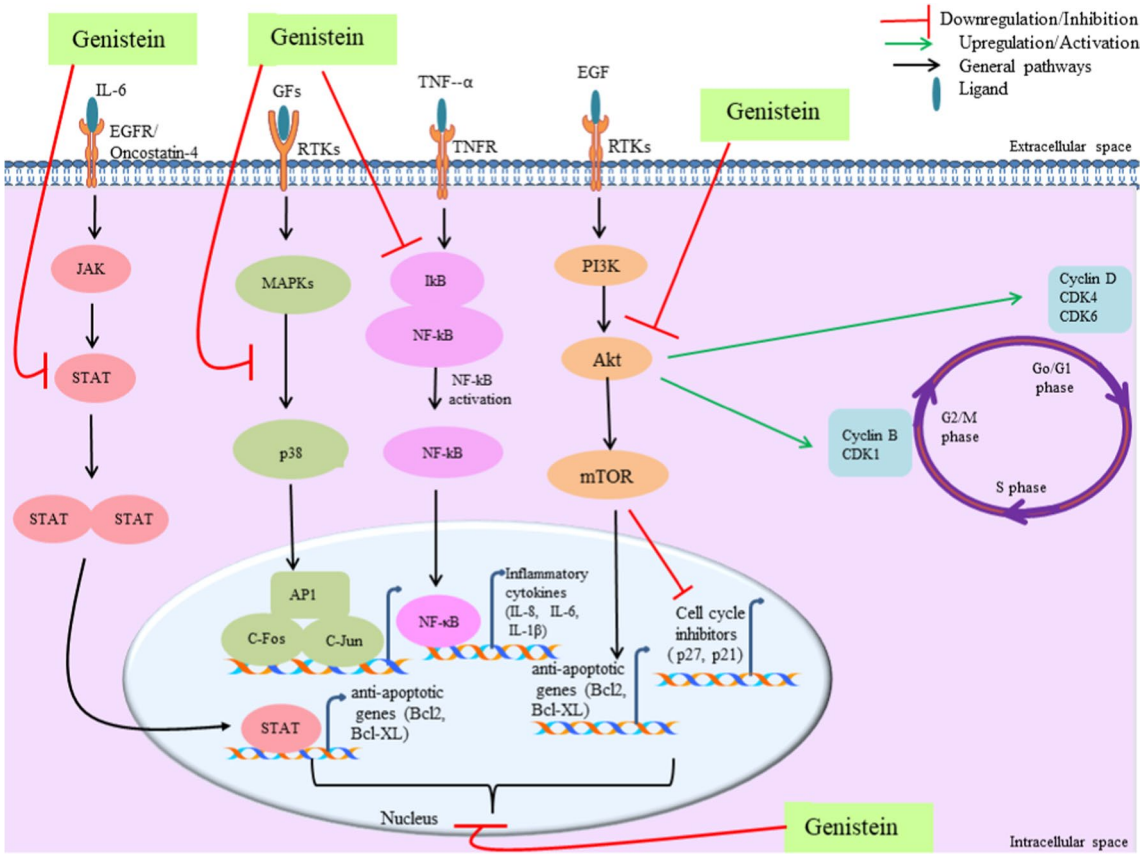

Fig. 3 The anti-cancer effect of genistein on several downstream mechanistic pathways

Targeting PI3K-Akt-mTOR pathway

The PI3K-Akt-mTOR signaling mechanism is a crucial signaling pathway of tumor proliferation, dissemination, and angiogenesis and is considered a significant therapeutic target for treating human cancers, and new medications are in development to inhibit specific components of this signaling pathway (Ahmad et al. 2013; Joshi et al. 2023; Tuli et al. 2023). As the name suggests, this signaling pathway contains three main components PI3K (phosphoinositide-3-kinase), Akt (protein kinase B), and mTOR (mammalian target of rapamycin); inactivation of these targets induces apoptosis and reduces cell survival as illustrated in Fig. 3. Suppression of Akt phosphorylation by genistein causing impaired PI3K-Akt-mTOR signaling cascade promotes G2/M cell cycle seize and increased expression of p21 which led to suppression of cancerous growth and potentiates cell death in various tumor cell lines, including breast cancer, NSCLC, human esophageal squamous carcinoma, and prostate cancer (Akimoto et al. 2001; Lian et al. 1998, 1999; Li et al. 1999a, 1999b). Genistein exerted its effects through the inhibition of Akt stimulation induced by epidermal growth factor (EGF) and inhibition of Akt-induced NF-κB activation via disrupting the cross-talk between Akt and NF-κB in prostate cancer, breast cancer, and myeloma (Li and Sarkar 2002; Gong et al. 2003; He et al. 2009). In a mechanistic study of genistein, it was revealed that Akt inhibition causes decreased telomerase enzyme activity as well as an elevated level of cell cycle progression inhibitor (i.e., p27) leading to apoptosis activation in breast cancer (Chinni et al. 2003). Similarly, genistein inactivates Akt protein in colon cancer cells via stimulation of the Foxo3 transcription factor that finally increased the p27 expression levels (Qi et al. 2011). Recently, genistein plus centchroman inhibited the phosphorylation of PI3K, NF-κB, and Akt which subsequently promoted apoptosis in breast adenocarcinoma by following events such as PARP cleavage, elevated Bax/Bcl_2 ratio, and stimulation of caspases 3 and 9 (Kaushik et al. 2019). Another synergistic study indicates that genistein combined with isoprenoid perillyl alcohol has a more potent inhibitory activity for PI3K-Akt-mTOR signaling cascade compared to individual PI3K and mTOR inhibitors in prostate and colon carcinoma (Peffley et al. 2007). Taken together, it was concluded that genistein alone or in combination with other inhibitors abrogates the

PI3K-Akt-mTOR signaling mechanism which successively potentiates the apoptosis in multiple tumor cell lines.

Targeting the JAK-STAT3 signal pathway

Signal transducer and activator of transcription (STAT3) is a transcription factor that is involved in relaying signals for cell proliferation, prosurvival, anti-apoptosis, angiogenesis, invasion, migration, and metastasis (Mohan et al. 2022, 2021a; Lee et al. 2020a). STAT3 undergoes activation upon receiving extracellular stimulus from upstream cytokines (IL-6 family cytokines) and growth factors (EGF), and the signal is mediated through Janus kinases (JAKs), epidermal growth factor receptor (EGFR), oncostatin M receptor, and other related cytokine receptors as represented in Fig. 3 (Mohan et al. 2021b; Sajith et al. 2021; Arora et al. 2021). Persistent activation of STAT3 is seen in different human cancers which contributes to cancerous growth and progression (Lee et al. 2020b, 2019b; Malojirao et al. 2020). Abrogation of the STAT3 signaling cascade has been identified as a good strategy to induce cytotoxicity in STAT3-positive tumor cells (Lee et al. 2019c; Baburajeev et al. 2016; Mohan et al. 2014). Genistein was found to display differential action against STAT3 activity, and the majority of studies have presented genistein to have inhibitory action towards the STAT3 signaling pathway. Gao and colleagues demonstrated that genistein suppresses JAK/STAT3 axis by downregulating the expression of EGFR in esophageal carcinoma cells and abrogating tumor growth in the xenograft mice model (Gao et al. 2020). Genistein was reported to inhibit the constitutive stimulation of the STAT3 signaling cascade in pancreatic tumor cells (Lian et al. 2004). In another study, it was found to impart anti-cancer function by activating STAT3 and increasing the levels of ROS in pancreatic tumor cells, whereas the treatment with ascorbic acid (a good antioxidant) reverted the genistein-induced generation of ROS (Bi et al. 2018). Sharma and colleagues performed molecular dynamic simulations and indicated that genistein displays excellent interaction with the IL-6/IL-6Rα to suppress the STAT3 pathway (Sharma et al. 2022). Pinski and coworkers demonstrated that genistein induces neuroendocrine differentiation of prostate cancer cells which was associated with the elevation of MAPK and STAT3 signaling cascades (Pinski et al. 2006). The normal prostate tissue comprises only < 1% of neuroendocrine cells, and the number of these cells significantly increases in prostate cancer. Neuroendocrine differentiation is correlated with disease progression and prognosis in individuals with prostate cancer (Hu et al. 2015). On the other hand, some studies have indicated that genistein can activate the STAT3 pathway. Zhen and coworkers demonstrated that genistein triggers the phosphorylation of STAT3 and increases the interaction of STAT3 with the hepcidin promoter in human hepatocytes (Zhen et al. 2013). Hepcidin is a peptide hormone and a critical regulator of iron metabolism whose expression is elevated in some types of human cancers (Fan et al. 2021; Julián-Serrano et al. 2021). Additionally, numerous experiments have targeted on the modulation of STAT3 signaling in different disease conditions including liver fibrosis, leiomyoma, epilepsy-induced brain injury, and rheumatoid arthritis (Xu et al. 2021; Shushan et al. 2007; Hu et al. 2021; Cheng et al. 2020).

Synergism of genistein

The synergism of genistein in combination with various therapeutic agents has been studied. This section offers insight into a few significant studies, as well as the potential for further research. A key advantage offered by therapeutic synergism is the improved cells' susceptibility to radiotherapy. Tang et al. explored the synergism of genistein and AG1024, a tyrosine kinase inhibitor, intending to improve treatment outcomes. These agents were observed to trigger cellular apoptosis and improved the radiosensitivity of cells, offering a significant advantage over monotherapy (Tang et al. 2018). The effects of the co-administration of genistein and sulforaphane have been evaluated as well, and these compounds have been observed to decrease cellular proliferation and trigger cell death. In vitro evaluation indicated the downregulation of biomarkers such as histone deacetylase (HDAC), chiefly HDAC2 and HDAC3, along with human telomerase reverse transcriptase (hTERT) levels. These results were further strengthened by in vivo testing in transgenic mice, and a marked reduction in tumor size and volume was observed (Paul et al. 2018). Concerning ovarian cancer, the cytotoxic effects of genistein in synergy with centchroman, a selective estrogen receptor modulator, have been evaluated. These agents have been observed to downregulate Bax and Bcl_2 levels, as well as inflammatory markers such as caspases. Following a comparative in vivo analysis in a mouse breast cancer model, it was concluded that combined usage of these agents was more effective than singular delivery (Kaushik et al. 2019). In a study undertaken by Lee et al., genistein was seen to exert an antiadipogenic effect, in combination with atorvastatin. The combination was observed to lower the levels of key adipogenic markers, such as mitogen-activated protein kinases (MAPKs), and peroxisome proliferator-activated receptor γ (PPARγ). This positive outcome offers potential for the usage of genistein in the management of metabolic disorders, chiefly in menopausal women (Lee et al. 2021).

The therapeutic potentials of the analogs of genistein have been explored as well. A study by Mesmar et al. explored the benefits of AXP107-11, a genistein analog, in improving the sensitivity of cells to chemotherapy. An in vivo study

indicated an enhancement in cellular sensitivity to gemcitabine, following treatment with genistein. This indicates an interesting avenue for synergistic therapy of genistein, in combination with conventional chemotherapeutic agents (Mesmar et al. 2019). Administration of genistein alongside doxorubicin has been evaluated as well, and key benefits include improved chemosensitivity in various cancers, such as lymphomas (Mohammad et al. 2003), as well as a marked reduction in the toxicity of synthetic chemotherapeutic agents (Chen et al. 2019a). Moving forward, there is a need to investigate the combinatorial effects of various natural and synthetic agents in combination with genistein, to assess adverse effects, synergistic mechanisms, and potentials for repurposing and improving the overall survival time and quality of life of patients.

Overview of recent clinical trials

As shown in Table 2, it gives an insight into recent clinical trials undertaken to evaluate the efficacy and safety profile of genistein. A major drawback in these studies was observed to be the relatively small size of the patient pool and scattered studies. There is a need to conduct a large number of multi-center clinical trials with diverse subject groups, to evaluate the safety and efficacy of genistein, and establish an optimum dosage for cancer management.

Nanodelivery of genistein

Despite the wide range of pharmacological benefits offered by genistein, it suffers from a variety of drawbacks commonly faced by phytoconstituents, such as weak water solubility, and a high first-pass effect in the native form. These greatly reduce its bioavailability, posing a challenge to formulators. Nanotechnology has been harnessed as a promising strategy to overcome these pitfalls and improve treatment outcomes (Joshi et al. 2019; Elmowafy et al. 2022). In addition to curative effects, genistein has also been evaluated for its prophylactic benefits. Landauer et al. evaluated the efficacy of a nanosuspension of genistein in radioprotection, in a mouse model. At a dosage of 150 mg/kg, in multiple intramuscular doses, genistein was observed to exert a protective action against exposure to full-body radiation (Landauer et al. 2019). Another study by Salem et al. evaluated the benefits of the administration of a genistein nanosuspension, through different routes. While nanotechnological interventions improve the bioavailability of the compound and offer a greater degree of radioprotection, there is a need to undertake further studies to establish efficacy pre- and post-exposure and to determine an optimal dosing and most suitable route of administration (Salem et al. 2022).

Other interesting advancements include the formulation of genistein-encapsulated nanoparticles using solvent-exchange methods, to improve surface characteristics to obtain an optimum release profile and safety (Soleimanpour et al. 2020). Kamel et al. explored the pulmonary delivery of genistein–lipid nanoparticles for lung cancer management, to provide a better release profile and improved uptake (Kamel et al. 2019). Additionally, there is potential to explore the delivery of genistein in combination with conventional chemotherapeutic agents, to reduce toxicity, overcome resistance, improve selectivity, and provide a synergistic action (Xue et al. 2014). These outcomes may be achieved by the application of nanotechnological interventions.

To enhance bioavailability and aqueous solubility, genistein-loaded mixed micelles have been designed. Post-encapsulation, improved pharmacokinetic properties were reported, including enhanced aqueous solubility and membrane permeability. In addition to this, a two-fold increase in oral bioavailability was reported, indicating that nanomicelles could be leveraged to deliver genistein (Shen et al. 2018). Nano-structured lipid carriers, developed with the aid of solvent emulsification and evaporation, were also studied, and it was revealed that they showed sufficient plasma concentration for a longer period and better distribution in rat ovarian tissues (Mittal et al. 2019). In a recent study, it was found that signal sensing, carrier-free, and triple combination nanomedicine developed provide improved drug loading and high permeability against NSCLC (Wang et al. 2022). So, this approach could be used to deposit genistein at specific cancer sites with a specific dose to alleviate the toxicity problems. However, while these novel technologies continue to gain popularity, there is a need to address challenges associated with their scalability and toxicity. This may be overcome by conducting a greater number of clinical studies, as well as designing technologies to facilitate easier translation from laboratories to a commercial scale. Table 3 offers a recent update of genistein nanoformulations, for cancer management. In addition to the composition of the nanoformulation, the cell line on which its action was evaluated and key benefits have also been documented.

Safety and toxicology studies

Isoflavones have been generally recognized to be non-toxic, according to the outcomes obtained from clinical experiments. However, mild side effects, primarily involving the gastrointestinal system, have been observed. These include nausea, constipation, and bloating. While there have been negative results concerning the safety of isoflavones such as S-equol in animal reproductive tissues, it is safe in human reproductive systems (Chen et al. 2019b). In a study undertaken by Serebrenik et al., an amorphous solid dispersion

Table 2 Overview of recent clinical trials of genistein for cancer management

Drug administered and dosage	Subjects	Study duration	Study design	Results	Reference
Genistein (30–600 mg/day) + FOLFOX (folinic acid, fluorouracil, and oxaliplatin)	13 chemotherapy-naïve patients with CRC cancer	Six treatment cycles, spanning over 3 months	Phase I/II clinical trial	Satisfactory safety profile on combining genistein with FOLFOX regimen for colorectal cancer management, low incidence of adverse effects, need for a greater number of clinical trials to establish the efficacy	Pintova et al. 2019)
Soy protein isolate (20 g/day), equivalent to 23 mg/day of genistein	Male subjects at risk of prostate cancer recurrence following prostatectomy ($n=73$), aged 44 to 75	A study spanning over 2 years	Randomized, placebo-controlled clinical trial	Improvement in hemoglobin levels, no disruption of endocrine levels or blood pressure, reduced predisposition to other metabolic disorders	Bosland et al. 2021)
Administration of soy isoflavones (of which genistein = 60 mg/day)	Premenopausal women ($n=99$ in the treatment group)	A study spanning over 2 years	Randomized, controlled clinical trial	Reduction in fatty breast tissue and fibroglandular breast tissue, which is a biomarker indicating breast cancer risk in premenopausal women. This effect was observed to be governed by the duration and concentration of isoflavones administered	Lu et al. 2022)
Soy protein isolate (20 g/day) (equivalent to 24–26 mg/day of genistein)	Male subjects at risk of biochemical recurrence following prostatectomy ($n=16$ in the treatment group)	6 to 8 months	Randomized, placebo-controlled clinical trial	Stable levels of prostate-specific antigen (PSA) throughout the treatment, improved serum genistein levels, and reduced cholesterol levels in the treatment group. This pilot study must be supplemented with trials on a larger scale	Bosland et al. 2022)
Administration of 50 and 100 mg/day of PhytoSERM (formulation comprising soy isoflavones, genistein, daidzein, and S-equol)	Perimenopausal women (aged 45 to 60)	12 weeks	Randomized, double-blind, placebo-controlled, phase 1b/2a clinical trial	The satisfactory safety profile of the formulation, low incidence of adverse effects, the establishment of an optimum dose of 50 mg/day for further clinical assessment	Schneider et al. 2019)

Table 3 Nanoformulations of genistein for cancer management

Composition of nanoformulation	Cell line	Key benefits	Reference
Genistein loaded onto gold nanoparticles	Malignant (PC3, DU 145, and LNCaP) and non-cancerous prostate cancer cell lines	Greater anti-cancer potential as compared to conventional genistein, satisfactory stability, antioxidant efficacy, and low toxicity	Vodnik et al. 2021)
Lactalbumin nanoparticles loaded with genistein	OSCC and fibroblast cell line	Selective induction of apoptosis, improved safety and bioavailability profile, demonstration of biocompatibility	Dev et al. 2021)
Loading of genistein onto Fe_3O_4 + carboxymethylated chitosan nanoparticles	Acute leukemia lymphoma (ALL) cell line	Satisfactory biocompatibility, improved water solubility, significant suppression of cellular proliferation even at low doses	Ghasemi Goorbandi et al. 2020)
Genistein loaded onto PEGylated PLGA (poly(lactide-co-glycolide)) nanoparticles	Ovarian cancer cell line (SKOV-3)	Sustained release profile, improvement in cellular uptake, and better targeting leading to enhanced therapeutic outcomes	Patra et al. 2022)
Genistein loaded onto serum albumin nanoparticles	F3II mammary carcinoma cell line	Improved cytotoxicity, reduced genotoxicity, satisfactory induction of apoptosis	Ferrado et al. 2023)
Genistein and doxorubicin loaded onto polypeptide nanoparticles	Mouse prostate cancer cell line (RM-1)	Reduction of tumor metastasis by regulation of DNA repair enzymes, induction of oxidative damage, lowering of side effects of doxorubicin monotherapy	Wang et al. 2018)
Genistein + miRNA-29b, loaded onto mucin-aptamer hybrid nanoparticles	Non-small cell lung cancer (NSCLC) A549 cell line	Improved cellular selectivity, downregulation of pro-inflammatory markers, greater induction of apoptosis	Sacko et al. 2019)
Genistein loaded onto bovine serum albumin nanovehicles	F3II mammary carcinoma cell line	Exertion of cytotoxic effects by induction of apoptosis, improved bioavailability, and slower elimination	Ferrado et al. 2021)
Genistein loaded onto PEGylated silica nanoparticles	HT29 human colon cancer cell line	Improved aqueous solubility and release profile, increased antioxidant potential by upregulation of antioxidant enzymes, betterment in the induction of apoptosis as opposed to native genistein	Pool et al. 2018)
Genistein + doxorubicin loaded onto nanoconstructs, composed of a lipid and polymeric component	Human breast cancer cell line	Synergistic effects owing to co-administration improved uptake and induction of apoptosis, and anti-angiogenic activity, offers a potential for exploring the benefits of the combined delivery of phytoconstituents and chemotherapeutic agents	Shukla et al. 2020)

of genistein was evaluated, to determine its safety profile at different doses. Mild- to moderate toxicities were reported, and no observable adverse reactions were recorded, on doses up to 500 mg. Based on the study results, the maximum safe dosage in humans was identified to be 3000 mg (Serebrenik et al. 2023).

An experiment designed by Godschalk et al. evaluated the implication of genistein exposure during pregnancy in a mouse model, and it was observed that the offspring may be at an increased risk of oxidative stress. This might trigger testicular abnormalities, due to DNA damage, impacting reproductive health and functioning (Godschalk et al. 2022). Similar studies on a larger scale would be necessary to fully comprehend the impact of genistein supplementation on various organ systems, including the reproductive system. While there are limited studies to establish the threshold for the dosage of soy isoflavones, the US FDA has established a safety limit of 25 g/day, with no toxic effects observed upon consumption up to this level (Sharifi-Rad et al. 2021). However, more studies are needed to assess the overall safety profile of soy isoflavones, as well as specific members belonging to this class of compounds.

Conclusions and future perspectives

As a multifaceted and complex disease, cancer exhibits a variety of different characteristics, with the most significant being uncontrolled cell growth and evading apoptosis. As one of mankind's most prevalent medical issues, chemopreventive approaches are a promising method to prevent the occurrence of cancer and death from it (Yang and Wang 2021; Liu et al. 2023). Despite having a number of drawbacks, such as non-specific targeting, an unfavorable pharmacokinetic profile of anti-cancer medications, low solubility and stability, sluggish metabolism, insufficient drug effectiveness, and inadequate biodistribution, conventional therapeutic modalities are still utilized to treat cancer. Therefore, it is crucial to create new anti-cancer medications that can handle the problems mentioned above and target tumors specifically without seriously impairing the functioning of healthy tissues. Next-generation anti-cancer medications should make use of specially designed nanoparticles to achieve the following qualities: increased solubility and stability, reduced protease degradation, longer half-life in the systemic circulation, site-specific targeting, enhanced biodistribution, sustained drug release, and delivery of multiple medications to reduce drug resistance.

A thorough review of the clinical and experimental studies on the potential proapoptotic function of genistein has been presented here. In addition, there is a comprehensive overview of its targets in the signaling transduction pathways. Genistein, as a natural compound, exhibits considerable variation in its therapeutic effects. Several *in* vitro and in vivo experiments have been carried out, but clinical studies are currently being performed using these agents at specific therapeutic doses. In addition, it is needed to perform clinical and pre-clinical experiments on genistein are to evaluate the therapeutic potential of this molecule. Despite extensive data collection, further research is necessary to determine the effectiveness of genistein as a pharmaceutical agent, based on the specific carriers of genistein for different clinical purposes.

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Data availability This document includes citations for all the data that were analyzed throughout the literature review.

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Authors and Affiliations

Hemant Joshi[1] · Dhruv Sanjay Gupta[2] · Nosheen Kamruddin Abjani[2] · Ginpreet Kaur[2] · Chakrabhavi Dhananjaya Mohan[3] · Jagjit Kaur[4] · Diwakar Aggarwal[5] · Isha Rani[6] · Seema Ramniwas[7] · Hadi Sajid Abdulabbas[8] · Madhu Gupta[9] · Hardeep Singh Tuli[5]

✉ Hardeep Singh Tuli
hardeep.biotech@gmail.com;
hardeep.biotech@mmumullana.org

Hemant Joshi
hemantjoshibcas@gmail.com

Dhruv Sanjay Gupta
Dhruvg2507@gmail.com

Nosheen Kamruddin Abjani
nosheenabjani@gmail.com

Ginpreet Kaur
ginpreet.aneja@gmail.com

Chakrabhavi Dhananjaya Mohan
cd.mohan@yahoo.com

Jagjit Kaur
1990jagjit@gmail.com

Diwakar Aggarwal
diwakaraggarwal@yahoo.co.in

Isha Rani
singlaisha8@gmail.com

Seema Ramniwas
seema.ramniwas@gmail.com

Hadi Sajid Abdulabbas
hadi-sajid@alameed.edu.iq

Madhu Gupta
madhugupta98@gmail.com

[1] School of Biotechnology, Jawaharlal Nehru University, New Delhi 110067, India

[2] Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKM's NMIMS, V. L. Mehta Road, Vile Parle (W), Mumbai 400056, India

[3] Department of Studies in Molecular Biology, University of Mysore, Manasagangotri, Mysore-570006, India

[4] Graduate School of Biomedical Engineering, Faculty of Engineering, The University of New South Wales, Sydney 2052, Australia

[5] Department of Biotechnology, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to Be University), Mullana, Ambala 133207, India

[6] Department of Biochemistry, Maharishi Markandeshwar College of Medical Sciences and Research (MMCMSR), Sadopur 134007, Ambala, India

[7] University Centre for Research and Development, University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Mohali 140413, India

[8] Continuous Education Department, Faculty of Dentistry, University of Al-Ameed, Karbala 56001, Iraq

[9] Department of Pharmaceutics, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India