Review Article

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A comprehensive review uncovering the anticancerous potential of genkwanin (plant-derived compound) in several human carcinomas

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Abstract: Plant-derived bioactive compounds displayed major therapeutic and chemo-preventive roles in the pathogenesis of numerous chronic malignancies such as cancer and enhanced oxidative stress and inflammation. Antioxidants found in food, such as genkwanin, may reduce oxidative stress and the release of cytokines or pathways that promote inflammation. The goal of this work is to summarize the potential for anticancer effects of genkwanin, a methoxyflavone that is present in a variety of plant species. This review examined and analyzed numerous research studies on identifying, isolating, measuring, and analyzing anticancer properties of genkwanin. The mechanisms involved cellular and molecular activities at various levels, including apoptosis induction and cancer cell growth and proliferation inhibition. Preclinical studies have demonstrated genkwanin's effects and mechanism of action; however, further research is required to investigate its therapeutic potential thoroughly. Additional research is needed to further our understanding of the pharmacodynamic effects of genkwanin. Additional toxicological study is necessary to evaluate the clinical efficacy and safety of genkwanin, which would help scientists to elucidate a potent drug candidate for cancer management.

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1 Introduction

Epidemiological studies have associated flavonoids with several health benefits, including a decreased chance of acquiring many cancers. Even though a large variety of flavonoids have been established to possess notable anticancer effects, only a few of these substances have proven effective enough to be tested as therapies in clinical trials [1]. The flavonoid family consists of 3-phenylchromen-4-one-based secondary metabolites of polyphenols. Numerous scientific studies have suggested that natural antioxidants may have beneficial biochemical effects against various diseases [2]. Many studies have focused on flavonoids among polyphenols because of their strong antioxidative, anti-inflammatory, anti-carcinogenic, or enzyme-inhibiting properties. They are subdivided into isoflavones, flavones, flavonols, anthocyanins, and flavanones [3]. A non-glycosylated flavone, genkwanin is isolated and present in various plant matrices, including *Rosmarinus officinalis*, *Salvia officinalis*, *Leonurus sibiricus*, and Genkwa Flos [4]. Inflammation and oxidative stress contribute to the onset and development of many chronic illnesses, such as diabetes, obesity, cancer, autoimmune diseases, cardiometabolic and neurological diseases, and critical contributors to the aging process [5,6]. Due to its potent action against pro-inflammatory mediators such as TNF-α, IL-1β, IFNγ, and IL-6 cytokines, as well as its inhibition of protein kinases and down-regulation of the p38, JNK, and microRNA-101-mediated AP-1 signaling pathway, genkwanin has been demonstrated to be a potential anticancer agent. These biomolecules have been shown to have both pro-tumor and antitumor effects in cancer via affecting cell proliferation, metastasis, and tumor microenvironment [7].

Genkwanin has been shown in this context to exert anticancer effects through the inhibition of PARP1, Bcl-2, and Bcl-xL proteins, as well as an increase in host

immunity and the reduction of inflammatory factor level, all of which lead to apoptosis induction in human breast cancer cell lines MCF-7, hepatocellular carcinoma HepG-2, and colon cancer cell lines HT-29, HCT-116, and SW-480 [8]. Among the isoflavonoid group of chemicals, genistein is present in large quantities in soy. Genistein has several different anticancer characteristics that have been discovered. According to several research, genistein suppresses angiogenesis, stops the cell cycle, promotes apoptosis, and so forth. In addition, genistein has been suggested to improve glucose metabolism and alleviate menopausal symptoms. In addition, genistein has been proposed as a beneficial natural remedy for many chronic conditions, including diabetes, rheumatoid arthritis, and cardiovascular disease. In women suffering from illnesses and menopausal symptoms, genistein has been shown to regulate the action of estrogen [9].

Moreover, it can alter proteins and pathways linked to the development of tumors, including Bcl-2, Bax, NF-κB, MAPK, P13K/Akt, and KIF20A. For improved treatment, it can also make cancer cells more sensitive to chemotherapeutic medications such as adriamycin and tamoxifen [10]. By controlling the metabolism of fats and carbohydrates, genistein aids in treating nonalcoholic fatty liver disease [11]. According to reports, female adult mice treated with genistein dietary supplements for their lives exhibit methylation of the BRAC 1 cytosine-guanine dinucleotide and reduced activation of the aryl hydrocarbon receptor in their offspring's mammary tissue. Upregulated expression of ERα was observed upon genistein administration. Antagonism of aryl hydrocarbon receptor demethylates BRCA1 upon genistein treatment. It also decreases the expression of Cyp1b1, a target for the ARH receptor [12]. Genistein also induces apoptosis significantly when its concentration is increased. It also arrests the cell cycle post-72 h in a dose-dependent manner, along with decreased levels of Notch-1, Bcl-2, Bcl-xL, and cyclin-1 expressions [13]. To our knowledge, this is the first thorough analysis outlining genkwanin's potential to cause cancer. Consequently, this review can direct future research to create efficient techniques for locating, isolating, and evaluating this flavonoid, which may help with future pharmaceutical industry and medical application applications.

2 Structure and biosynthesis of genkwanin

The O-methylated flavone genkwanin (4′,5-dihydroxy-7-methoxyflavone) has one hydroxyl group that is methylated [14] (Figure 1a). *In vitro* and *in vivo* research studies have displayed health benefits of including flavonoid- and flavone-rich diet [15]. Genkwanin has been shown to have therapeutic potential in several conditions, including type 2 diabetes, cancer, cardiometabolic diseases, and neurodegenerative illnesses (Figure 1b). The beneficial impacts of genkwanin have been linked to its ability to regulate apoptosis, cellular cycle arrest, oxidative stress, and inflammation [16].

Numerous plant matrices have been shown to contain genkwanin. It was the most significant compound that was separated from the *Vernonia fasciculata* leaf chloroform extract that was obtained from the United States, the *Eremanthus elaeagnus* hydromethanolic extract stem parts, and the Daphne genkwa flower that was gathered from China and Korea. In addition, the high concentration of genkwanin identified the propolis of *Apis mellifera* honeybees (Table 1).

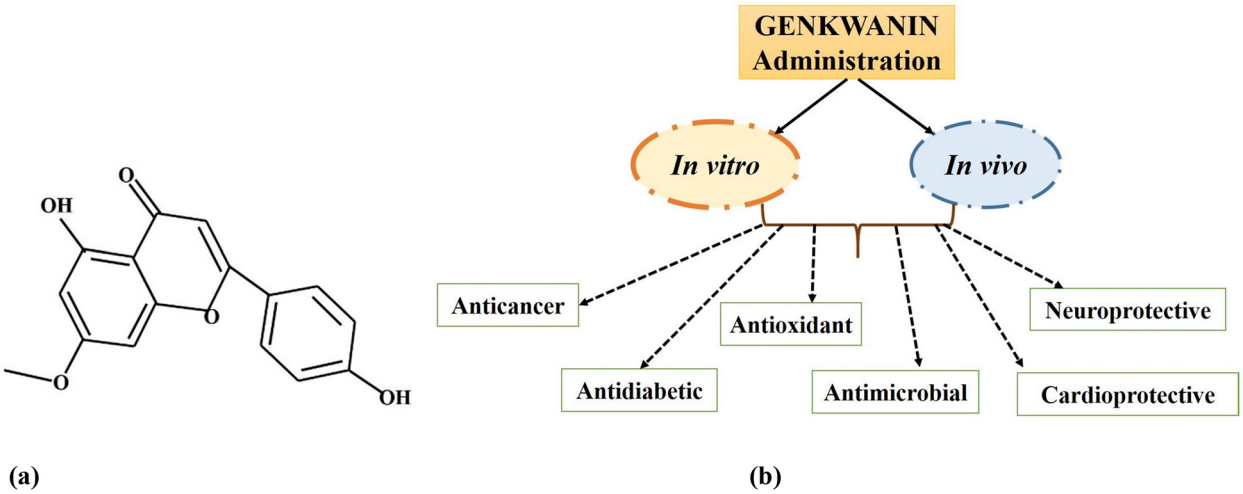

Figure 1: (a) Structure of genkwanin and its (b) medicinal potential.

Table 1: Genkwanin isolated from plant species

Plant part	Plant species	Family	Country	Reference
Leaf (chloroform extract)	*Vernonia fasciculate*	Asteraceae	United States	[17]
Stem (hydromethanolic extract)	*Eremanthus elaeagnus*	Asteraceae	China	[18–21]
Flower	*Daphne genkwa*	Thymelaeaceae	Korea	[22]
Leaves	*Ocimum basilicum*	Lamiaceae	Brazil	[23]
Aerial parts	*Baccharis trimera*	Asteraceae	Brazil	[24]
Stems	*Daphne gnidium*	Thymelaeaceae	Italy	[25,26]
Seeds	*Salvia officinalis*	Lamiaceae	Portugal and Tunisia	[27,28]
Flowers, leaves, roots, and stems (aqueous and methanolic extracts)	*Rosmarinus officinalis*	Lamiaceae	Spain	[29–33]
Leaves	*Nepeta*	Lamiaceae	Iranian	[34]
aerial parts (methanolic extract)	*Artemisia iwayomogi*	composite asteraceae	Korea	[35]
Leaves and roots (hydromethanolic extract)	*Rumex induratus*	Polygonaceae	Portugal	[36]
Seeds	*Alnus glutinosa*	Betulaceae	United Kingdom	[37]
Leaves	*Combretum erythrophyllum*	Combretaceae	South Africa	[38]
Leaves	*Aquilaria crassna*	Thymeleaceae	Japan	[39]
Leaves	*Phegopteris decursive-pinnata*	Thelypteridaceae	Bangladesh	[40]
Whole plant (methanolic extract)	*Tinospora crispa*	Menispermaceae	Bangladesh	[40]

Phenylalanine is the precursor for synthesizing additional flavonoid groups in the genkwanin biosynthesis pathway (Figure 2). This synthesis requires several enzymes, including chalcone synthase, chalcone isomerase, flavone synthase, phenylalanine ammonia lyase, cinnamic acid4-hydroxylase, 4-coumarate-CoA ligase, and flavonoid-7-*O*-methyltransferase. While apigenin itself has several biological properties, such as anti-inflammatory, antidepressant, and anticancer properties [41–44], regioselective O-methylation of apigenin (to produce genkwanin) confers additional biological properties, such as antibacterial, antiplasmodial, radical scavenging, chemopreventive, and inhibiting 17β-hydroxysteroid dehydrogenase type 1 activities [25,45–49].

3 Pharmacological potential and sources of genkwanin

Flavonoids are effective antioxidants and can scavenge free radicals because of their polyphenolic structure. Table 2 enumerates the genkwanin compound's physical and

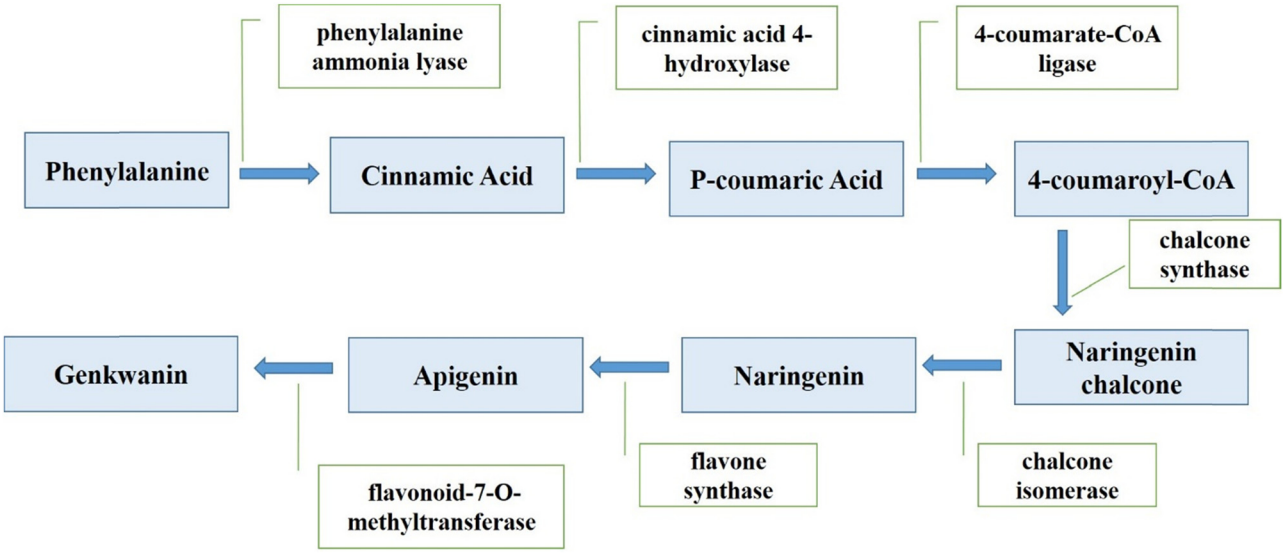

Figure 2: Biosynthesis pathway of genkwanin.

chemical characteristics that enhance its potential for therapeutic development.

4 Genkwanin: a potential antitumor bioactive compound against several human carcinomas

As a typical bioactive, non-glycosylated flavonoid, genkwanin (GKA) is used as a representative marker to ensure the quality of medicines prescribed by traditional Chinese medicine. According to earlier research, GKA possesses several pharmacological actions, such as expectorant, anti-inflammatory, antibacterial, antiplasmodial, chemopreventive, and radical scavenging properties [50]. Furthermore, reports have indicated that GKA possesses a specific anti-tumor activity. Wang et al. found that GKA reduced the levels of inflammatory cytokines and enhanced host immunity to some extent, which hindered the multiplication of tumor cells [51]. According to Androutsopoulos et al., GKA reduced the *in vitro* proliferation of MDA-MB-468 breast cancer cells at micromolar doses. Additionally, GKA demonstrated anti-proliferative action against granulomas generated by cotton pellets and B16F10 melanoma cells [52]. The potential of nanosuspensions to make insoluble pharmaceuticals more soluble and their adaptability to different delivery methods have made them a popular new class of nanoscale drug delivery technology [53]. Genkwanin nanosuspensions showed a constant drug release pattern and stronger cytotoxicity compared to free genkwanin in 4T1, MCF-7, HeLa, A549, HepG2, A549, BT474, and MDA-MB-453 cells. Additionally, in tumor-bearing nude mice genkwanin nanosuspensions (60 mg/kg, i.v.) showed better safety (at a minimal dose of 320 mg/kg) and therapeutic efficacy (62.09% vs 61.27%) in comparison to paclitaxel doses (8 mg/kg, i.v.) [54]. Hydroxy genkwanin nanosuspensions showed more potent cytotoxicity than the hydroxyl genkwanin solution in MCF-7 breast cancer cell [55]. In female nude mice and Kumingy mice, hydroxy genkwanin nanosuspensions (40 mg/kg) exhibited therapeutic efficacy similar to paclitaxel (8 mg/kg) injection. The highest dose of Hydroxy genkwanin nanosuspensions (360 mg/kg) presented 100% survival and safety in mice models [8].

Genkwanin treatment attenuated lung cancer progression and repressed cell proliferation and migration via modulating PI3K/PKB (phosphatidylinositol 3-kinase/protein kinase B) cell signaling pathway in A549 and H69AR cancer cells [56]. Genkwanin-loaded self-nano emulsifying drug delivery system formulation displayed boosted oral bioavailability and tremendous anti-colitis-associated colorectal cancer efficacy in AOM/DSS-induced C57BL/6J mice model [57]. Further, genkwanin induced reduction in melanin synthesis via inhibition of tyrosinase activity in B16F10 melanoma cells [58]. Genkwanin displayed better antitumor efficacy partly via augmenting host immunity and reducing expression levels of inflammatory cytokines $APC^{Min/+}$ mice. Hydroxygenkwanin (HGK) suppressed NSCLC progression by enhancing EGFR degradation in TKI-resistant NSCLC cells [59].

The antitumor impact of genkwanin on colorectal cancer was studied *in vivo* on $APC^{Min/+}$ mice and *in vitro* on human colorectal cancer lines HT-29 and SW-480 [59]. While genkwanin effectively suppressed the proliferation of human colorectal cancer cells HT-29 and SW-480 and the release of the inflammatory cytokine IL-8, six different inflammatory cytokines in a cell culture system boosted the development of two cancer cells in a concentration-dependent manner. After receiving 12.5 and 25 mg/kg/day of genkwanin orally, the body weights, spleen and thymus indexes, and immune cytokine secretions in the $APC^{Min/+}$ mice were dramatically improved [51]. In addition, two groups treated with genkwanin showed significantly reduced inflammatory cytokine levels and tumor multiplicity alterations. Besides, there was an apparent amelioration of the dysplastic adenomatous modifications in the gut histology. Together, these data suggested that genkwanin's superior anticancer efficacy was partly caused by raising host immunity and lowering inflammatory cytokine levels. Genkwanin regulated tumor necrosis factor-α-induced HaCaT cancer cell proliferation and inflammatory cytokines in Psoriasis via regulating nuclear factor-kappa B cell signaling pathway in human immortal keratinocyte HaCaT cells [60]. Treating colorectal cancer with genkwanin may be a successful chemotherapeutic approach [51]. Figure 3 projects a possible mechanism associated with the anticancerous efficacy of genkwanin in several human carcinomas.

With an average diameter of 261.1 ± 4.8 nm, a narrow particle size distribution (PDI of 0.12 ± 0.01), spherical morphology, high drug-loading content (39.9 ± 2.3%, w/w), and good stability in several physiological mediums, the resulting HGK nanosuspensions (HGK-NSps) were observed. The obtained nanosuspensions of HGK slowly released HGK, and HGK-NSps proved safe for intravenous injection at low concentrations. *In vitro*, HGK-NSps demonstrated more significant cytotoxicity against several tumor cells than free HGK. The IC50 value was 5-fold lower than the HGK solution, specifically against MCF-7 cells, at 1.0 μg/mL. The therapeutic efficacy of HGK-NSps (40 mg/kg) in the *in vivo* antitumor activity trial was comparable to that of the paclitaxel

Table 2: Physical and chemical properties of genkwanin

Physicochemical properties	
Molecular weight	284.070
Number of hydrogen bond acceptors	5
Number of hydrogen bond donors	2
Number of rotatable bonds	2
Number of rings	3
Number of heteroatoms	5
Topological polar surface area	79.900
Log of the aqueous solubility	−3.724
Log of octanol/water partition coefficient	3.670
GI absorption	High
PPP-Permeant	No
P-gp (P-glycoprotein) substrate	No
CYP1A2 (member of cytochrome P450 superfamily of enzymes) inhibitor	Yes
CYP2C19 (enzyme involved in the hepatic metabolism of drug) inhibitor	No
CYP2C9 (enzymes that break steroids and fatty acids) inhibitor	Yes
CYP2D6 (enzyme expressed in liver)inhibitor	Yes
CYP3A4 (cytochrome P450 isoforms) inhibitor	Yes
Toxicity profiling	
hERG blockers (human ether-a-go-go related gene)	Excellent (no blockage to hERG gene associated with cardiac regulation)
H-HT (human hepatotoxicity)	Excellent (no toxicity to liver)
DILI (drug-induced liver injury)	Poor (toxic)
AMES toxicity	Poor (mutagenic)
Rat oral acute toxicity	Excellent (low toxicity)
FDAMDD (toxic dose threshold of chemicals in humans)	Poor (toxic)
Skin sensitization	Poor (sensitizer)
Carcinogenicity	Medium (non-carcinogen)
Eye corrosion and irritation	Excellent (non-corrosives/non-irritants chemicals)
Respiratory toxicity (a major cause of drug withdrawal)	Good (non-respiratory toxicants)
Nuclear receptor (NR) signaling pathway	
AR (androgen receptor) dependent pathway: steroid/nuclear hormone receptor	AR agonist
Ligand-binding domain (LBD) of androgen receptor	Significant binding efficacy with LBD
AhR (aryl hydrocarbon receptor) signaling pathway	Activator (mediator of cellular response to environmental pollutants)
Aromatase: catalyzes the conversion of androgen to estrogen (maintains the androgen and estrogen balance)	Aromatase inhibitor
Estrogen receptor (ER): nuclear hormone receptor	Poor binding with ER receptor
ER-LBD (ER ligand binding domain)	Inactive
Stress response pathways	
p53 (tumor suppressor protein)	Activates p53, leading to cancer cell death
Mitochondrial membrane potential (effect on mitochondrial potential)	Active
Heat shock factor response element (HSE)	Activation of heat shock response
ATPase family AAA domain-containing protein 5	Active (more DNA Damage to cancer cells)

Source: PubChem https://pubchem.ncbi.nlm.nih.gov/and ADMET https://admetmesh.scbdd.com/service/evaluation/cal.

injection (8 mg/kg). According to the preliminary acute toxicity test, HGK-NSps had 100% of the mice survived even at the highest dose of 360 mg/kg (iv), and every mouse was in good condition, indicating a maximum tolerable dose of more than 360 mg/kg. HGK-NSps have shown a robust antitumor effect and good tolerance, suggesting that they could potentially develop into a safe and valuable antitumor medication in the future for the treatment of breast cancer [55].

Another study reported a new flavonoid called HGK, which selectively kills all of the NSCLC cells we tested [61]. The present investigation evaluated the anticancer activity of HGK on TKI-resistant NSCLC cells using a xenograft mouse model and NSCLC cells with EGFR mutations. *In vitro* and *in vivo* suppression of cancer cell viability was demonstrated by HGK, according to the data. According to whole-transcriptome research, the alterations in gene

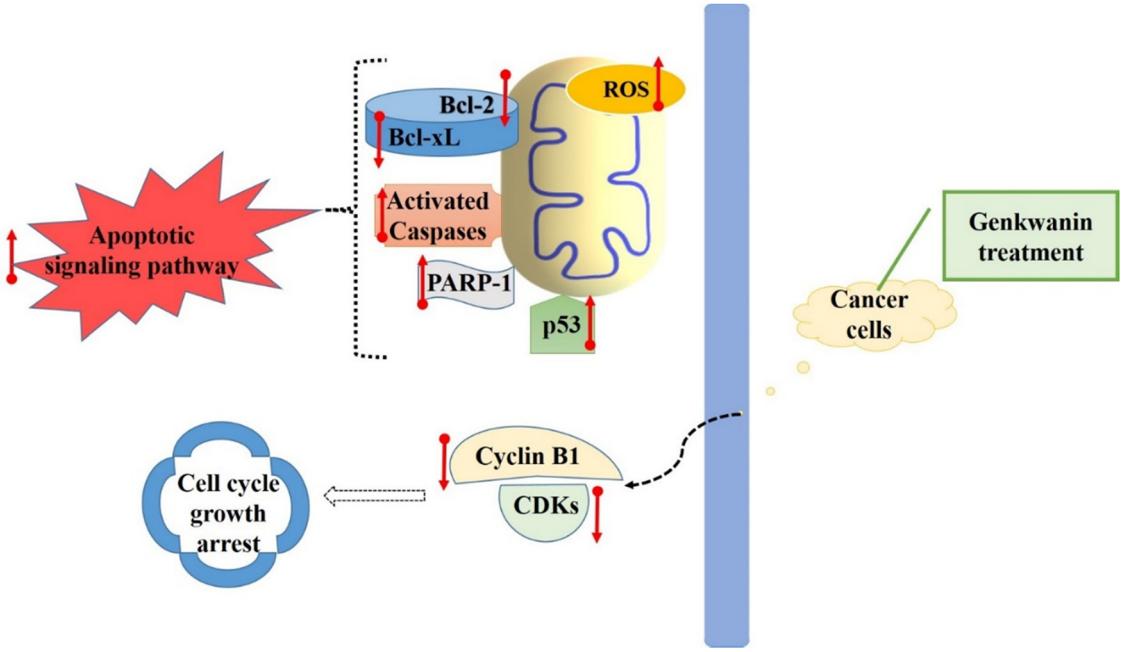

Figure 3: Proposed mechanism associated with the anticancerous potential of genkwanin. Pharmacokinetic analyses showed that GKA-SNEDDS has a 353.28% higher relative bioavailability when compared to GKA suspension. In addition, GKA-SNEDDS (self-nanoemulsifying drug delivery system) significantly reduces the histological scores of inflammatory cytokine levels and enhances the disease activity index (DAI). In the AOM/DSS-induced CAC mice model, it also prevents weight loss and inhibits the formation of colon tumors by inducing tumor cell apoptosis. Improved oral bioavailability and superior anti-CAC activity were demonstrated by the generated GKA-SNEDDS. In conclusion, GKA-SNEDDS can be used as a possible drug delivery method to enhance the therapeutic application of GKA since it uses lipid nanoparticles as the drug delivery carrier [62].

expression caused by HGK may include EGFR as an upstream regulator. We provided proof that HGK blocked many EGFR downstream signaling and decreased the amount of EGFR to corroborate this analysis. These findings suggest that HGK's anticancer action against TKI-resistant NSCLC cells may be mediated by improving EGFR degradation [61].

Further anticancerous efficacy of genkwanin has been investigated in lung cancer cells. MTT assay was then employed to assess the antiproliferative effects of genkwanin (20, 40, and 80 μM) against H69AR cells. Quantitative real time PCR and Western blot experiments further reported inhibition of the PI3K/Akt signaling pathway, significantly reducing PI3K/Akt mRNA protein and mRNA expression levels. Transwell test further reported inhibition of invasion and migration levels in genkwanin-treated cancer cells via inhibiting the PI3K/Akt pathway. Transwell test further reported inhibition of invasion and migration levels in genkwanin-treated cancer cells via inhibiting the PI3K/Akt pathway. Hence, genkwanin displayed significant inhibition of lung cancer cell growth, invasion, proliferation, and migration via inhibition of PI3K/Akt pathway, thus presenting a solid alternative therapy for lung tumor growth and metastasis [60].

Gnidia latifolia, *Gnidia glaucus*, *Dendrostellera lessertii*, *Daphne odorata*, and *Daphne genkwa* are the primary sources of genkwadaphnin, a daphnane diterpene ester molecule. Research has indicated that genkwadaphnin may be used therapeutically to treat leukemia, squamous cell carcinoma, human colon cancer, and hepatocellular carcinoma. It also plays an integral part in melanogenesis, skeletal disorders, inflammatory cytokines, natural killer cells, and innate immunity. On the other hand, the current work also covered pharmacokinetic and metabolomics features of genkwadaphnin. Moreover, additional scientific information on human clinical studies is required to ensure the safety and efficacy of genkwadaphnin in medicine [16].

Genkwanin exhibited prominent anti-cancerous efficacy against B16F10 melanoma cells by inducing growth arrest at G0/G1 phases after 24 and 48 h of incubation. Furthermore, genkwanin treatment also reduced melanin synthesis via inhibition of tyrosinase activity. This research has also projected the potential of genkwanin in cosmetic formulations as a skin-whitening agent [58].

At submicromolar and micromolar doses, respectively, sinensetin and genkwanin were demonstrated to cause a higher number of metabolites and to strongly inhibit the *in vitro* proliferation of MDA-MB-468 cells while having no discernible effect on the viability of MCF-10A cells. On the other hand, genkwanin and sinensetin suppressed

MDA-MB-468 cell proliferation more than chrysin, baicalein, and scutellarein. CYP1A1 and CYP1B1 promoted the metabolism of chrysin to baicalein and genkwanin to apigenin. When the findings are combined, they indicate that CYP1 family enzymes increase the antiproliferative action of dietary flavonoids in breast cancer cells by converting them into more potent forms [52]. AFB1-induced damages in the rats were wholly reversed by genkwanin therapy. Combining its antioxidant, anti-inflammatory, and anti-apoptotic qualities, the current work highlights the possible application of GKA as a therapeutic drug to stop AFB1-induced testicular damage [63].

Another study found that oral genkwanin treatment prevented mice from developing colitis caused by oral DSS administration, as shown by decreased weight loss, colon lengthening, and histopathological scores. Moreover, genkwanin reduced the synthesis of proinflammatory cytokines and alleviated oxidative stress. *In vitro* experiments showed that genkwanin treatment resulted in enhanced mitochondrial functioning and reduced ROS generation in human intestinal epithelial cells. In addition, genkwanin increased the expression of SIRT1, and the protective effect of genkwanin against oxidative stress and mitochondrial dysfunction was partially reversed by lentivirus-mediated SIRT1 knockdown. Clinical trials using genkwanin as a therapy for IBD have a strong foundation thanks to results from cell culture and murine model studies [64].

Flavonoids obtained from *Tephroseris kirilowii* (Turcz.) Holub were tested for their anticancer properties in human cancer cells. Three of the eight flavonoids from *T. kirilowii* (IH: isorhamnetin, GN: genkwanin, and Aca: acacetin) were extracted and identified for the first time to have the ability to suppress the proliferation of various human cancer cell lines. These potent flavonoids promoted apoptosis and autophagy in human breast cancer cells, producing cell cycle arrest at the G2/M phase. According to molecular docking analysis, these flavonoids dock in the ATP binding pocket of PI3Kγ. The administration of these flavonoids resulted in a significant reduction in the concentrations of PI3Kγ-p110, phospho-PI3K, phospho-AKT, phospho-mTOR, phospho-p70S6K, and phospho-ULK. Flavonoids-mediated inactivation of p70S6K, AKT, ULK, mTOR, p70S6K, and apoptosis was enhanced by pretreatment with the PI3Kγ-specific inhibitor AS605240. Together, these results provide a unique method by which these flavonoids-induced cell cycle arrest at the G2/M phase, apoptosis, and autophagy may be largely dependent on the downregulation of PI3Kγ-p110 and the subsequent disruption of the PI3K/Akt/mTOR/p70S6K/ULK signaling network. This research offers fresh perspectives on the anticancer properties of particular flavonoids and how they might be applied in anticancer treatment [65].

Another study developed an animal model of acute lung damage generated by cecal ligation and puncture (CLP). Genkwanin decreased inflammation, apoptosis, and lung edema (or damage) in CLP mice. Furthermore, these data mechanically verified that genkwanin ameliorated inflammatory injury in CLP mice by controlling the NF-κB signaling pathway. Hence, these findings supported the possibility that genkwanin would be a helpful medication in the management of acute lung injury brought on by sepsis [66].

5 Conclusion

Genkwanin is a group of readily accessible flavonoids with minimal toxicity that have demonstrated notable health advantages for humans, including specific anticancer characteristics. Genkwanin can improve well-being, prolong life, and have anti-aging effects by reducing ROS and inflammatory cytokine levels, blocking the NF-κB signaling pathway and carcinogenesis, and altering enzymes necessary for brain function. The current review has also demonstrated that anticancer flavonoids and genkwanin nanoparticles can be combined to create new and powerful antitumor medications. In contrast to free GKA, GKA-NSps have overcome the limited solubility of genkwanin and successfully increased anticancer efficacy against numerous tumor cell lines. Furthermore, GKA-NSps enhanced the bioavailability by long-lasting drug release and robust stability in various physiological mediums without hemolysis. More investigation is necessary to ascertain genkwanin's safety and efficacy in people through conducting clinical trials. Further research will delve deeper into the beneficial properties of genkwanin and help develop strategies for preventing and managing oxidative stress and inflammatory conditions.

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Ethical approval: The conducted research is not related to either human or animal use.

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