Minireview

Galangin: A metabolite that suppresses anti-neoplastic activities through modulation of oncogenic targets

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Impact statement

Galangin is known to have therapeutic potential against various cancers. It interacts with a variety of recognized cellular targets and inhibits cancer cell proliferation. Current review highlights the apoptotic, cell cycle arrest, anti-metastasis, and anti-angiogenic effect of galangin. In addition, synergistic and nanotherapeutic actions of galangin have also been discussed. The uniqueness of the review is to present all the possible anti-cancer interactions of galangin at a single platform.

Abstract

With the dramatic increase in cancer incidence all over the world in the last decades, studies on identifying novel efficient anti-cancer agents have been intensified. Historically, natural products have represented one of the most important sources of new lead compounds with a wide range of biological activities. In this article, the multifaceted anti-cancer action of propolis-derived flavonoid, galangin, is presented, discussing its antioxidant, anti-inflammatory, antiproliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic effects in various cancer cells. In addition, co-effects with standard chemotherapeutic drugs as well as other natural compounds are also under discussion, besides highlighting modern nano-technological advancements for overcoming the low bioavailability issue characteristic of galangin. Although further studies are needed for confirming the anti-cancer potential of galangin *in vivo* malignant systems, exploring this natural compound might open new perspectives in molecular oncology.

Keywords: Galangin, absorption, anti-cancer, epigenetics, synergistic, nano-delivery

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Introduction

Although our understanding about the etiology and molecular mechanisms of carcinogenesis has dramatically improved in the recent years, cancer is still considered as an incurable disease in many cases. Moreover, the incidence of this dreadful public health concern has rapidly increased during the last decades and is unfortunately estimated to further rise, reaching 28.4 million new cases in 2040.[1,2] This rapid increase in incidence has intensified investigations into novel more potent and safe anticancer agents.[3] As natural products have historically provided an important source for identifying several chemotherapeutic drugs that are currently approved for the use in clinical settings,[4] studies on the potential anticancer effects of diverse plant-derived compounds have become more and more popular all over the world.

Galangin (3,5,7-trihydroxyflavone) is a flavonol-type naturally active polyphenol found primarily in propolis and the roots of *Alpinia officinarum* Hance, but also in *Plantago major* L., *Alnus pendula* Matsum. and *Scutellaria galericulata* L. Numerous studies have reported the diverse biological activities of galangin, exerting antioxidant, anti-inflammatory, antiviral, and antimicrobial effects.[5] In addition, this flavonol has been demonstrated to exhibit also anticancer potential against a variety of malignant neoplasms, including lung cancer,[6] breast cancer,[7] ovarian

cancer,[8] gastric cancer,[9] colon cancer,[10] hepatocellular carcinoma,[11] glioblastoma,[12,13] and osteosarcoma.[14] Such anticancer action of galangin comprises antiproliferative, pro-apoptotic, antiangiogenic, and antimetastatic effects, through interacting with different molecular targets and affecting activity of various intracellular signaling pathways.[15] Furthermore, galangin can modulate also the action of conventional cancer treatment modalities, leading to augmentation of therapeutic responses in diverse tumor cells and malignant tissues,[16,17] thereby ameliorating adverse side effects induced by anticancer drugs.[18]

Although the current *in vitro* data suggest galangin as a very promising anticancer agent, this compound, like other natural flavonoids, undergoes extensive metabolic conversion in *in vivo* systems, resulting in the formation of several glucuronidated, sulfated, and methylated derivatives.[19] Several modes have been proposed to overcome the issue of such low bioavailability, including preparation of different nanoparticles encapsulating galangin.[20]

In this review article, the current knowledge about anticancer activities of galangin in diverse *in vitro* cancer cell lines as well as *in vivo* tumor models is compiled, with the aim to highlight the strong potential of galangin as a novel anticancer agent and emphasize the necessity for further studies with this natural compound.

Absorption and metabolism studies

The chemical moiety present in galangin is 4H-1-benzopyran-4-one,3,5,7-trihydroxy-2-phenyl or 3,5,7-trihydroxyflavone which can be synthesized by refluxing 2-methoxy-1–(2,4,6-trihydroxyphenyl) ethanone with benzoic acid and benzoyl chloride. Studies have proven that galangin is converted in the liver to kaempferol and quercetin by cytochrome P450, both of which have anti-oxidant properties. Galangin has three hydroxyl groups on its carbon rings, acts as an enzyme modulator, and can reduce chemical genotoxicity. Galangin has been shown to be a strong inhibitor of the aryl hydrocarbon receptor in earlier studies. It has also been found to exert a range of biological functions in organisms at non-toxic doses. From the 4′-position, human liver microsomes metabolize galangin to kaempferol (Figure 1). The cytochrome enzymes CYP1A1, CYP1A2, and CYP2C9 catalyze this reaction.[21] Galangin is seen to be glucuronidated and sulfated seven times more frequently than it is oxidized.[22] The UDP-glucuronosyltransferase (UGT) 1A9 isoform in the liver appears to catalyze glucuronidation efficiently.[21,23] Interestingly, UGT1A9, as well as UGT1A1 and UGT2B15, were shown to glucuronidize the 7-position of galangin.[24] Galangin and its metabolites are usually excreted in the feces.[25]

According to the study done by Goran Benković *et al.*, CYP2C19 and CYP2D6 enzymes were found to be responsible for galangin metabolism. Incubations of CYP2C19 and CYP2D6 revealed the production of one metabolite—kaempferol—similar to the studies using human liver microsomes, suggesting that this enzyme catalyzes the aromatic hydroxylation of galangin at position 4′ of ring B.[26]

Liu *et al.* identified two galangin metabolites in rat plasma using ultra-fast liquid chromatography coupled with electrospray ionization triple quadrupole tandem mass spectrometry (UFLC-MS/MS). After oral treatment, two galangin metabolites, galangin-3-O—D-glucuronic acid (GG-1) and galangin-7-O—D-glucuronic acid (GG-2), were identified, reiterating the result that galangin was glucuronidated.[19]

Chen *et al.* investigated galangin metabolites in rat plasma after oral (p.o.) and intravenous (i.v.) administration. Female Sprague-Dawley (SD) rats were chosen.

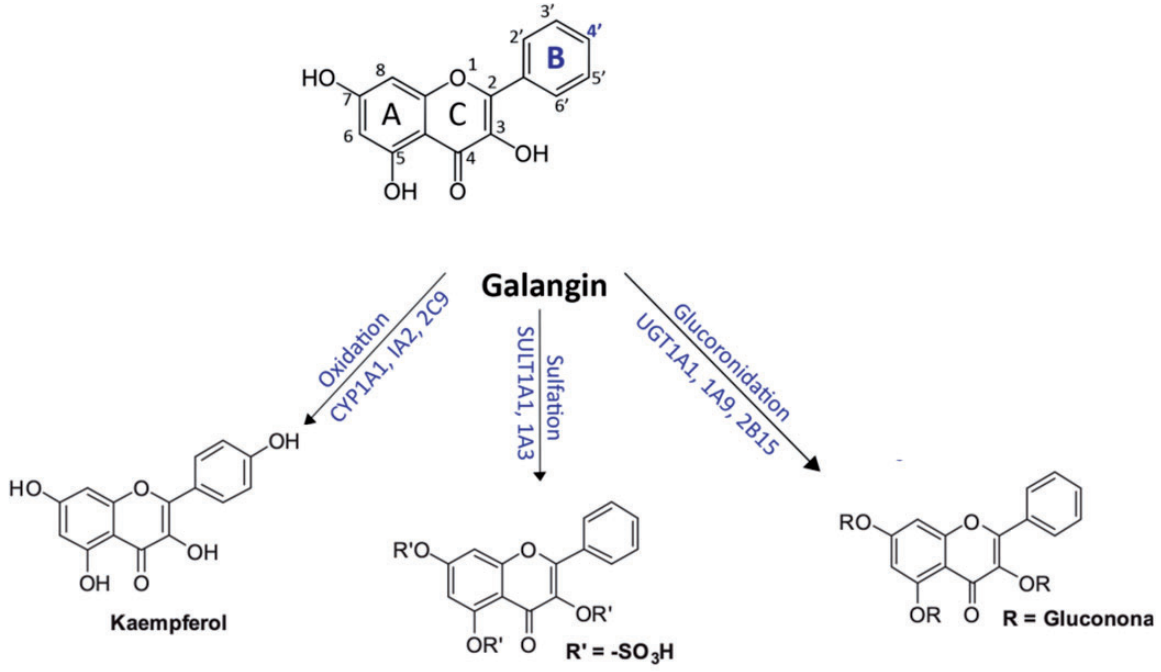

Figure 1. Principle metabolic pathways of galangin.

Each group received 10 mg/kg oral galangin and 2 mg/kg intravenous galangin. The routes of administration, according to the findings, have a substantial influence on the systemic exposure level of galangin and its metabolites. They also reported that after p.o. and i.v. administration, galangin was glucuronidated and sulfated, and that the parent galangin's oral bioavailability was extremely poor.[27]

When Curti *et al.* investigated a mouse animal model, they observed a similar result. They used 29 mature male C57BL/6 mice in their study (8 weeks old, 20 g average weight). Brown propolis preparations were found to have approximately identical quantities of two compounds, galangin and chrysin. However, only glucuronated galangin was identified in the blood, indicating that galangin is likely adsorbed and promptly glucuronidated after oral administration, suggesting that it has weak bioavailability in mice.[28]

Given the myriad of biological applications of galangin, such as anti-cancer,[10,29,30] anti-inflammatory,[31,32] lipid lowering effects[33,34] and anti-oxidative effects,[35,36] with certain studies showing that galangin glucuronidated metabolites have better bioactivities than parent galangin, biological activity of galangin metabolites must be evaluated more to be more efficient or safe for biological use.

Anti-cancer potential of galangin

Apoptosis and cell cycle arrest effect

Natural compounds potentiate their anti-cancer effects through modulating multiple signaling pathways including apoptosis and cell cycle arrest. In line with apoptotic inducing potential of natural compounds (Figure 2), galangin has been shown to induce apoptosis-related decreased cell viability at 43.45 µg/mL and 168 µg/mL for 48 h in MCF-7 and LNCaP cells, respectively. However, no such effect was observed in primary fibroblast cells.[37] Similarly, in gastric cancer, galangin reduced cell viability in MGC803 cells but not normal gastric mucosal epithelial GES-1 cells.[9] Apoptotic promotion by galangin in MGC803 cells was supported by decreased Bcl-2 and inactivated JAK2/STAT3 pathway, cleaved caspase-3 and PARP. These findings were further corroborated by the authors in nude mice xenografted with MGC 803 cells suggesting the involvement of STAT3/ROS axis in galangin-induced apoptosis.[9] It has also been reported that galangin may exert its apoptotic effect through inhibition of glyoxalase-1 thereby inducing oxidative and carbonyl stress.[38] It has been reported that galangin promotes apoptosis in cholangiocarcinoma cells by downregulating mir-21 which targets PTEN. Probable mechanism suggests that the downregulation of mir-21 allows galangin to maintain PTEN levels,[39] which leads to reduced phosphorylation of Akt controlling downstream survival and apoptosis of cholangiocarcinoma cells.[40] In another report, it has been shown that galangin induced down regulation of H19 and mir 675, promotes p53 expression and apoptosis in hepatocellular carcinoma cells MHCC97H cells.[11] As stated before, preferential anticancer effects of galangin against cancer cells only have also been reported in ovarian cancer. It has been shown that galangin induced apoptosis in A2780/CP70 and OVCAR-3 cells more effectively as compared to normal IOSE 364 cell line. Galangin acted through both p53 dependent intrinsic and extrinsic pathways possibly mediated through Akt/p70S6K pathway.[8] Galangin also induced apoptosis in U251, U87MG, and A172 glioblastoma cells in a dose-dependent manner as compared to normal human astrocytes.[13] In kidney cancer cell line A498, galangin promotes apoptosis through suppressive targeting of

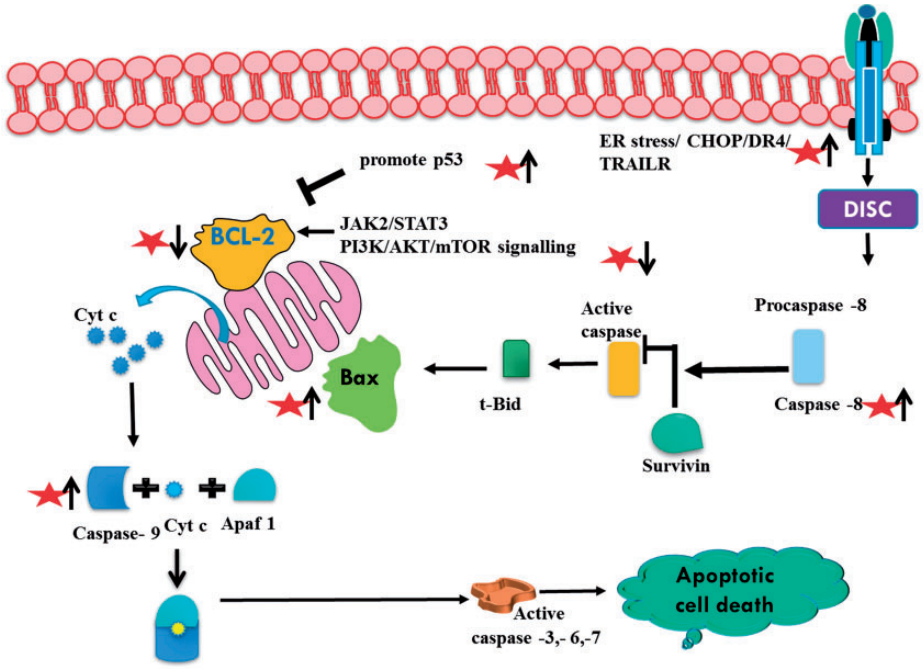

Figure 2. Apoptotic effect of galangin (represented as star) in cancer. It up-regulates and down-regulates apoptotic (p53, caspases, Bax) and anti-apoptotic (Bcl-2, survivin) proteins respectively. (A color version of this figure is available in the online journal.)

PI3K/AKT/mTOR signaling pathway supported with decreased bcl-2 and increased Bax,Cyt-c.[41,42] Similarly, in breast cancer MCF-7 cells, galangin promotes apoptosis through mitochondrial pathway and PI3K/Akt inhibition.[7] Galangin induces endoplasmic reticulum stress by promoting the expression of CHOP and DR4 gene. The ER stress leads to TRAIL sensitization, Caspases activation and AMPK phosphorylation-mediated apoptosis in human breast cancer cells.[43] Galangin-induced TRAIL-mediated apoptosis was also reported in renal carcinoma Caki, ACHN, and A498 cell lines. NF-kB pathway was inactivated which mediated down regulation of bcl-2, cFLIP, Mcl-1, and survivin associated apoptosis.[44] In human nasopharyngeal carcinoma, PI3K/Akt pathway-mediated apoptosis was p53 independent and therefore, effect of galangin treatment may exhibit apoptotic potential independent of p53.[45]

Potential anti-cancer effect of galangin also includes its ability to arrest cancer cells. It has been reported that galangin arrests MCF-7 breast cancer cells by regulating proteins involved in cell cycle regulation. In particular, galangin treatment leads to downregulation of cyclin D3, cyclin B1, cyclin-dependent kinases CDK1, CDK2, CDK4, and upregulation of p21, p27 and p53.[7] Galangin has been reported to arrest nasopharyngeal carcinoma cells in S phase independent of p53 status.[45] Inhibition of p38 by galangin in laryngeal carcinoma is reported to be the cause for cell cycle arrest,[42] whereas galangin-induced GO/G1 cell cycle arrest in human head and neck squamous cell carcinoma cells accompanied with reduced expression of cyclin D1, CDK4, and CDK6.[46] Similar observation of cell cycle arrest at GO/G1 stage by galangin treatment was also reported in leukemic Bcr-Abl+ cells and human mammary tumor cell line Hs578T.[17,47]

Anti-angiogenic and anti-metastatic effect

Angiogenesis or neo-vasculature is considered as an important characteristic of developing tumor. Growing blood vessels not only provide nutrition and oxygen to the cancer cells but also facilitates tumor migration.[48–51] Therefore, a diverse range of synthetic and natural compounds are being investigated to inhibit tumor angiogenesis and metastasis.[52–57] Huang *et al*. investigated the anti-angiogenic potential of galangin in HUVECS, CAM, and ovarian cancer cell culture models.[58] Galangin was found to inhibit the secretion of vascular endothelial growth factor (VEGF) via downregulating the expression of p-Akt, p-70S6K and hypoxia-inducible factor-1α (HIF-1α). In tumor microenvironment, high expression of HIF-1 considered to upregulate the expression of VEGF which is known to be a primary cytokine for angiogenesis. Angiogenic environment further supports tumor invasion and metastasis. In a study, the effects of galangin in human glioma cancer (A172) cells revealed downregulation of ADAM9 via extracellular signal regulated kinase (Erk)1/2 activation to inhibit tumor invasion.[59] In another study using human glioblastoma cells, Xiong *et al*. found galangin inhibited Skp2 (an oncogene) expression which is accountable for epithelial-to-mesenchymal transition (EMT). Similarly, using renal cell carcinoma (786 0 and Caki 1) galangin inhibited EMT through downregulation of E-cadherin.[12] Upregulated CD44, another important characteristic hall mark in several tumors was found to be suppressed by galangin treatment. Consequently, promising anti-angiogenic and anti-invasive effects were seen in glioma (U87 and U251) cells.[15] In 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced invasive HepG2 liver cancer cell culture model Chien *et al.* investigated the anti-metastatic effect of galangin. Results of the study revealed that galangin reduced enzymatic activity of MMPs 2, 9 via ERK1/2, c-Fos, c-Jun, nuclear factor kappa B (NF-κB), and activator protein 1 (AP-1). The incidences of biliary tumors including cholangiocarcinoma (CCA) are increasing globally. In CCA cancer, galangin treatment was found to upregulate the expression of PTEN and downregulates the phosphorylation of AKT via miR-21inhibition. Another important oncogene, i.e., *H19* is known to associate with tumor progression, proliferation, and migration. Using hepatocellular carcinoma (MHCC97H) cells, galangin was found to inhibit the expression of *H19* and miR 675 via upregulating p53 levels. Figure 3 depicts the anti-angiogenic and anti-metastatic mechanisms of action of galangin.

Antioxidant and anti-inflammatory effect

The body in its normal physiological state can maintain a dynamic balance between antioxidation and oxidation by eliminating the smaller proportions of ROS generated. However, when this balance is disturbed, i.e., ROS accumulates at a higher speed than their elimination from body, it leads to the propagation of various diseases like Alzheimer's disease, pulmonary fibrosis, cerebral ischemia, and Parkinson's disease. These diseases can be prevented by the antioxidants such as galangin. Galangin (3,5,7-trihydroxyflavone) serves various medicinal properties such as anti-viral, anti-tumor, anti-microbial, anti-mutagenic, antioxidant, and anti-inflammatory.[60–62] The anti-inflammatory properties of galangin were observed in different diseases such as asthma, acute lung injury, arthritis, acute kidney injury, and paw edema. It also helps in reducing renal inflammation[18,63] by the activation of NLRP3 inflammasomes and inhibition of PI3K/AKT and NF-κB pathways (Figure 4). It reduces the inflammation caused by uric acid by inhibiting the caspase-1 activity and ASC adaptors as well as decreasing the levels of IL-18 and IL-1β.[63]

The inflammatory response in the body is regulated by various pathways such as NLRP3 inflammasome, PI3K/AKT, and NF-κB. PI3K/AKT is closely associated with inflammation and helps in the activation of NF-κB (Chien *et al.* 2015). NF-κB mediates the expression of mediators (PGE-2 and NO) and cytokines (IL-1β and TNF-α) to prevent inflammation and aids in host defense. The NLRP3 inflammasomes help in inhibiting the inflammation to various agents by activation of cysteinyl aspartate-specific proteinase-1 (caspase-1) and secretion of mediators or cytokines.

Despite possessing different medicinal properties, galangin has a limited number of applications due to its

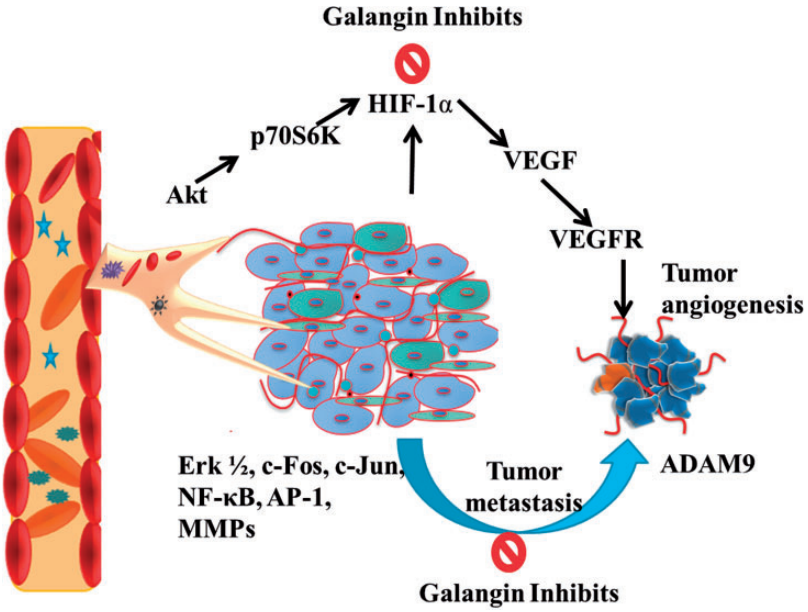

Figure 3. Anti-angiogenic and anti-metastatic actions of galangin by inhibiting p-Akt, p-70S6K, HIF-1, VEGF/R and Erk1/2, c-Fos, c-Jun, NF-κB and AP-1 pathways respectively. (A color version of this figure is available in the online journal.)

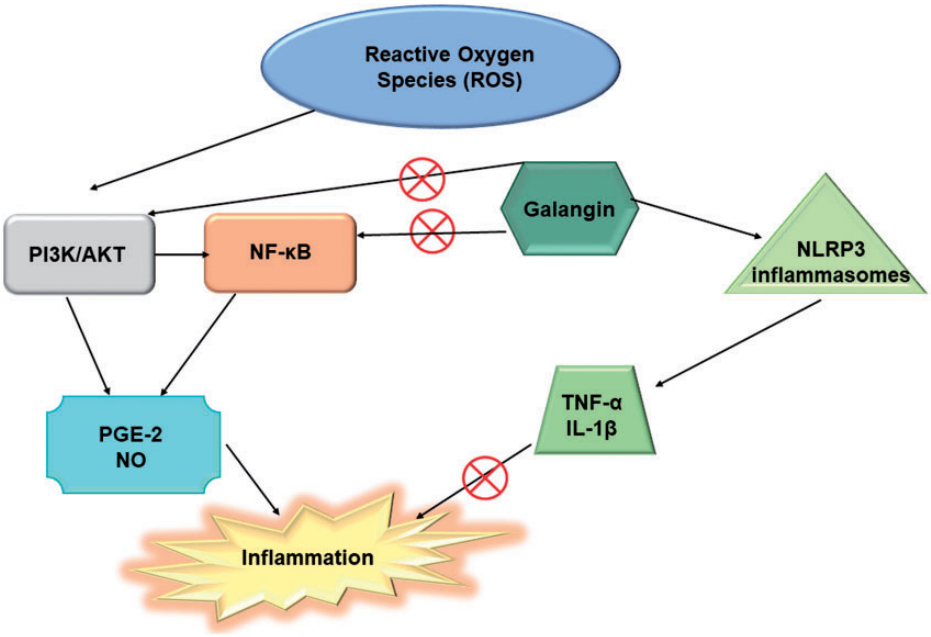

Figure 4. Antioxidant mechanisms of galangin to prevent the inflammation. It modulates the expression of PI3K/AKT, NF-κB, PGE-2, IL-1β and TNF-α during oxidative stress. (A color version of this figure is available in the online journal.)

insoluble nature, semi-permeability to gastrointestinal barriers, and sensitive nature to environmental parameters like pH, temperature, and light.[64] Its bioavailability can be enhanced by immobilizing into various carriers such as β-cyclodextrin (βCD), hydro xypropyl-β-cyclodextrin (HPβCD).[65]

Epigenetic effects

Galangin triggered autophagy and apoptosis in cancer cells through epigenetic modifications, such as histone acetylation and DNA methylation. Numerous studies reported that epigenetic alterations are responsible for gene dysregulation in several human cancers.[66–68] Galangin possesses tremendous potential to treat triple-negative breast cancer by epigenetically restoring estrogen levels via reduction of hypermethylation level of the BRCA1 gene in the HCC38 tripe-negative breast cancer cell. Thus, in the future, it may be used as anti-hormonal therapy for triple-negative breast cancer.[69] For example, Li *et al*. demonstrated that galangin induced autophagy in hepatocellular carcinoma cell HepG2 by deacetylation of

LC3 (Light Chain 3) by SIRT1 (Sirtuin 1).[70] Mechanistically, galangin promoted the conversion of LC3 I to LC3 II and decreased the acetylation of LC3. However, in SIRT1 knockdown cells, galangin failed to reduce the acetylation of LC3 in vector-infected cells. These results suggest that deacetylation of endogenous LC3 by SIRT1 is essential for galangin-induced autophagy in HepG2 cells.[70] Overall, galangin induces autophagy via the deacetylation of endogenous LC3 by SIRT1 in HepG2 cells. Moreover, Lei *et al.* showed reduced A172 cell migration and invasion upon treatment with various concentration of galangin 0, 5, 10, 25 μM for 24 hours compared to non-treated cells.[59] Mechanistically, the authors analyzed the invasion associated protein ADAM9 inside the cell and observed that galangin reduced the ADAM9 protein expression via activation of ERK1/2 following treatment with different doses of galangin.[59] Taken together, *in vitro* and *in vivo* studies suggested that galangin played a widespread role in cancer management through blocking the vital oncogenic pathways, activated during cancer manifestation.

Recently, galangin also acts as an effective molecule for treating Alzheimer's disease (AD). Generally, the aberrant acetylation pattern in the BACE1 (Beta-Secretase 1) gene leads to the pathogenesis of AD. It was shown that galangin decreases the acetylation level of the BACE1 promoter region by increasing the deacetylation pattern of HDAC1 (Histone Deacetylase 1).[71]

Synergistic effects of galangin

Naturally occurring compounds like flavonols play remarkable roles in cancer therapy due to their multi-targeted actions and lack of considerable toxicity. In order to have maximum therapeutic efficacy and minimum side-effects with little or no drug resistance, various synergistic chemo-preventive strategies in combination with established chemotherapeutic drugs, had gained a lot attention in the recent years.[72–75] Galangin (GA, 3,5,7-trihydroxyflavone), one of the most important and naturally active flavonoids, is a polyphenolic compound extracted primarily from the roots of *Alpinia officinarum* Hance, *Alnus pendula* Matsum., *Plantago major* L., *and Scutellaria galericulata* L (*S. scrodifolia* Fisch.), have been applied as herbal medicines for various ailments in Asian cultures for centuries.[5] The activity of natural compound is associated with the ability of flavonols to influence membrane-dependent processes and a broad range of biological properties, including prohibitive effects on bacteria, fungi, viruses, the control of hypertension and diabetes, and chemoprevention of several cancers.[5] In addition, galangin has also been found to enhance the chemo preventive potentiality (Figure 5) of various other therapeutic drugs. Studies have demonstrated that the combination of galangin with berberine synergistically resulted in cell growth inhibition, apoptosis, and cell cycle arrest at G2/M phase with the increased intracellular reactive oxygen species (ROS) levels in esophageal carcinoma cells.[76] Furthermore, this bioactive compound has been documented to exhibit potent synergism with fisetin (FTN) and quercetin (QTN) and thus correlated the biological activity of these molecules with their interaction and localization in dipalmitoyl phosphatidyl choline (DPPC) bilayers, using differential scanning calorimetry (DSC) and nuclear magnetic resonance (NMR) methods. Results indicated that galangin interacts to the alkyl chains of the lipid bilayer involving hydrophobic interactions and play an important role in membrane binding and thereby in biological activity.[77] The compound has also been known to synergize with other cytotoxic natural flavonoids quercetin and chrysin to show effects on cisplatin (cis-Pt)-induced apoptosis of human promyelocytic leukemia HL-60 cells and murine leukemia L1210 cells.[78] Recently, it was investigated that the combination of galangin with cisplatin at a low concentration induced the apoptosis of lung cancer cells, even in cells with resistance to cisplatin through inactivation of p-STAT3/p65 and Bcl-2 pathways.[16] Additionally, this natural flavonoid has also been reported to simultaneously induce apoptosis, pytoptosis, and protective autophagy in human glioblastoma multiforme

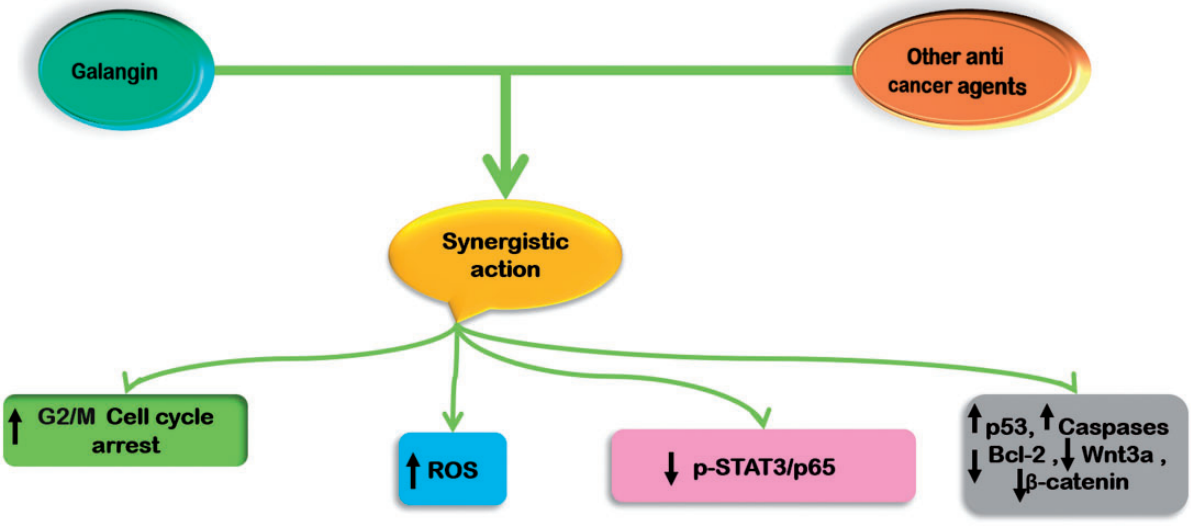

Figure 5. This illustration represents synergistic mechanisms of action of galangin in cancer. (A color version of this figure is available in the online journal.)

(GBM) cells, indicating that combination treatment of galangin with autophagy inhibitors may also be an effective therapeutic approach for GBM i.e. one of the most common and deadly primary malignant tumor of the central nervous system in humans.[13] Likewise, studies also revealed that the galangin therapeutic development as synergistic with gold nanoparticles against human breast cancer cell line (SKOV-3) through induction apoptosis instantiated biological mechanism increasing expression of p53, caspase-8 respect therapeutic targets via mitochondria pathway.[79]

Role of nanotechnology in galangin delivery

Galangin is a flavonoid with poor pharmacokinetic profile, low water solubility, and incompatibility in physiological media, which limits its therapeutic application.[19,80] Among flavonoid molecules like quercetin, kaempherol, morin, and myricetin, it is the most lyophilic. The development of new drug delivery methods might not only overcome solubility barriers, but also enhance effective drug concentration in tumors while reducing drug accumulation in normal tissues, reducing undesirable side effects.[5,81–85] Nanoparticular delivery methods might therefore be created to enhance galangin's therapeutic benefits, as an anticancer medication.

Ahmed M Al-Shammari *et al.* investigated the safety of AuNPs nanoparticles in conjunction with galangin in the treatment of ovarian cancer. Galangin therapeutic development as a synergistic with gold nanoparticles against human breast cancer cell line (SKOV-3) by induction apoptosis indicated a biological mechanism boosting p53, caspase-8, and therapeutic targets via mitochondria pathway, according to the findings.[79] Hui Yao *et al.* developed galangin-loaded PEG-modified liposomes and tested their targeting to liver cancer cells *in vitro*, as well as the pharmacokinetic characteristics in rats (*in vivo*). Under experimental storage circumstances, Gal entrapment efficiency was 80%, with minimum leakage. PEG-modified liposomes have enhanced solubility, antitumor effectiveness, and pharmacokinetics when compared to free Gal.[86] To improve galangin's low permeability and poor water solubility, Yinghua Li *et al.* designed Ga-functionalized SeNPs (selenium nanoparticles) and enhanced the anti-cancer potential against hepatocellular carcinoma. It induced caspase-3-mediated HepG2 cell death via ROS production, according to the underlying molecular processes.[20] Jing Zhu *et al.* effectively produced galangin-liposomes utilizing a thin-film hydration technique to test its oral bioavailability. When compared to free galangin, the galangin-liposomes demonstrated higher hepatoprotective benefits in ameliorating CCl4 toxicity in mice, according to biochemical and histological analyses.[87] A study done by Hamed Hajipour confirmed that the GA loaded-Arginyl-glycyl-aspartic acid nanostructured lipid carrier could significantly improve the anticancer potential of doxorubicin. Arginyl-glycyl-aspartic acid-nanostructured lipid carrier, increases galangin accumulation in malignant cells via integrin-mediated endocytosis, according to uptake tests. In comparison to doxorubicin and galangin loaded-Arginyl-glycyl-aspartic acid nanostructured lipid carrier, doxorubicin and galangin loaded-Arginyl-glycyl-aspartic acid nanostructured lipid carrier demonstrated greater cytotoxicity and apoptotic effects.[88] Table 1 summarizes the galangin's anticancer effects in combination with nanoformulation.

Toxicity studies using galangin

Galangin as a natural compound is generally considered to be safe. However, the experimental evidence confirming this statement is still rather scarce, pointing to the necessity for further thorough studies on safety profile of galangin. Based on the recently reported data, orally administered

Table 1. Anti-cancer activity of galangin nanoformulation in different models.

Sr.no	Nanoformulation	Experimental model	Dose	Results	Ref.
1	Galangin - gold nanoparticles(18)	SKOV3,ovarian cancer cell line, and HBL, human epithelial breast tissue	5,10, 25, 50, 100 μg/ml	Synergistic cytotoxic effect against ovarian cancer cells	30
2	Galangin loaded PEG- modified liposomes(19)	Hep G2 cells, Male Wistar rats	5 μM 5 mg/kg	PEG-modified liposomes have a greater cytotoxic impact. Hep G2 cells had a 1.34-fold increase in overall apoptosis when compared to Gal-loaded unmodified liposomes.	31
3	Galangin loaded selenium nanoparticle(20)	HepG2 cells(normal human liver cell line)	10 μM	Cytotoxic effect, Induced apoptosis of cancer cells	32
4	Galangin-loaded liposomes(21)	ICR mice	300 mg/kg	Increase in oral bioavailability by 470.12% in encapsulated galangin Better hepatoprotective effects observed compared with free galangin	33
5	Galangin loaded-NLC-RGD (loaded-Arginyl-glycyl-aspartic acid nanostructured lipid carrier) (22)	Human lung carcinoma (A549) cell line	3 mg/mL	When galangin was used in the form of GA loaded-NLC-RGD, its effects on the expression of the ABC transporter were amplified. Increased Apoptosis and Cytotoxic Effect (123.4 μM GA -NLC-RGD).	34

Table 2. Anti-cancer effects of galangin based on *In vitro* studies.

Type of Cancer	Cell lines	Effects	Mechanisms	Concentration	References
Glioblastoma	U87, U251 and U87-luciferase	Induces apoptosis	↓ GBM cell growth, migration, and invasion, ↓ Skp2, ↓ Zeb1, ↓ N-cadherin, ↓ snail, ↓ vimentin , ↑ Skp2 gegradation through the Ubiquitin-Proteasome-Dependent pathway	0, 10, 20, 40 and 80 μM	12
	U87 and U251	Inhibited angiogenesis,	↓ proliferation, migration and invasion of cancer cells , ↓ mRNA and protein levels of CD44, ↓ Snail, ↓ Vimentin ↓ ZEB1, ↓VEGF	0, 5, 10, 20 and 40 μM	15
	U251, U87MG, and A172	Induces apoptosis, pytoptosis, and protective autophagy	↓ viability and proliferation of GBM cells, induces G0/G1 Cell Cycle arrest, ↓ CCND1, ↓ CDK4, ↓ PCNA, ↓ cyclin-dependent kinase inhibitor p21, ↓ Bcl-2, ↑ BAX, ↑ cleaved PARP-1, ↑ nuclear DNA damage in GBM cells, ↑ formation of autophagic vesicles, ↑ MAP1LC3B-II, ↓ SQSTM1, ↑ AMPK activity, ↓ mTOR , ↓ P-AMPKα (Thr172)	0, 50, 100, 200, 400 μM	13
	A172	Induces apoptosis	↓ A172 cell migration and invasion, ↓ ADAM9 expression, ↑ p-ERK1/2, ↓ total expression of ERK1/2	0,5,10 and 25 μM	7
Nasopharyngeal	NPC-TW 039 and NPC-TW 076	Induces p53-independent S-phase arrest and apoptosis	↑ numbers of apoptotic bodies and ↑ condensed/fragmented nuclei, ↑ DNA fragmentation, ↓ PI3K-AKT Signaling Pathway, ↑ Cleavage of procaspase-3 and PARP, induced caspase-3 activation, ↑ apoptotic cells (sub-G1-phase population), ↓ p-AKT (Ser 473), ↓ PI3K, ↓ AKT, ↑ cleavage of pro-caspase-9, ↑ p21, ↑ BAX, ↑ BAD, ↑ BAK protein expression, ↓ BCL-2, ↓ BCL-xL protein levels	0–100 μM	45
Laryngeal	TU212 and M4e	Activating apoptosis and autophagy	↓ carcinoma cell viability, migration, invasion and proliferation, ↑ Bax, ↓ Bcl-2, ↑ caspase-3, ↑ caspase-9, ↑ PARP cleavage, ↑ LC3I, ↑ LC3II, ↑ Beclin 1, ↓ Raf, ↓ Ras. ↓ p-p38, ↓ PI3K/AKT, ↓ PI3K-Akt-mTOR signaling pathway, ↑ TSC1 (inhibitor of mTOR activation), ↓ p- mTOR	0, 2.5, 5.0, 10.0, 20.0, 30.0 and 40.0 μM	42
Esophageal(galangin and berberine)	Eca9706,TE-1, and EC109	Induces apoptosis	↓ survival and growth cancer cells, cell cycle arrest at G2/M phase, ↑ ROS levels, ↓ Wnt3a, ↓ β-catenin, ↓ Cyclin B, ↓ Cyclin D, ↓ Cyclin E, ↓ CDK1, ↓ CDK2, ↓ CDK4, ↓ CDK6, ↓ transition of G2/M phase, ↑ P21, ↑ P27, ↑ P53, ↑ cleaved PARP, ↑ Caspase-3, ↓ Bcl-2, ↓ Mcl-, ↓ XIAP, ↑ Bax, ↑ PI3K, ↑ Rac, ↑ p-JAK2, ↑ p-STAT3	Galangin 0,2.5,5.0, 10.0,20.0,30.0,40.0 and 50 μM + Berberine 0,10,30,60, 90,120,160 and 200 μM	76
Retinoblastoma	Y-79, C-33A, and WERI-Rb-1	Induced apoptosis	↓ Human retinoblastoma cell proliferation and migration. ↑ PTEN, ↓ protein kinase B (Akt) phosphorylation, ↑ PIP3, ↑ PIP2, ↑ caspase-3, ↓ KI-67 positive levels, ↓ p-Akt (S473 and T308 sites), ↓ PIP2 , ↑ active Caspase-9, ↑ Caspase-3 expression levels	0, 5, 10, 20, 40, 80, and 100 uM	39
Osteosarcoma	MG-63 and U2-OS	Induced apoptosis	↓ cell proliferation, ↑ mRNA levels of Col I, ALP, OPN, and OC (osteoblastic differentiation markers), ↑ protein level of Runx2, ↑ TGF-b1 production, ↑ phosphorylation of Smad2 and Smad3	0, 25, 50 and 100 μM	90
	MG63 and U20S	Induces apoptosis	↓ proliferation, migration and invasion osteosarcoma cells, ↓ PI3K and Aktp (Thr308), ↓ cyclin D1, ↓ MMP 2/9, ↑ p27Kip1, ↑ caspase-3, ↑ caspase-8	0, 5, 10, 25, 50, 100, 200 and 300 μM	14
Fibrosarcoma	HT-1080	Inhibited metastasis	↓ MMP-9 secretion, ↓ *MMP-9* mRNA, ↓ p-JNK, ↓ activation of NF-κB and AP-1, ↑ p-IκBα, ↓ IκBα	0,10, 30 and 100 μM	91

(continued)

Table 2. Continued.

Type of Cancer	Cell lines	Effects	Mechanisms	Concentration	References
Breast	MCF-7	Induces apoptosis	↑ Bax and decreased the expression of Bcl-2, ↑ cleavage of caspase-9, ↑ caspase-8, ↑ caspase-3, ↑ Bid, ↑ Bad, ↓ p-PI3K, ↓ pAkt, ↓ cyclin D3, ↓ cyclin B1, ↓ CDK1, ↓ CDK2, ↓ CDK4, ↑ p21,↑ p27, ↑ p53	10, 20, 40, 80, and 160 μM	7
	MCF-7 and T47D	Induce apoptosis	↓ cancer cell lines viability, proliferation, ↓ BCl-2, ↑ ROS production, ↑ NADPH, ↑ caspase-3 activity, ↑ Caspase-9 activity, ↑ p-PERK, ↑ GRP78, ↑ CHOP, ↑ p-eIF2a, ↑ ATF4, ↑ p-AMPK, ↑ DR4, ↑ Caspase-9, ↑ Caspase-3 cleavage, ↑ Bax	Galangin 20 and 40 μM + TRAIL 100 and 200 ng/ml	43
Lung (galangin and cisplatin)	A549, DDP-resistant variant A549/DDP cells	Induce apoptosis	↓ cell proliferation, viability, migration and colony formation, ↓ p65 in nucleus, ↓ p-IκBα in whole cells, ↑ IκBα, ↓ p-STAT3, ↑ cleaved Caspase-3, ↑ PARP, ↓ Bcl-2, ↑ Bax, ↑ Bid	0, 2, 5 and 10 μM galangin + 2 μM DDP (cisplatin)	16
Colon	HCT-15 and HT-29	Induced apoptosis and DNA condensation	↓ cancer cell viability, ↑ nuclear rounding and shrinkage, ↓ caspase-3, ↓ caspase-9, ↑ release of apoptosis inducing factor from the mitochondria into the cytoplasm, alteration of mitochondria membrane potential and dysfunction	0, 5, 25, 50, 100 and 200 μM	10
Hepatocellular	MHCC97H	Promoted cell apoptosis	↓ *H19*, ↓ cell migration and invasion, ↓ S phase cells, mRNA of *TP53*- and p53-related genes (*CDIP1, FOS,* and *CREB3L3*) were significantly differentially expressed	0, 20, 50, 100 and 150 μM	11
	HepG2	Induces apoptosis	↓ HepG2 cell proliferation and viability, ↑cytoplasm shrinkage, disappearance of microvilli, ↑ shrinkage cytoplasm, distorted organelles and condensed chromatin ↓ mitochondrial membrane potential ↑ mitochondrial dysfunction, ↑ caspase-3 ↑ ROS production	Selenium nanoparticles with galangin (11 μM)	20
	HepG2, Hep3B and PLC/PRF/5	–	↓ proliferation of HCC cells, ↓ glucose absorption, ↓ lactate production, ↑ pyruvate kinase, ↓ Warburg effect, ↑ aerobic metabolism, ↓ glycolysis, ↓ glucose absorption, ↓ lactate production, ↑ glycolytic rate-limiting enzyme pyruvate kinase activity, ↓ Glut1, ↓ PKM2, ↓ LDHA, ↓ PDHK, ↑ HKII, ↑ PKM1, ↑ PDH, ↑ CS	0, 65, 130 and 260 μM	92
	HepG2	Induces autophagy	↑ binding of SIRT1-LC3, ↓ acetylation of endogenous LC3, ↑ LC3 II, ↑ Beclin1, ↑ ratio of LC3 II to LC3 I, ↓ p62, activating the TGF-β receptor/Smad pathway, ↑ AMP/TAN ratio, ↑ p53, ↑ glucose starvation	130 μM	70
	HepG2	Induced autophagy	↑ TGF-β receptor/Smad pathway activity, ↑ TGF-β receptor I (RI), ↑ TGF-β RII, ↑ Smad1, ↑ Smad2, ↑ Smad3, ↑ Smad4 levels, ↓ Smad6, ↓ Smad7, ↑ Beclin1, ↑ ATG16L, ↑ ATG12, ↑ ATG3 and ↑ LC3-II, ↑ number of cells with LC3 foci, ↑ TGF-β RI, ↑ TGF-β RII, ↑ phosphorylation of Smad1, Smad2 and Smad3, ↓ subG1 ratio	0, 37, 74 and 148 μM	93
	HepG2, Hep3B and PLC/PRF/5	Induce apoptosis	↓ proliferation and viability of carcinoma cells, ↑ endoplasmic reticulum stress, ↑ Ca2+ levels, ↑ GRP94, ↑ GRP78, ↑ CHOP, ↑ p38 MAPK, ↑ JNK, ↑ ERK	134.0, 87.3 and 79.8 μM	29
	HepG2, Hep3B, and PLC/PRF/5	Induced autophagy	↑ AMP/TAN, ↑p-AMPK, ↑ p- LKB1, ↓ p-AKT, ↓ p-mTOR, ↑ PARP, ↑ LC3-II, ↑ formation of autophagic vacuoles, ↑ cellular relative AMP level	0, 65,130 and 260 μM	30

(continued)

Table 2. Continued.

Type of Cancer	Cell lines	Effects	Mechanisms	Concentration	References
Liver	Chang liver, AGS, Hep3B, and HepG2	Inhibited metastasis	↓ viability of cancer cells, ↓ TPA-induced enzyme activity, ↓ MMP-2 and MMP-9, ↓PKCα, PKCδ, ↓ p-ERK1/2, phospho-IκBα, ↓c-Fos, ↓ c-Jun, ↓ NF-κB	0, 1, 2.5, 5, 10, 15, 20, 25, and 30 μM	62
Cholangiocarcinoma	HCCC9810 and CCA cell line TFK-1	Induces cell apoptosis	↓ proliferation, migration, and invasion of cancer cells, ↓ microRNA-21 (miR-21) expression, ↓ p-AKT, ↓ MMP9, ↓ Vimentin, ↑ PTEN, ↑ cleaved caspase 3 protein expression, ↑ ratio of Bax to Bcl-2	0, 50, 100, 150, or 200 μM	40
Gastric	MGC 803	Promoted apoptosis	↓ cancer cell proliferation, ↓ Ki67, ↓ PCNA, ↓ Bcl-2, ↑ cleaved caspase- 3, ↑ cleaved PARP, inactivated JAK2/STAT3 pathway, ↑ ROS, ↓ Nrf2, ↓ NQO-1, ↑ HO-1, ↓ caspase-3, ↓ p-JAK2, ↓ p-STAT3	0, 5, 10, 20, 40, 80, 120, 160 and 200 μM	9
	SNU-484	Induces apoptosis	↓ viability of SNU-484 cells, ↑ chromatin condensation and DNA damage, ↑ Bax, ↓ Bcl-2, ↓ Bcl-xl, ↑ caspase-3, -9, and PARP, protein ↓ levels of glutathione S-transferase P, ↓ peroxiredoxin 5, ↓ cytochrome c oxidase subunit 5A (mitochondrial), ↓ Bfl-1 in complex with Noxa Bh3 peptide, ↑ carboxylterminal hydrolase isozyme L1,↑ nucleoside diphosphate kinase A, ↑ eukaryotic translation initiation factor 5A-1, ↑ galectin-1	0, 25, 50,7 5, 100, 125, 150, 175 and 200 μM	94
Pancreatic	PANC-1	Induced apoptosis	↓ cell proliferation viability, ↓p-Thr-179 site at Smad3 linker region, ↓ p-CDK4, ↑ p21 (TGF-b1-induced tumor suppressor), ↑ PARP, ↑ caspase-3	0, 25, 50 and 100 μM	95
Renal	A498	Induction of Mitochondrial mediated apoptosis	↑ protein expression of Bax and Cyt-c ↓ Bcl-2, ↓ motility, Invasion and migration of the A498 cells, ↓ p-PI3K, ↓ pAKT, ↓ p-mTOR proteins, ↓ *PI3K/AKT/mTOR signaling pathway,*	0, 10, 20 and 40 μM	41
	Caki, ACHN and A498	Induce apoptosis	↑ sub-G1 population, ↑ PARP cleavage, caused chromatin damaged in the nuclei, ↓ Bcl-2 ↓ NF-κB activation, ↓ cFLIP, ↓ Mcl-1, ↓ survivin expression (at the post-translational levels), ↑ proteasome activity	0. 50. 100, 50. 200 and 250 μM + TRAIL 100, 200, 300 and 400 ng/ml	44
Prostate	PC3M and DU145,	Induced apoptosis	↓ cell proliferation viability, ↓p-Thr-179 site at Smad3 linker region, ↓ p-CDK4, ↑ p21 (TGF-b1-induced tumor suppressor), ↑ PARP, ↑ caspase-3	0, 25,50, and 100 μM	95
Cervical	HeLa	Induction of apoptosis	↓ proliferation and migration of HeLa cells, ↑ ROS production, ↓ cytotoxic metabolite methy glyoxal, ↓ Nrf-2 (a trascription factor), ↓ glyoxalase-1, ↑ oxidative and carbonyl stress, ↑ total carbonyl content (an indicator of oxidation damage)	0, 25, 50,100 and 150 μM	38
Ovarian	A2780/CP70 and OVCAR-3	Induces apoptosis	↓ proliferation of ovarian cancer cells, ↑ cleaved caspase-3, caspase-7 and PARP-1, ↓ procaspase-3, ↓ procaspase-7, ↑ DR5, ↑ cleaved caspase-8 and ↓ procaspase-8 , ↑ Bax protein, ↓ Bcl-2, ↓ procaspase-9, ↑ p53, ↑ p21 protein expressions , ↓ p-Akt, ↓ p-p70S6K, ↓ cmyc protein levels	0,10, 20, 40, 80 and 160 μM	8
	OVCAR-3 and A2780/CP70	Anti-angiogenic	↓ VEGF, ↓ p-Akt,↓ p-70S6K, ↓ HIF-1α proteins, ↓ secretion of VEGF by the Akt/p70S6K/ HIF-1α pathway,	0, 10, 20, 40, 80 and 160 μM	58

Table 3. Anti-cancer effects of galangin based on *in vivo* studies.

Type of cancer	Animal models	Effects	Mechanisms	Dosage	Duration	References
Glioblastoma	Male BALB/C Nude mice administered with 1×10^6 U87-luciferase cells	Inhibited tumor proliferation	↓ Skp2, ↓ EMT, ↑ survival galangin treated mice, ↑ ubiquitination of Skp2 in the intracranial	100 mg/kg	21 days	[12]
	Female BALB/C Nude Mice Injected Intracranially With U87-Luciferase Cells (5 × 10 5 Cells)	Inhibited tumor growth	↓ CD44 levels, ↓ vessel density, ↓ CD44, ↓ N-cadherin, ↓ Vimentin, ↓ Snail, ↓ VEGF	200 mg/kg/	28 days	[15]
	Male BALB/C Athymic mice xenografted with 3×10^5 U87MG cells	Suppressed tumor growth	↓ Ki67, ↓ cyclin-dependent kinase inhibitor p21, ↓ Bcl-2, ↑ BAX, ↑ cleaved PARP-1,	100 mg/kg	21 days	[13]
Retinoblastoma	Male, Nude mice subcutaneously injected with HXO-RB44/Y-79 suspensions (2×10^6cells)	Suppressed tumor growth	↓ KI-67, ↑ PTEN, ↑ Caspase-3, ↓ p-Akt (S473 and T308), ↓ PIP2, ↓ PIP3	15 and 30 mg/kg	21 days	[39]
Laryngeal	SPF Male BALB/C Nude Mice Subcutaneously Injected With U212 Cell Suspension (2×10^7 Cells)	Tumor suppression	↓ Ki-67, ↑ TUNEL	10, 20 and 30 mg/kg	42 days	[42]
Esophageal	SPF male BALB/C Nude mice injected subcutaneously with ECA 9706 (2×10^7 cells)	Inhibited the tumor growth	↑ TUNEL, ↑ P53, ↓ Ki-67, ↓ Wnt3a, no significant effect on AST, ALT and ALB compared to the control group	galangin group (25 mg/kg), berberine group (20 mg/kg)	35 days	[76]
Osteosarcoma (galangin and berberine)	Male BALB/C Nude mice subcutaneously injected with 1×10^7 MG-63	Tumor volume was obviously decreased	↑ Col I, ALP, OPN, and OC (osteoblastic differentiation markers), ↑ protein level Runx2, ↑ TGF-b1 production, ↑ phosphorylation of Smad2 and Smad3	50 or 100 mg/kg	28 days	[90]
Breast	Athymic nude male mice subcutaneously injected with 5×10^5 MCF-7 cells	Inhibited tumor growth	↓ toxicity to mice, ↑ CHOP, ↑ p-AMPK, ↑ DR4, ↑ cleavage Caspase 3,9	20 mg/kg and TRAIL (100 μg/mouse)	28 days	[43]
Lung (galangin and cisplatin)	Athymic Nude Male, mice injected subcutaneously with A549/DDP (5×10^6 cells)	Suppressed tumor growth	↓ p-STAT3-, ↓ p-NFκB and ↓ Bcl-2-, ↑ Cleaved Caspase-3 and PARP levels	10 mg/kg + DDP (cisplatin) 5 mg/kg	28 days	[16]
	Male swiss albino mice administered with B(a)P (50 mg/kg body weight dissolved in corn oil, orally)	Inhibits tumor initiation	↓ Cytochrome P450, ↓ Cytochrome b5, ↓ NADPH Cytochrome P450 redcutase ↓ NADPH Cytochrome b5 reductase (phase I), ↑ GST, ↑ UDP-GT, ↑ DTD	20 mg/kg body	14 days	[6]
Hepatocellular	Female nude mice xenografted with PCDNA3.1-H19, and H19-KO cells (3×10^5cells)	Inhibited tumor growth	↓ *H19*, ↓ cell migration and invasion, ↓ S phase cells, mRNA of *TP53*- and p53-related genes (*CDIP1, FOS,* and *CREB3L3*) were significantly differentially expressed	20 mg/kg	14 days	[11]
	BALB/C Athymic nude mice injected subcutaneously with HepG 2 cells (2×10^6 cells)	Suppressed tumor volume	↓p- AKT, ↓ mTOR, ↑ p-AMPK	70 mg/kg, 35 mg/kg or 17.5 mg/kg	28 days	[30]

(continued)

Table 3. Continued.

Type of cancer	Animal models	Effects	Mechanisms	Dosage	Duration	References
Gastric	Male Nude mice inoculated subcutaneously with MGC 803 cells (5×10^6 cells	Inhibited tumor growth	↓ p-JAK2/JAK2, ↓ p-STAT3/STAT3, ↓ Bcl-2, ↓ caspase-3, ↓ Ki67, ↑ cleaved caspase-3, ↑cleaved PARP	120 mg/kg	21 days	[9]
Renal	Male albino wistar rats	Ameliorates cisplatin induced nephrotoxicity	↑ Bax, ↓ Bcl-2, ↓ DNA fragmentation, ↓ NFκB ↓ p38, ↓ JNK, ↓ ERK1/2	25, 50 and 100 mg/kg (Administered orally)	10 days	[96]
Ovarian	Ovcar-3 cells (1.2×106 cells) implanted into the chorioallantoic membrane (cam) of the 9-day-old chicken embryo	Inhibit *in vivo* angiogenesis	↓ blood vessels, ↓ HIF-1α, ↓ phosphorylation of Akt and p70S6K, no effect on the expression of PTEN and NFκB (p50)	40 μM	9 days	[8]

galangin displayed no signs of toxicity in male Wistar rats at doses up to 320 mg/kg.[89] In addition, no significant histological changes were observed in the liver, renal, heart, and lung tissues of male nude mice injected intraperitoneally with galangin at 30 mg/kg, along with no alterations in the serum ALT and AST levels.[39] Tables 2 and 3 represent a bird eye view of various *in vitro* and *in vivo* anticancer applications of galangin to support its promising chemopreventive candidature in near future, respectively.

Conclusions

With the ever-increasing global cancer incidence, there is a rising need for the identification of new efficient and safe compounds as molecular leads for novel cancer drugs. In this article, the natural compound galangin is represented as a potential anticancer agent. Despite the strong *in vitro* basis of chemopreventive and chemotherapeutic properties of this compound, more *in vivo* studies with different types of tumor models are definitely needed to be performed in the future. Also, the safety issue of galangin must be clarified before moving on with the clinical trials. Last but not least, it is hoped that the use of modern nanotechnological methods will reveal the best carrier systems for delivering enough amounts of parent bioactive galangin to the target malignant tissues.

AUTHORS' CONTRIBUTIONS

HST: Literature analysis and concept; KS: Contributed in abstract and introduction section; SA and GK: Contributed in absorption and nanotechnology section; DA: Designed *in vitro* and *in vivo* tables; JK: contributed in anti-inflammation section; MK: contributed in structural description of galangin; NCP: Contributed in synergistic section; GP: contributed in apoptosis and cell cycle arrest; US and AJ: contributed in epigenetic section

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