REVIEW

Natural gypenosides: targeting cancer through different molecular pathways

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Abstract: The second foremost cause of mortality around the word is cancer. Conventional therapies, such as radiation, surgery, and chemotherapy have limited accessibility owing to secondary resistance. Therefore, convenient, safe, and nonresistant drugs are urgently needed. Plant-derived natural products have attracted considerable interest owing to their high efficacy, low toxicity, and convenience. Gypenosides (Gyp) inhibit invasion, migration, metastasis, and proliferation and induce apoptosis in different cancers, including oral, lung, colorectal, hepatocellular, and leukemic cancers through different molecular pathways. This review summarizes Gyp studies on cancer to serve as a reference for further research and clinical trials.

Keywords: cancer, surgery, chemotherapy, radiation therapy, Gyp, oral, lung, leukemic, colorectal, hepatocellular

Introduction

According to the WHO, cancer causes more deaths than stroke or any coronary heart disease.[1] Cancer cases increase because of numerous risk factors, aging, and population growth.[2] The continuous global epidemiologic and demographic transition signal shows that cancer will increase in the next decades, particularly in low- and middle-income countries and is expected to have an annual record of 20 million new cases in 2025.[3] In a 2012 cancer report, approximately 14.1 million new cases and 8.2 million deaths were recorded from 20 large areas of the world, and lung cancer was the most common (1.82 million), followed by breast cancer (1.67 million), and colorectal cancer (1.36 million). The major cause of death was also lung cancer (1.36 million), followed by liver cancer (0.745 million) and stomach cancer (0.723 million).[4] Available clinical treatment for cancer includes surgery, chemotherapy, and radiotherapy.[5] Furthermore, radiotherapy and chemotherapy can develop gradual resistance against therapy in cancer cells.[6] Therefore, novel, affordable, and effective anticancer drugs must be developed.[7] Medicinal plants provide a common alternative treatment for cancer in various countries.[8,9] Numerous natural products (NPs) were approved by the Food and Drug Administration for the treatment of cancer.[10] Many researchers reported new antitumor NPs, but their main molecular mechanisms remain incompletely understood. NP function contains different natural compounds and thus function through different pathways.[11] Systematic biology is an emerging approach that focuses on molecular interactions in biological systems.[12] Cancer is subject to complicated cell transformation processes that result in changes at the genetic, epigenetic, and

cellular levels.[13] Therefore, systematic biology can help us understand the molecular mechanisms of NPs and ultimately uncover the new window to cancer treatment.

Gynostemma pentaphyllum (GpM)-derived extracts and fractions and its derivative compounds show anticancer activity in vivo and in vitro. Several clinical trials showed that GpM has a potential curative effect on cancer.[14] GpM (Thunb) Makino, known in China as Jiaogulan, belongs to the plant family Cucurbitaceae that abundantly grows in Korea, Japan, and southern China. It is a well-known folk medicine in China; in fact, it was reported for the first time as a vegetable in a book named "Herbs for Famine," which was published in 1368–1644 AD during the Ming Dynasty.[15] Various dammarane-type gypenosides (Gyp; >170 types), which have been isolated from GpM since 1976, have attracted interest because of its potential in treating wheeze, cough, hepatitis, bronchitis, and cancer.[16–18] The major component of the GpM Makino extract is Gyp, which is a popular folk medicine in China and is often used for treating several diseases, including hyperlipoproteinemia,[19] cardiovascular diseases,[20] and hepatitis.[21] Moreover, the extract has antioxidative,[22] anti-inflammatory,[22] and anticancer properties.[14,23,24] Recently, its anticancer activities against different cancer cell lines, including esophageal cancer Eca-109 cells, human colon cancer SW620,[25] oral cancer SAS cells,[26] and cervical epidermoid carcinoma cells, have been reported.[27] However, further investigation is needed for the satisfactory definition of antitumor mechanisms of GpM[28] and its derivative (Gyp). Li et al reviewed the anticancer studies on the entire plant of GpM (Thunb);[14] however, they did not explain the anticancer effect of the compound they extracted from GpM. Gyp derived from GpM is an active compound for cancer treatment. Therefore, in this review, we summarize available studies on Gyp to provide a comprehensive reference for further research and clinical trials.

Targeting cancer with Gyp through oxidative stress

In biological systems, oxidative stress refers to the physiological disbalance in ROS level, such as H_2O_2 or O_2, as well as the capability of the body to remove it. Furthermore, oxidative stress can be defined as the disturbance in redox signaling and control.[29] ROS produced throughout the body are the by-products of cellular aerobic metabolism, ongoing stress, and exposure to UV light or X-ray.[30] It plays an important role in cell signaling and in the regulation of cytokine, growth factor, hormone action, transcription, ion transport, neuromodulation, immunomodulation, and apoptosis.[30,31] Furthermore, ROS has a fundamental role in different types of cellular processes, such as gene expression, cell survival, differentiation, proliferation, enzyme regulation, and elimination of foreign particles and pathogens.[32,33] Multiple studies showed that oxidative stress in cancer cells is high, which increases cell proliferation, survival, metastasis, and angiogenesis and disrupts cell death signaling and drug resistance.[34–36] ROS promotes tumor proliferation, although a recent research confirms that ROS is useful in cancer treatment. The phytochemical induces ROS generation in cancer cells above a threshold level, thereby killing these cells.[34,36–38] Gyp induces ROS generation in various types of cancers. In SW-480, oesophageal cancer Eca-109, SW-620, Caco2, WEHI-3, SAS, human hepatoma HepG-2, and Huh-7 cells, Gyp can induce apoptosis and inhibit cell growth and proliferation through oxidative stress and by increasing ROS generation and mitochondrial membrane potential (MMP) depolarization. Furthermore, the ROS generation can be reversed through N-acetyl-Lc-cysteine pre-treatment.[24,25,39–45] However, the exact molecular mechanism is unexplored in cancer cells and needs further clarification. Once the oxidative stress is generated, it activates several apoptotic pathways, including mitochondrial-dependent pathways (MDPs).

Targeting cancer with Gyp through intrinsic apoptosis pathway

Mitochondrial-dependent apoptosis is an important pathway for the induction of apoptosis, and disturbance in this pathway can inhibit apoptosis. The intrinsic pathway is controlled through B-cell lymphoma 2 (Bcl-2) family protein, which either increases or decreases the mitochondrial membrane permeability for the release of cytochrome-c (Cyt-c) and other apoptotic proteins.[46] A group of antiapoptotic proteins, including Bcl-2, B-cell lymphoma-extra-large (BclxL), Bcl-w, Bcl-2 related protein A1, and myeloid cell leukemia 1, possess sequence similarity in its all Bcl2-homology 1–4 domains and increase cell survival. Proapoptotic proteins include multidomain Bcl-2-associated X (BAX), Bcl-2 homologous killer (BAK), and BH3-only protein. These proteins function as receptor mediators that induce endoplasmic reticulum (ER) or mitochondrial stress-dependent apoptosis.[47]

BH3-only proteins have two subclasses, one of which one is an "activator" and includes total BH3 interacting-domain death antagonist and Bcl-2-like protein 11. This subclass directly activates the BAX/BAK to cause MMP depolarization. The second subclass includes "sensitizers/derepressors," such as Bcl-2 interacting killer, Bcl-2-associated death promoter, Bcl-2-modifying factor, phorbol-12-myristate-13-acetate-induced protein 1, hara-kiri, and p53 upregulated modulator of apoptosis. This subclass neutralizes antiapoptotic proteins instead of directly activating BAX/BAK.[48,49] Meanwhile, antiapoptotic proteins block death signaling by directly inhibiting the activation of BAX/BAK or activator BH3-only proteins.[50] Antiapoptotic proteins, including Bcl-2 and Bclxl, are involved in cancer progression[51] and thereby induce the resistance of tumor cells to many types of apoptotic stimuli, including cytotoxic anticancer drugs.[49] Gyps target MDPs through pro- and antiapoptotic protein modulation and promote apoptosis. In Colo 205, WEHI-3, HL-60 cells, SCC-4, SAS, and human hepatoma Huh-7 and A549 cells, Gyps induce morphological changes and apoptosis and inhibit cell proliferation by targeting MDPs.[40,41,43–45,52–54] Moreover, Gyps inhibit Bcl-xl and Bcl-2 and upregulate BAX, thus promoting the release of Cyt-c and Endo G from the mitochondria. Upon Cyt-c release, caspase-3,9 is activated, and poly (ADP-ribose) polymerases (PARP) are subsequently upregulated. The PARPs then enter the nucleus and cause DNA damage, alter cell morphology, inhibit proliferation, and induce apoptotic death.[40,41,43–45,52–54]

Targeting cancer with Gyp through extrinsic apoptosis pathway

The extrinsic pathway is activated through tumor necrosis factor (TNF) family proteins, including Fas or TNF receptor-1 [TNFR1]). These proteins engage the death domain (DD)-containing receptors and activate the death effector domain, which contains capases. Moreover, the death legends expressed on cytotoxic T cells, natural killer cells (NKs), and other types of relevant cells eradicate transforming cells.[55] Fas or TNFR1 activates caspase-8 through the Fas-associated death domain protein and forms a death-inducing signaling complex that activates caspase-3 and promote cell death.[56,57] Gyp modulates the extrinsic apoptosis pathway. In SAS cells, Gyp activates the extrinsic pathway and then caspase-8 through the activation of Fas/FasL. It also activates caspase-3 and PARP and damages the DNA and induces apoptosis.[44,53]

Targeting cancer with Gyp through ER stress

The ERis involved in sensing, synthesis, and signaling in eukaryotic cells. The ER must tightly regulate oxidizing and Ca2+-rich folding environments to perform these functions. Protein folding and Ca^{2+} buffering in the ER are regulated by several chaperones, including calreticulin, calnexin, protein disulfide isomerases, and glucose-regulated protein GRP78 (BiP). Several pathophysiological conditions, such as hypoxia, ER-Ca^{2+} depletion, hypoglycemia, viral infections, and oxidative injury affect the homeostasis of ER and disrupt protein folding load and capacity, thereby causing ER stress. The ER responds to these changes by activating an integrated signal transduction pathway, and this process is called unfolded protein response (UPR).[58] The UPR regulates ER homeostasis by coordinating the complex processes of gene transcription, activates ER folding machinery components, and controls ER quality and ER-associated degradation (ERAD) pathway. However, as ER stress intensifies, the UPR consequently changes from prosurvival to prodeath response and usually ends in the activation of intrinsic apoptosis.[59] In mammals, protein kinase RNA-like endoplasmic reticulum kinase (PERK), activating transcription factor-6 (ATF6), and inositol-requiring enzyme 1 are ER stress transducer proteins that activate survival and apoptotic pathways. When the UPR exhibits prosurvival response, it activates ER chaperones, translational attenuation, and ERAD; conversely, it activates C/EBP homologous protein 10 (CHOP)/GADD153 and caspase-12 when the response is proapoptosis.[60] In cancer, ER stress apoptotic proteins are usually downregulated, and Gyp increases ER stress and consequently induces cell apoptosis. In HL-60, WEHI-3 cells Gyp ROS mediate ER stress by increasing GADD153, GRP78, PERK, and ATF6-α ATF4-α levels, thereby activating caspase-12, which in turn activates caspase-3,7 and PARP; these processes instigate DNA fragmentation and compel the cells toward apoptosis.[39,40,41,52,54]

Targeting cancer with Gyp through the cell cycle pathway

Cell growth is regulated by a major process called the cell cycle and at different checkpoints by different cyclin interactions among specific cyclin-dependent kinases (CDKs) that form active complexes. The process at each checkpoint completes before the progression to the next phase of the cell cycle.[61] Moreover, different CDK inhibitors

negatively regulate CDKs. Among CDKs, p21 regulates cell cycle at different checkpoints.[62,63] The failure of the checkpoints induces mutation and genomic rearrangements, causing genetic disturbance, and ultimately cancer.[63] Meanwhile, p53 has a key component role in cell cycle regulation. It becomes active to a wide range of damage and stresses.[64,65] When activated by genotoxic stress, p53 regulates the p21WAF1/CIP1/SDI1 gene encoding CDK universal inhibitors that inhibit cell cycle progression.[66] Many studies suggest that anticancer compounds arrest the cell cycle selective checkpoints and cause death to cancer cells through apoptosis.[67] Gyp induces cell cycle arrest in different types of cancer cells. Gyp causes DNA damage in SCC-4, SW-620, Caco2, SW-480, and rat hepatic stellate cells. DNA damage activates checkpoint protein 2 (Chk2), which in turn activates p53 and p21, inhibits Cdk2 and cyclin E, and promotes G1S and G0G1 phase cell cycle arrest. Furthermore, Gyp activates p27, p21, and p16, which inhibit Cdk2, cyclin E, and cyclin D1/3K, CDK4/6 and promote G1S and G0G1 phase cell cycle arrest.[39–42,52–54,68]

Targeting cancer with Gyp through DNA repairing pathway

Cell homeostasis is maintained through the preservation of its genomic integrity. DNA damage response (DDR) reverses intrinsic and extrinsic DNA damage and transmits the genome to new dividing cells, which are required for cell survival during replication. Genotoxic drugs and radiations are used for treating cancer, but the DNA repair mechanism contributes to resistance to chemotherapy and radiotherapy. Resistance can be prevented, and the efficacy of cancer therapies can be increased by using inhibitors against DDR major components, including ataxia telangiectasia mutated (ATM), ATM and Rad-related (ATR), DNA-dependent protein kinase, catalytic subunit (DNA-PK), and checkpoint protein 1 and 2 to confer chemo- and radiosensitivity in cancer cells.[69] Gyp has an important role in DNA-repairing gene regulation for overcoming cancer. Specifically, Gyp decreases cell viability and induces death in SAS cells and human oral cancer, and these processes are correlated with inreased DNA migration and decreased expression levels of 14-3-3σ, DNA-PK, ATM, ataxia-telangiectasia, p53, ATR, and breast cancer gene 1 at mRNA. Furthermore, Gyp induces DNA damage in SAS cells and inhibits the expression of DNA-repairing genes.[70]

Targeting cancer with Gyp through the PI3K/AKT/mTOR pathway

Phosphatidylinositol-3-kinase, protein kinase B, and the mammalian target of the rapamycin signaling pathway increase cell survival and growth through different mechanisms.[71,72] In different types of human cancers, the PI3K/AKT pathway is overexpressed through different mechanisms.[73–76] The phosphorylation of two AKT residues, including serine 473 and threonine 308, leads to AKT activation.[77] Subsequently, AKT enters the nucleus and modulates the activities of several factors regulating transcription. The mammalian target of rapamycin (mTOR) becomes phosphorylated because of the PI3K/AKT signaling, and its overexpression is associated with poor recovery. NPs have attracted considerable interest because they potentially kill cancer cells through different mechanisms. For example, Gyp inhibits the proliferation of SAS, SCC-4, and PDGF-induced rat hepatic stellate cells through the PI3K/AKT pathway and by downregulating PI3K, AKT, and P70SK phosphorylation.[26,68,78] Furthermore, in SAS cells and SCC-4 cells, Gyp targets the PI3K pathway through downregulation of son of sevenless (SOS), RAS, urokinase-type plasminogen activator (uPA), and focal adhesion kinase (FAK), which further inhibit PI3K and Rho-A. As a result, they inhibit MMP-2,7,9 and ultimately inhibit cell invasion, migration, and metastasis, as shown in Figure 2 and Table 1.[26,78]

Targeting cancer with Gyp through nuclear factor-kB (NF-kB) pathway

The NF-kB is a transcription factor complex consisting of hetero- and homodimers of five members of a Rel family, such as RelA (p65), RelB, c-Rel, NFkB1 (p50/p105), and NF-kB2 (p52/p100.[79] The functions of NF-kB are mostly deregulated in cancer.[80] NF-kB activation, which has been found in a variety of cancers, including leukemia, lymphoma, colon, breast, liver, prostate, pancreas, and ovarian cancers, is associated with aggressiveness, tumorigenesis, poor survival, and chemoresistance.[81–83] NF-kB activation occurs in response to DNA damage, which consequently activates various NF-kB target genes, including COX-2[84] and iNOS.[85] These genes have a pivotal role in prosurvival antiapoptosis. Therefore, NF-kB is the candidate of therapeutic resistance in different cancers. Gyp targets the NF-kB pathway to cure cancer. In SAS cells and SCC-4 cells, Gyp targets NF-kB pathway through

Table I Effect of Gyp on different cancer cell lines, proteins or genes involved and its mechanism

Cancer Name	Cell lines	Ions/ Genes/ Proteins involved	Animals Model	Mode of action	Ref
Colorectal cancer	Colo-205 cells	Ca+↑,ROS↑, MMP↓, Bcl-xl↓, Bcl-2↓ BAX↑ p53↑, p21↑, Cytochrome-c↑, Caspase-3↑ DNA fragmentation↑	No	Cell cycle arrest, Apoptosis	52
	SW-480 cells	Dym↓, ROS↑, DNA fragmentation↑	No	Apoptosis, Collapse microfilament network	24
	Eca-109, SW620 cells	ROS↑, MMP↓	No	Apoptosis, Inhibit cells proliferation and migration	25
	SW-620, Caco2, SW-480	ROS↑, Caspase-3,9↑, PARP↑, p-53↑	Mouse model	G0/G1 phase cell cycle arrest, Apoptosis	39
Leukemic Cancer	WEHI-3 cells	Ca2+↑, ROS↑, MMP↓, Bcl-2, BAX↑ Cytochrome c↑, AIF↑, Endo G↑ ATF4-α↑, ATF6-α↑ GADD153↑, GRP78↑, DNA fragmentation↑	Mouse model	G0/G1 phase cell cycle arrest, ER stress, Apoptosis	40
	HL-60 cells	DNA fragmentation↑, ROS↑, MMP↓, BAX↑, Bcl-2↓, Ca2+↑, ATF4↑, ATF6↑	Mouse model	G0/G1 phase cell cycle arrest, apoptosis	41
Oral Cancer	SAS cells,	14-3-3σ↓, DNAPK (DNA-dependent serine/threonine protein kinase) ↓, ATM↓, ataxia-telangiectasia↓, p53↓, ATR↓, BRCA1↓, DNA damage↑	No	Apoptosis	70
	HSC-3 cells	MMP↓, GTP binding protein↑, Serpine peptidase inhibitor↑, clade E↑, member 1↑; ras homolog family member B↑, interleukin 11↑, kelch repeat↑, BTB domain containing 8↑; activating transcription factor 3↑; Cytochrome P450↑, family 1↑; ADP-ribosylation factor-like↑; transfer RNA selenocysteine 2↑; and syntaxin 11↑, Six-transmembrane epithelial antigen of prostate family member 4↓; γ-aminobutyric acid A receptor↓; transcriptional-regulating factor 1↓; serpin peptidase inhibitor↓, clade B, member 13↓; apolipoprotein L1↓; follistatin↓; uncharacterized LOC100506718↓; fibronectin leucine rich transmembrane protein 2↓; microRNA 205↓; neuregulin 1↓; G protein-coupled receptor 110↓.	No	G2/M phase cell cycle arrest, Apoptosis	42
	SCC-4 cells	ROS↑, MMP↓, Ca2+ release↑, Bclxl↓, Bcl-2↓, BAX, Cytochrome c↑, Endo G↑, GADD153↑, DNA fragmentation↑	No	G0/ G1 phase cell cycle arrest and apoptosis	43
	SAS cells	ROS↑, intracellular Ca2+ levels↑, MMP↓, Bcl-2↓, Bclxl↓, BAX↑, Cytochrome-c↑, Endo G↑, GADD153↑,	Murine Xenograft Model	G0/G1 phase arrest, Apoptosis	78
	SAS cells	NF-kB↓, COX-2↓, MMP-9,2↓, ERK1/2↓, SOS↓, Ras↓, uPA↓, FAK↓, Akt↓ proteins, MMP-2,7, 9↓ at mRNA	No	Inhibits migration and invasion	26
	SCC-4 cells	ERK1/2↓, MMP-9↓, RAS↓, NF-kB↓, COX-2↓	No	Inhibit invasion and migration	44
Hepatocellular cancer	HSC	Akt↓, P70SK↓, Cyclin D1 and D3↓	No	Cells inhibition, G1 phase cell cycle arrest	68
	Huh-7 cells	(Ca)2+)↑, ROS↑, MPT↓, ERK↓, Bcl-2↓, BAX↑,	No	Apoptosis	45

(Continued)

Table 1 (Continued).

Cancer Name	Cell lines	Ions/ Genes/ Proteins involved	Animals Model	Mode of action	Ref
Lungs Cancer	A549 cells	Bcl-2↓, BAX↑, DNA degradation factor 35 KD↑, p53↑, p21↑, Cyclin A↑, Cyclin B↑	No	Growth inhibition, Apoptosis, S phase and G2/M phase cell cycle arrest	53
	A549 cells	Bcl-2↓, BAX↑, Caspase-3,9↑, p53↑, p21↑, p27↑, p16↑, Cyclin E↓, CDK2↓	No	Apoptosis, G0/G1 phase cell cycle arrest	54

Abbreviations: MMP, mitochondrial membrane potential; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; ATF, activating transcription factor; ATM, ataxia telangiectasia mutated.

downregulation of SOS, RAS, uPA, and FAK. These genes further downregulate AKT, NF-kB, iNOS, and COX-2, which activate p53. As a result, MMP-2,7,9 is inhibited, which decreases cell invasion, migration, and metastasis as depicted in Figure 2 and Table 1.[26,78]

Targeting cancer with Gyp through mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) (Ras-Raf-MEK-ERK) pathway

MAPK/ERK pathway, also known as the Ras-Raf-MEK-ERK pathway, possesses several cascades and is mostly deregulated in human cancers.[86] It regulates many cell functions, including apoptosis, differentiation, cell growth, proliferation, senescence, and migration.[87] The MAPK/ERK pathway molecules are activated through its phosphorylation. When ERK is activated, it enters the nucleus where transcription factor phosphorylation occurs due to it. When these transcription factors phosphorylate, they bind to the promoter region of various genes including cytokines and growth factors. Such genes are responsible for the reduction in apoptosis and elevation in cell proliferation.[88] When the normal signaling of this pathway is disturbed, they cause senescence, drug resistance, and tumorigenesis.[87,89,90] In many human cancers, failure is detected in this pathway.[91,92] Therefore, targeting the MAPK/ERK pathway, especially with NP including Gyp, may open a new window for cancer treatment. In SAS cells and SCC-4 cells, Gyp targets the ERK1/2 pathway through downregulation of SOS, RAS, uPA, and FAK). These genes further downregulate side ERK1/2, and directly downregulate the matrix metalloproteinase-2,7,9, thereby inhibiting cell invasion, migration, and metastasis as illustrated in Figure 2 and Table 1.[26,78]

Conclusions

The studies indicated that Gyp has therapeutic potential in the treatment of different cancers owing to its low toxicity owing and a long history of human use. Furthermore, it induces apoptosis through different molecular pathways and can thus be used in combination with other drugs to overcome resistance to available targeted drugs. More preclinical and clinical studies are needed to design and conduct a definite dose of Gyp for various types of cancer and for specific pathways or genes. Available anticancer
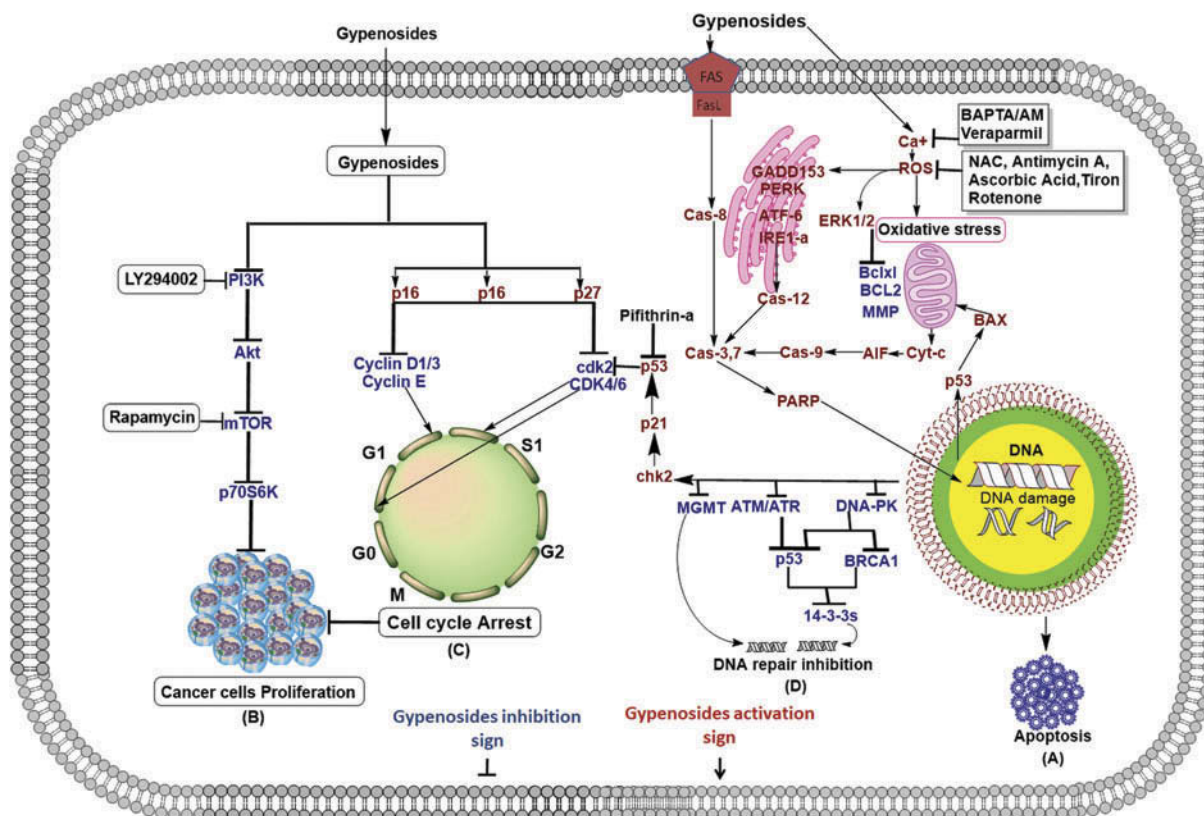
Figure 1 Gyp induces apoptosis, causes cell cycle arrest, and inhibits cell proliferation and DNA repair. (**A**). Gyp increases Ca+ and ROS generation. ROS inhibits MMP and modulates the mitochondrial proteins directly or through the activation of ERK1/2. Consequently, the rate of cytochrome C and AIF translocation from the mitochondria to the cytoplasm increases, and activated caspase-9, in turn, activates caspase-3,7. However, ROS generation induces endoplasmic reticulum stress by activating oxidation-inducing proteins GADD153, PERK, ATF6, and IRE-α. Consequently, they activate caspase-12, which further activates caspase-3,7. Similarly, caspase-3,7 is activated by activating Fas, Fasl, and caspase-8. Activated caspase-3,7 causes DNA damage in cancer cells, leads to cell apoptosis and (**B**) activates chk-2, p53, and p21, which inhibit CDK2 and cyclin E. However, Gyp inhibits CDK2 and cyclin E by activating p16, p21, and p27. Then, the cells undergo S and G0G1 phase cell cycle arrest. Furthermore, the activated p16, p21, and p27 inhibit the cyclin D1/3k and CDK4/6, leading to S phase cell cycle arrest. (**C**) Gyp inhibits cancer cell proliferation through two mechanisms. First, when the cell cycle arrest occurs, cell proliferation is inhibited. Second, Gyp inhibits PI3K, AKT, and p70S6K and cell proliferation. (**D**). Gyp inhibits DNA-repairing genes including MGMT, DNAPK, ATM/ATR, p53, BRCA1, and 14–3–3σ at mRNA level and inhibits DNA repair.
Abbreviations: Gyp, gypenosides; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; ATF6, activating transcription factor-6; BRCA1, breast cancer gene 1; IRE, inositol-requiring enzyme; ATM, ATM, ataxia telangiectasia mutated; ATR, ATR, ATM and Rad-related.

information about Gyp is summarized in Table 1 and Figures 1 and 2.

Abbreviation list

GpM, *Gynostemma pentaphyllum;* Gyp, gypenosides MMP, mitochondrial membrane potential; Bcl-2, B-cell lymphoma 2; Cyt-c, cytochrome-c; BclxL, B-cell lymphoma-extra-large; Bfl-1/A1, Bcl-2-related protein A1; Mcl-1, myeloid cell leukemia 1; BH1-Bh4, Bcl2-homology 1–4; BAX, Bcl-2-associated X; BAK, Bcl-2 homologous killer; tBid, total BH3 interacting domain death antagonist; Bim, Bcl-2-like protein 11; Bik, Bcl-2 interacting killer; Bad, Bcl-2-associated death promoter; BmF, Bcl-2-modifying factor; Noxa, phorbol-12-myristate-13-acetate-induced protein 1; Hrk, harakiri; Puma, p53 upregulated modulator of apoptosis; MDP, mitochondrial-dependent pathway; PARP, poly (ADP-Ribose) polymerases; DNA, deoxyribonucleic acid; TNF, tumor necrosis factor; TNFR1, TNF receptor-1; ER, endoplasmic reticulum; ; UPR, unfolded protein response; ERAD, ER-associated degradation; PERK, protein kinase RNA-like endoplasmic reticulum kinase; ATF6, activating transcription factor-6; IRE1, inositol-requiring enzyme 1; CHOP, C/EBP homologous protein 10; CDKs, cyclin-dependent kinases; DDR, DNA damage response; ATM, ataxia telangiectasia mutated; ATR, ATM and Rad-related; DNA-PK, DNA-dependent protein kinase, catalytic subunit; Chk1, Chk2, checkpoint protein 1 and 2; BRCA1, breast cancer gene one; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor-kB; MAPK/ERK, mitogen-activated protein kinase/extracellular signal regulated kinases; uPA, urokinase type plasminogen activator; FAK, focal adhesion kinase.
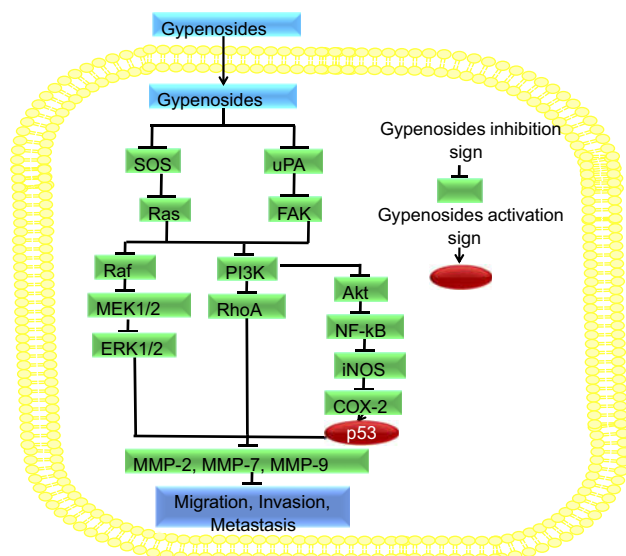
Figure 2 Gyp inhibits migration, invasion, and metastasis. Gyp downregulates SOS, RAS, uPA, and FAK, which in turn downregulates Raf, MEK1/2, and ERK1/2. These proteins directly downregulate MMP-2,7,9. On the other side, they inhibit PI3K, which downregulates Rho-A, as well as Akt, NF-kB, COX-2, which further inhibit MMP-2,7,9 and invasion, migration, and metastasis.
Abbreviations: Gyp, gypenosides; MMP, mitochondrial membrane potential.

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Disclosure

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