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REVIEW

An Updated Review of Molecular Mechanisms Implicated with the Anticancer Potential of Diosgenin and Its Nanoformulations

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Abstract: Dietary components have gained broader recognition in preventing and managing numerous human carcinomas. Plant-derived natural compounds offer several benefits, including their limited toxicity and multi-targeted agents in modulating deregulated oncogenic pathways, including PI3K/AKT, NF-κB/STAT3, and HIF-1α, and hence, they emerged as better chemotherapeutic alternatives. Diosgenin (phytosteroidal saponin) and its nanoformulations have been extensively reported to impact cancer progression and metastasis. Research has indicated that diosgenin and its nanoformulations possess significant anticancer potential with improved bioavailability. However, novelty of this review relies on compiling the updated anticancer role of diosgenin and its nanoformulations in modulating numerous oncogenic targets associated with carcinogenesis and metastasis. Diosgenin has also been utilized with traditional therapies to enhance the sensitivity of cancerous cells towards normal chemotherapeutic processes. More focus should be given to gain detailed insights about the mechanisms associated with the anticancer potential of diosgenin and its nanoformulations, which can further potentiate its candidature in developing efficient cancer therapies. However, more preclinical studies are warranted to exploit the anticancer efficacy of this plant-based compound in an efficient manner.

Keywords: diosgenin, nano-formulations, sapogenin, anticancer, signaling pathways, chemotherapeutics

Introduction

The modern era has been witnessing an escalating number of cancer cases, thereby making it a significant contributor to mortality and morbidity globally.[1,2] The pathophysiology of cancer is complex, involving environmental, genetic, and epigenetic factors.[3,4] Numerous research has highlighted the utilization of dietary components in elucidating potent anticancer agents.[5] Several strategies have been elucidated to explain the metastasis and progression of various human carcinomas.[6,7] One such strategy involved the utilization of bioactive compounds for modulating these oncogenic signaling pathways, which is crucial in chemoprevention and treatment.[8,9] Natural compounds regulating these oncogenic signaling pathways emerged as a prospective candidate for cancer therapeutics.[10] High toxicity and deleterious effects of prevalent chemotherapeutic agents have instigated researchers, medical practitioners, and patients to focus on phytomedicine.[11] Phytochemicals exhibited significant anticancer efficacy at various phases of cancer progression, including minimal side effects and cost-effectiveness.[12] Steroidal sapogenins are reported in numerous natural compound

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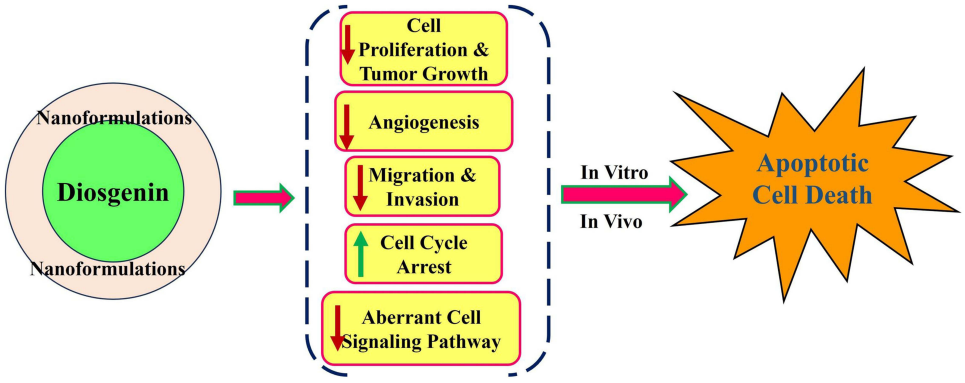
Graphical Abstract



in glycoside form, which helps in improving overall health.[13] Most steroidal sapogenins projected pharmacological benefits in vitro and several preclinical animal studies.[14]

Diosgenin (natural sapogenin) is a principal bioactive steroid reported in dietary fenugreek seeds.[15] Diosgenin is a breastfeeding aid with hypocholesterolemic,[16] gastroprotective,[17] hepatoprotective,[18] antioxidant, anti-inflammatory,[19] antidiabetic,[20] and anticancerous properties.[21] Diosgenin has been demonstrated to exhibit beneficial effects against several malignancies, including lung, pancreatic, colon, liver, prostate, breast, and leukemia. Diosgenin suppressed the proliferation of human leukemia (chronic myeloid) cells and promoted megakaryocytic differentiation via multiple pathways.[22] Diosgenin has been suggested as an optimal hydrophobic moiety in the cationic liposomal formulation for significant gene transfection.[23] Diosgenin also inhibited the proliferation of cancer cells by obstructing the thioredoxin pathway.[24] Due to its safety and multifaceted anticancer properties, diosgenin can be a promising phytoconstituent in cancer treatment. Diosgenin is reported as an essential precursor needed for the synthesis of steroids used in medical and health industry.[25] Diosgenin performs multiple functions, including serving as a principal energy source and as precursors associated with the synthesis of cellular lipids and regulating gene expression via transcription factors. Numerous studies suggested that diosgenin functions as a potent multitargeted chemopreventive drug in cervical cancer management.[26] Therefore, more potent techniques should be investigated for extracting diosgenin from various natural sources and establishing prescription dosages for its administration. This biologically active steroidal sapogenin possesses a structure analogous to cholesterol and other steroids. The pharmaceutical industry has utilized it as a precursor in the manufacture of steroid hormones and various medications. Previous investigations have demonstrated that diosgenin can inhibit tumor formation and progression.[27] The exact methods via which diosgenin induces anticancer effects in several cancer cells have yet to be completely clarified. Substantial gaps persist regarding the impact of diosgenin on various cancer hallmarks, particularly the metabolic reprogramming characteristic of cancer cells, which is marked by increased glycolytic activity and lactate production at the expense of oxidative phosphorylation, even under aerobic conditions.[28]

Nanotechnology is employed in the pharmaceutical sector for ailment diagnosis and treatment,[29,30] which entailed both creation and utilization of devices functioning at the nanoscale level. As the NIH states, nanomedicine uses nanotechnology for diagnostic and therapeutic purposes.[31] Nanomedicine is emerging as a prominent therapeutic strategy for cancer. Nanosized carriers, including polymeric nanoparticles, liposomes, and micelles, are leading innovations in efficiently delivering therapeutic drugs to tumor sites.[31] Nanoparticles (NPs) significantly enhance pharmaceutical administration due to their superior stability and reduced drug leakage.[32–34] Limited reviews have deciphered the anticancerous potential of diosgenin which motivated us to compile this study in order to project a potent lead candidate for the management of human carcinoma. This comprehensive review investigates the role of diosgenin and its nanoformulations in the treatment of diverse human carcinomas. Overall, diosgenin nanoparticles exhibited considerable

anticancer efficacy relative to the free drug in cancer cells. This comprehensive review investigated the anticancer mode of action of diosgenin along with its nanoformulations against numerous human carcinomas.

Plant Sources of Diosgenin

Diosgenin ($C_{27}H_{42}O_3$) is a naturally occurring steroidal sapogenin classified within the spirostanol group. The compound was identified as (3β, 25R)-spirost-5-en-3-ol, also known and found prevalent in species belonging to *Leguminosae* family and Dioscorea genus. Major diosgenin sources comprised *Trigonella foenum graecum, Dioscorea Linn, Rhizoma polygonati, Smilax China, Solanum xanthocarpum, Dioscorea villosa*, and *Solanum incanum*. Commercial extraction has been performed using wild yam tubers and rootstocks.[35] Dioscorea species have been reported to prevent the degradation of traditional meals and regarded as arbitrary medicines during deprivation and threat. The bioactive component reported in yams, ie, diosgenin, has garnered significant attention from researchers due to potential benefits of this compound.[36] Diosgenin distribution was observed in the rhizomes, seeds, tubers, and plant roots. *Costus speciosus* and *Trivilium govanium* exhibited diosgenin concentrations of 2.12% and 2.5%, respectively. The seeds of fenugreek[16] and DZW are reported to be the significant diosgenin sources, which are present in glycoside form.[20] Approximately 137 Dioscorea species were identified in which about 41 species exhibited diosgenin concentrations exceeding 1%. Diosgenin is a potential constituent of numerous edible tubers and pulses. It has been predominantly reported in the tubers of plants from both *Costus* and *Dioscorea* families, along with the seeds of Trigonella. Additionally, it can be obtained in the form of saponins, which are characterized by glycosidic linkages that connect rhamnose or glucose to its aglycone structure. Diosgenin is also present in rhizomes of *Paris polyphylla* and is also reported at higher concentrations in *Kallstroemia pubescens* tubers.[37,38] Another plant, namely *Asparagus officinalis* L., also contained a range of chemical constituents, including flavonoids and steroidal saponins. The predominant compounds identified in the edible shoots were diosgenin and sapongenin. Among these, *Dioscorea nipponica Makino* (tuberous perennial herb) is primarily used for diosgenin production.[39]

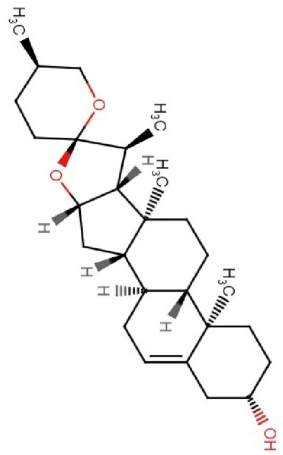
Biosynthesis and Bioavailability of Diosgenin

Diosgenin is classified as a C27 spiroketal steroid, with its IUPAC formulae being (3β, 25R)-spirost-5-en-3-ol.[40] It is manifested as an amorphous (light) powder or crystalline structure resembling white needles. Diosgenin exhibited remarkable stability under a range of physical conditions, including temperature, thermal, chemical, and light variation.[41] Diosgenin is not soluble in water and possesses a pronounced hydrophobic nature, with its solubility (approx. 0.7 ng/mL) in aqueous medium. Nonetheless, it exhibited remarkable solubility in a range of nonpolar organic solvents, namely propyl acetate, chloroform, ethyl acetate, propanol, and dichloroethane, as well as in partial polar solvents like methanol, acetone, and anhydrous ethanol.[42,43] Diosgenin is synthesized in various plants from cholesterol via the isoprenoid pathway. This pathway mainly encompasses acetyl-CoA and entails several stages for generating squalene, which subsequently undergoes cyclization to form lanosterol and is then transformed into cholesterol through a series of enzymatic reactions. Cholesterol undergoes a sequential transformation into spirostanols, glycosides, and furostanols. Furthermore, glycosides get transformed into spirostanols followed by the elimination of glucose molecules at C26 position, which finally resulted in ring closure during glucosidase-mediated catalysis. These carbohydrate moieties augmented solubility and efficacy of diosgenin.[44,45] Diosgenin exhibited near-total insolubility in water, with a log P-value (5.7).[46]

Pharmacological Relevance of Diosgenin

Pharmacokinetic studies revealed that degradation rates of diosgenin in gastric (8.59%) and intestinal juices (4.8%) over a 2-hour period were thereby indicating superior stability in GI tract over dioscin.[47] Chemical structure of diosgenin constrains its solubility and dissolution rate, with low bioavailability (only 7%).[48] Thus, one efficient way to increase diosgenin's oral absorption is to make it more soluble through processes like prodrug creation, micronization, and solid dispersion;[49] however, this method is not without its drawbacks, including the requirement for substantial matrix material, limited drug loading capacity, and an extended preparation duration. Furthermore, information related to ADMET properties, physicochemical properties, and drug-likeness profile of diosgenin is shown in Table 1.

Table 1 Physiochemical and Drug Likeliness Properties of Diosgenin

Compound	Property	Parameters	
Diosgenin 	Physiochemical and drug-likeliness	MW (g/mol)	414.31
		mLogP	5.679
		No. H-bond acceptors	3
		Molar Refractivity	121.59
		No. H-bond donor	1
		TPSA	38.69
		nRot	0
		Lipinski's Rule	Yes
		Muegge's Rule	No
		Veber's Rule	Yes
		Egan's Rule	Yes
		Ghose's Rule	No
	Absorption	Intestinal absorption-(human)	0.003
	Distribution	Volume Distribution	1.77
		BBB permeability	0.447
		Plasma Protein Binding	96.01%
	Metabolism	CYP1A2 inhibitor	No
		CYP3A4 inhibitor	No
		CYP2C9 inhibitor	No
		CYP2D6 inhibitor	No
		CYP2C19 inhibitor	No
	Toxicity	AMES toxicity	No
		Hepatotoxicity	No
	Excretion	Clearance	13.253
		$T_{1/2}$	0.074

Therapeutic Potential of Diosgenin and Its Analogs Against Human Cancers

Numerous diosgenin compounds have been documented to provide considerable anticancer efficacy. Two series of novel-synthesized diosgenin derivatives including [1,3,4-oxadiazole (6a−6e and 7a−7e) or 1,3,4-thiadiazole (8a−8e and 9a−9e) moieties] were evaluated for their cytotoxicity in four cancer cells (MCF-7, HepG2, A549, and HCT-116) as well as normal human gastric epithelial (GES-1) cells utilizing MTT assay (in vitro). Compounds 8d and 9d demonstrated substantial cytotoxicity against A549 and HepG2 cells, exceeding the potential of their parent (diosgenin) molecule. The thiadiazole compound series typically demonstrated enhanced cytotoxicity relative to oxadiazole series against A549 and HepG2 cells, with the incorporation of a 3-pyridyl group at C5 position of thiadiazole ring being the optimal choice for exhibiting notable cytotoxic effects. Compound 8d displayed significant cytotoxicity action against A549 cell line, surpassing diosgenin potency. Furthermore, chemical 8d exhibited less toxicity towards GES-1 cells, demonstrating selectivity between normal and malignant cells. Subsequent investigations into A549 cellular mechanisms revealed

mitochondrial-mediated apoptotic induction via reduced MMP, upregulated Bax, downregulated Bcl-2, and activated caspase cascade.[50] Angiogenesis is considered as crucial parameters involved in cancer progression and occurrence. There has been significant interest in advancing anti-angiogenesis therapies to impede tumor vascularization. Diosgenin suppressed tumor angiogenesis via modulation of GRP78-mediated VEGF/VEGFR and HIF-1α signaling pathways. Diosgenin inhibited angiogenesis by inducing apoptosis and reducing the cell viability of hypoxic HUVEC. Hypoxic microenvironment markedly enhanced expression levels of VEGF/VEGFR, HIF-1α, GRP78, FAK, PI3K/AKT, and ERK proteins in angiogenesis-related pathways and further augmented their phosphorylation. Following the suppression of GRP78, the angiogenesis-associated pathway proteins HIF-1α and VEGF/VEGFR were notably reduced, thereby reducing the activation of FAK, AKT, and ERK1/2 FAK. The anti-tumor angiogenesis of diosgenin involved the inhibition of PI3K/AKT, HIF-1α, GRP78, FAK, VEGF/VEGFR, ERK1/2, and PI3K/AKT signaling pathways.[51] Consequently, we have encapsulated the anticancer efficacy of diosgenin and its derivatives across many human carcinomas, including breast, liver, lung, osteosarcoma, pancreatic, and squamous cell carcinoma (Table 2).

Table 2 Anticancer Potential of Diosgenin (With Their Mode of Action) in Several Human Carcinomas

Cancer Type	Cancer cells/Animal model	Molecular Mechanism	IC50 Value	Reference
Breast Cancer	MDA-MB-231 cells	Via inhibition of actin polymerization, Vav2 phosphorylation and Cdc42 activation	5 μM	[52]
	Human MCF7 and MDA-MB-231 cells	Via reducing cell invasion, apoptosis induction and Skp2 suppression	50 μM	[53]
	MCF-7 cells	Via inhibition of cell proliferation and apoptosis induction	45.54 μM	[54]
	MCF-7 and Hs578T cells	Via cell growth inhibition, cell cycle arrest, and mitochondria-mediated apoptosis induction	15.12 μM	[55]
	NMU-induced female Sprague Dawley rats	Via reducing peroxidation reaction and marker enzymes through enhancing the intrinsic antioxidant defense system	50 μM	[56]
	MCF-7 cells	Via inhibiting cell viability and increasing DR4 and caspase-3 expression levels	32.62 μg/mL	[57]
Prostate cancer	PC-3 cells	Via reducing MMPs expression and inhibiting ERK, JNK, NF-κB and PI3K/Akt signaling pathways	30μM	[58]
Prostate cancer	PC-3 cells	Via inhibiting NEDD4 expression levels, cellular growth, promoting apoptosis and cell cycle arrest	50 μM	[59]
Prostate cancer	DU145 cells	Via inhibiting autophagy and increasing apoptosis induction through the inhibition of the PI3K/Akt/mTOR signaling pathway	6.757 μg/mL	[60]
Prostate cancer	Transgenic mouse model	Via abrogating tumor progression in transgenic mice	50 μM	[61]
Prostate cancer	DU145 cells	Via inhibiting Mdm2 and vimentin expression levels by down-regulating phosphorylated Akt and mTOR	5 μM	[62]
Prostate cancer	Xenograft mice	Via inducing UHRF1 protein degradation and reducing genomic DNA methylation level thereby elevating the expression of p21, p16 and LXN. Induced cell cycle arrest, cellular senescence and the inhibition of xenograft tumor growth	40 μM	[63]

(*Continued*)

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Table 2 (Continued).

Cancer Type	Cancer cells/Animal model	Molecular Mechanism	IC50 Value	Reference
Hepatocellular carcinoma	Bel-7402, SMMC-7721 and HepG2 cells	Via inducing G2/M cell cycle arrest and apoptosis by inhibiting Akt phosphorylation, upregulating p21, activating p27 expression and caspases activation	35 μM	[64]
Hepatocellular carcinoma	HepG2 cells	Via inhibiting cell growth, apoptosis induction, and, suppressed cell migration	75 mm	[65]
Hepatocellular carcinoma	HCC cells	Via abrogation of the STAT3 signaling pathway leading to suppression of STAT3 activation. Inhibition of c-Src, JAK1/JAK2 activation, and downregulation of STAT3-regulated gene products (Bcl-xL, cyclin D1, Bcl-2, survivin, VEGF, and Mcl-1) leading to potentiation of apoptotic effects of paclitaxel and doxorubicin	2106 /mL	[66]
Hepatocellular carcinoma	HepG2 and SMMC-7721 cells	Via inhibiting cell proliferation, triggering apoptotic cell death, inducing G2/M phase arrest, and suppressing cell migration with upregulated DDX3	100 μM	[67]
Hepatocellular carcinoma	HepG2 cells	Via activating caspases and cleavage of poly-ADP-ribose polymerase (PARP) and releasing cytochrome c	30 μM	[68]
Hepatocellular carcinoma	HepG2 cells	Via eliciting DNA damage and reducing cell viability	50 μM	[69]
Colon cancer	HT-29 cells	Via activating p38 MAPK pathway and increasing COX-2 expression thereby promoting TRAIL-induced apoptosis	40 μM	[70]
Colon cancer	SW480 cells	Via reducing Ki67 expression was markedly reduced and increasing Bax and caspase3 expression levels	100 μmol/L	[71]
Colon cancer	SPF grade BALB/C nude mice aged 6 weeks	Via reducing tumor volume and mass of diosgenin treated mice	100 μmol/L	[71]
Colon cancer	HT-29 and HCT-116 cells	Via increasing COX-2 expression and increasing 5-LOX and leukotriene B4 expression levels	40 μM	[72]
Gastric cancer	AGS and SGC-7901 cells	Via inducing G0/G1 phase arrest, and inhibiting Rho/ROCK signaling and downregulating EMT-related molecules expression levels	20.02 μM and 17.40 μM	[73]
Esophageal cancer	Eca109 cells	Growth inhibitory potential Via inhibiting p38 expression levels	50 μg/mL	[74]
Cholangiocarcinoma	HuCCT1 cells were used to build animal model. Nude mice (BALB/c)	Via inducing cleavage of cleavage of Caspase, reducing $\Delta\Psi m$, downregulating cyclinB1, increasing p21, cytosolic cytochrome C, cleaved-PARP1 and Bax/Bcl-2 ratio thereby inducing growth arrest at G2/M phase	40 μM	[75]
Pancreatic cancer	Patu8988 and Panc-1 cells	Via inhibiting EZH2 and Vimentin expression levels and inducing growth arrest at G2/M phase (enhanced PTEN)	50 μM and 75 μM	[76]
Lung cancer	A549 cells	Via preventing telomerase activity by down regulating hTERT gene expression	43 μM	[77]

(*Continued*)

Table 2 (Continued).

Cancer Type	Cancer cells/Animal model	Molecular Mechanism	IC50 Value	Reference
Non-small-cell lung cancer	A549 and PC9 cells	Via inducing cell cycle arrest and abrogating NF-κB/STAT3 activation leading to suppression of protein kinases and reporter gene activity	11.8 and 15.2 μM	[78]
Osteosarcoma	MG63 cells	Via inhibiting Cdc20 expression levels	80 μM	[79]
Osteosarcoma	MG63 and U2OS cells	Via inhibiting MAPK signaling pathway and inhibiting EMT initiation via p38MAPK signaling pathway	76.2 and 40.15 μM	[80]
Oral squamous cancer	PE/CA-PJ15 cells	Via reducing cell viability, increasing apoptosis and altering cell cycle	50 μM	[81]
Squamous cell carcinoma	A431 and Hep2	Via increasing LIVE/DEAD cytotoxicity, sub-G1 population, chromatin condensation, caspases activation, DNA laddering, Bax/Bcl-2 ratio, and cleavage of poly ADP ribose polymerase and inhibiting Akt and JNK phosphorylation	40 μM	[82]
Optic nerve sheath meningioma	HBL-52 cells	Via inducing G0/G1 cell cycle growth arrest, mitochondrial-mediated apoptosis, and autophagy	7.5μM	[83]
Chronic myeloid leukemia	CML cells	Via inducing autophagy and enhancing ROS generation and inhibiting mTOR signaling pathway	12 μM	[84]
Human thyrocytes	FRTL-5 cell lines	Via activating caspase cascades in IGF-1-stimulated human thyrocytes	25 μMl/l	[85]
Melanoma	Melanoma-bearing C57BL/6 mice	Via inducing antitumor immunity and improving the efficacy of immune checkpoint antibody and augmenting T-cell responses	25 μM	[86]
Glioblastoma	C6 and T98G cell lines	Via inducing differentiation, angiogenesis and decreasing MMP2/9 and FGF2 expression levels	15 μM	[87]

Breast Cancer

Diosgenin has shown significant anticancerous potential against breast carcinoma via reducing cell viability and inducing apoptosis. For instance, in MDA-MB-231 cells, diosgenin inhibited the migration via suppression of Vav2 activity. Diosgenin significantly inhibited Cdc42 activation, actin polymerization, and Vav2 phosphorylation, which ascribed to the anti-metastatic potential of diosgenin.[52] Overexpressed Skp2 (oncogenic F box proteins) have been reported to stimulate breast cancer cell growth.[88,89] S-phase kinase-associated protein 2 (Skp2) plays an oncogenic role in breast carcinogenesis and progression. Diosgenin treatment inhibited cell viability, reduced cell invasion, and stimulated apoptosis induction via inhibiting Skp2 expression in breast (MCF7, and MDA-MB-231) cancer cells.[53] Diosgenin exhibited anticarcinogenic efficacy by reducing peroxidation reaction and marker enzymes and enhancing the intrinsic antioxidant defense system against NMU-induced experimental mammary carcinogenesis.[56] Several natural compounds are widely used in developing redox system-targeted strategies for breast cancer therapeutics.[90] Diosgenin exhibited highest cytotoxicity against MCF7 cell lines[54] (Figure 1).

In another research, diosgenin treated MCF-7 and Hs578T cells exhibited significant cellular growth inhibition, apoptosis induction, and growth-phase arrest. Diosgenin-treated cells were constricted in the G2/M phase due to altered cyclin B and phosphorylated cyclin checkpoint1 expression. Diosgenin reduced MMP via downregulating Bcl-2 expression levels leading to activated caspase signaling and cytochrome c release. Diosgenin induced G2/M phase arrest via modulating the Cdc25C-Cdc2-cyclin B pathway and mitochondria-mediated apoptosis in human breast cancer cells (Liao et al, 2019). In MCF-7 cells, diosgenin treatment resulted in high inhibition in the cell viability, whereas when combined

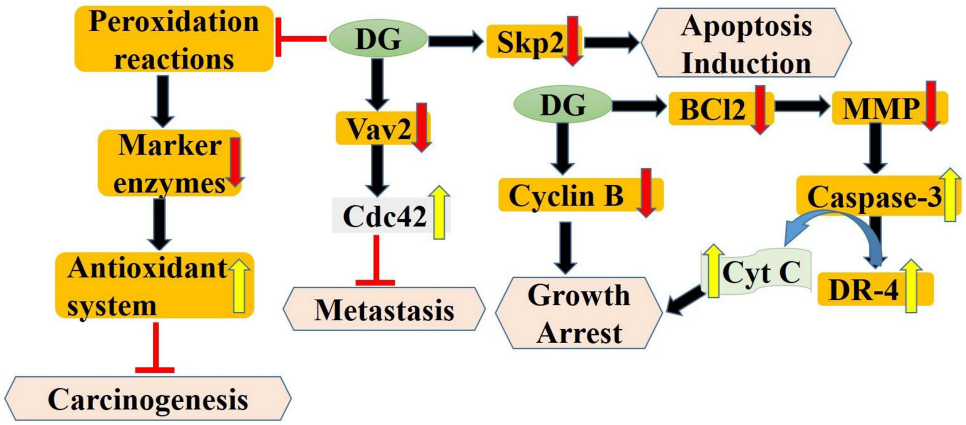

Figure 1 Anticancer potential of diosgenin in breast cancer.
Abbreviations: Dg, diosgenin; Vav2, member of the VAV oncogene family; Cdc42, Cell division cycle 42; Skp2, S-phase kinase-associated protein 2; Cyt C, cytochrome c; DR-4, Death receptor-4; MMP, Mitochondrial membrane potential; BCl2, B-cell lymphoma/lymphoma 2.

with paclitaxel, it resulted in more pronounced growth inhibition than alone. The levels of DR4 and caspase-3 were significantly increased in diosgenin alone and paclitaxel combined with treated MCF-7 cells.[57] Altogether, these findings provided a promising strategy to utilize diosgenin as a potent molecule-targeted drug for breast cancer management.

Prostate Cancer

Apoptosis is universally recognized as a crucial process for cell death.[91] Comprehending intercellular communication and apoptosis regulation in normal prostate glands and prostate cancers is crucial for developing effective customized therapeutics for advanced prostate cancer.[92] Furthermore, autophagy has been shown to play a role in carcinogenesis.[93,94] Consequently, other research examined the impact of diosgenin on the proliferation, apoptosis, and autophagy of prostate cancer cells. Diosgenin suppressed the growth of DU145 cells by inducing apoptosis and autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway.[60] Diosgenin suppressed the migration and invasion of PC-3 cells by waning MMPs expression. It also suppressed the PI3K/Akt, ERK, and JNK signaling pathways, along with NF-κB activity. These findings indicated a novel therapeutic potential for diosgenin in anti-metastatic treatment.[58] NEDD4 is an E3 ligase that possess oncogenic effect by degrading numerous proteins in human cancer.[95] The research identified diosgenin as a potential novel inhibitor of NEDD4 in prostate cancer cells. Diosgenin therapy inhibited cell growth, apoptosis, and cell cycle arrest by suppressing NEDD4 expression in human PC-3 prostate cancer cells.[59] The pertinent associations among the deregulated signaling pathways, including PI3K/Akt/mTOR,[96,97] NF-κB/STAT3,[98] c-Met pathway,[99] and ubiquitin-proteasome pathway,[100] alongside cell survival and prostate cancer, present significant therapeutic targets for management of prostate cancer. Diosgenin has been implicated in the modulation of dysregulated cell signaling pathways in prostate cancer, specifically the PI3K/Akt/mTOR and NF-κB/STAT3 pathways. Diosgenin decreased cell proliferation in DU145 cells by activating apoptosis while simultaneously suppressing the autophagy and PI3K/Akt/mTOR signaling pathways.[60] Diosgenin inhibited NF-κB/STAT3 activation by suppressing protein kinases and reporter gene activity, resulting in a significant decrease in the expression of many tumorigenic gene products in prostate cancer (Figure 2).

Diosgenin, when included in the food and administered to transgenic mice, inhibited tumor growth in vivo. Diosgenin was identified in serum and had effective oral absorption.[61] Significant stimulation of the hepatocyte growth factor (HGF)/c-Met pathway resulted in the migration of cancerous cells in prostate cancer.[101] The phosphorylation cascade following HGF, especially the PI3K/Akt signaling pathway, governs epithelial-to-mesenchymal transition. Research indicated that diosgenin inhibited HGF-induced scattering and invasion of DU145 cells. Diosgenin substantially suppressed the HGF-induced elevations in Mdm2 and vimentin by down-regulating phosphorylated Akt and mTOR. Consequently, these data indicated diosgenin as a promising agent for prostate cancer treatment, specifically targeting the primary HGF-induced EMT pathway.[62] Diosgenin has been recognized as a small molecule natural substance that selectively targets the UHRF1 protein by directly adhering to it, hence inducing UHRF1 protein degradation via the

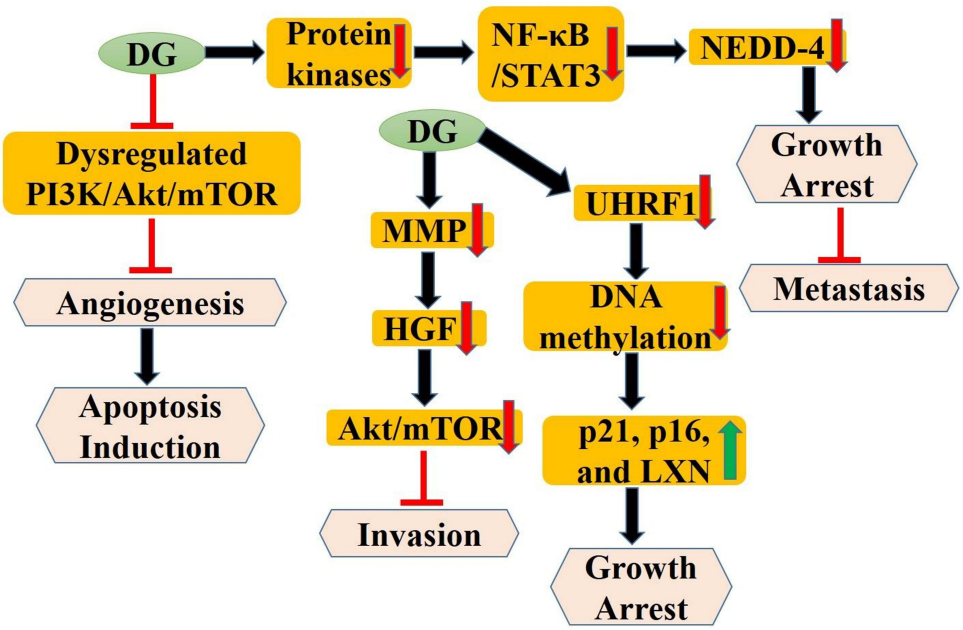

Figure 2 Anticancer potential of diosgenin in prostate cancer.
Abbreviations: NEDD-4, neural precursor cell expressed developmentally down-regulated protein 4; HGF, Hepatocyte growth factor; LXN, latexin gene; mTOR, Mammalian target of rapamycin.

ubiquitin-proteasome pathway. Significantly, DG prompted the breakdown of UHRF1 protein by diminishing its association with the deubiquitinase USP7. Diosgenin diminished genomic DNA methylation levels and increased the expression of tumor suppressor genes [p21, p16, and LXN] leading to cell cycle arrest, cellular senescence, and the suppression of xenograft tumor growth.[63] Collectively, these findings indicate that diosgenin may serve as a potential therapeutic adjuvant in prostate cancer via inhibiting cell proliferation through the modulation of oxidative stress and the regulation of aberrant cell signaling pathways in prostate cancer.

Lung Cancer

Elevated telomerase activity has been observed in most malignant carcinomas, including lung cancer.[102] Telomerase activity is absent in normal healthy cells, whereas it is reactivated in cancerous cells.[103] Treating A549 lung cancer cells with pure diosgenin and fenugreek extract led to the downregulation of hTERT expression. The findings demonstrated that pure and impure diosgenin inhibited telomerase activity via downregulating hTERT gene expression in A549 lung cancer cell line.[77] Multiple Di derivatives were synthesized to identify novel steroid-based anticancer drugs. Diosgenin (steroidal sapogenin) has demonstrated anticancer properties in preclinical investigations.[104] Multiple diosgenin derivatives were synthesized and evaluated, with FZU-0021-194-P2 (P2) demonstrated enhanced cytotoxic efficacy against human non-small-cell lung (A549 and PC9) cancer cells. P2 phytosomes (P2Ps) were formulated to enhance the water solubility of P2. The P2Ps more effectively limit the growth of lung cancer cells compared to Di phytosomes by triggering cell cycle arrest and death. Thus, P2Ps might be a promising anticancer formulation for non-small-cell lung cancer.[78] Another derivative demonstrated that DG-8d suppressed cell proliferation and caused effects in A549 cells via decreasing the PI3K/Akt pathways. LY294002 [PI3K inhibitor] enhanced the influence of DG-8d on cell proliferation and apoptosis on A549 cells. Furthermore, the impact of DG-8d on apoptosis was additionally validated by mitochondrial depolarization and increased intracellular reactive oxygen species (ROS). DG-8d or DG-8d, in conjunction with LY294002, decreased the signaling molecules p-Akt, p-FoxO3a, PI3k, and Bcl-2 while enhancing the signaling molecules Bax and Bim. Thus, DG-8d may be developed as a potential medication for lung cancer treatment[105] (Figure 3).

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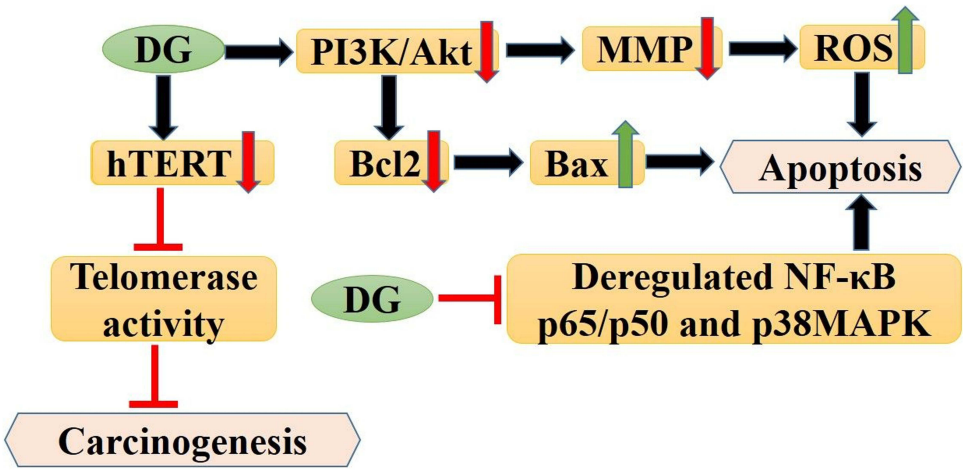

Figure 3 Anticancer potential of diosgenin in lung cancer.
Abbreviations: MMP, Mitochondrial membrane potential; ROS, Reactive oxygen species, hTERT, Human telomerase reverse transcriptase; Bax, Bcl-2-associated X protein; Bcl2, B-cell lymphoma/lymphoma 2; Akt, Protein kinase B.

Surmounting resistance to apoptosis and antimitotic chemotherapy is essential for effectively treating lung cancer.[106] Diosgenin has been reported with the modulation of multiple molecular pathways involved in tumorigenesis in human carcinomas. Diosgenin decreased cell viability while augmenting the incidence of multinucleated cells, especially binucleated cells arising from daughter cell fusion. This effect was linked to genes that regulated cytokinesis (RAB35, AURKB, OCRL, and BIRC5). Diosgenin-induced cell death was associated with necroptosis, as demonstrated by elevated intracellular ROS generation and the expression of TRAF2, RIPK3, MLKL, and HSPA5 genes. Diosgenin augmented spheroid volume, triggered cellular apoptosis, and impeded proliferative recovery and clonogenic growth in tumor spheroids.[107] Diosgenin facilitated cisplatin-induced apoptosis via oxidative DNA damage in A549 non-small cell lung carcinoma cells. Co-treatment of DG with cisplatin enhanced cellular cytotoxicity by elevating ROS levels, generating oxidative DNA damage, and diminishing cellular antioxidant defense, thus resulting in significant activation of death in tumor cells.[108] Diosgenin inhibited the NF-κB p65/p50 and p38MAPK pathways, mitigating acute lung damage caused by lipopolysaccharide in mice. Diosgenin markedly inhibited the activation of NF-κB p65/p50, p38, and the production of inducible nitric oxide synthase (iNOS) in LPS-induced THP-1 cells, implicating its potential in the treatment of acute lung injury.[109] Diosgenin has demonstrated considerable anticancer potential by targeting many oncogenic elements within cell signaling pathways related to lung carcinogenesis.

Liver Cancer

Diosgenin markedly suppressed the proliferation of Bel-7402, SMMC-7721, and HepG2 hepatocellular carcinoma cells in a concentration-dependent fashion. Diosgenin administration for 24 hours resulted in growth (G2/M cell cycle phase) arrest and apoptosis in hepatoma cells. Diosgenin suppressed Akt phosphorylation and elevated expression levels of p21 and p27, while no effects on p53 expression, indicating that diosgenin-induced elevation of p21 and p27 in HCC cells. Diosgenin prompted apoptosis in HCC cells by activating caspase cascades −3, −8, and −9. Diosgenin, however, did not influence the levels of Bcl-2 and Bax.[64] DEAD box polypeptide 3 (DDX3) participates in oncogenesis and regulates cancer advancement.[110] A separate investigation indicated significant cell proliferation and migration suppression, accompanied by enhanced apoptosis induction and G2/M phase arrest in HepG2 and SMMC-7721 cells treated with diosgenin.[67] Numerous investigations indicate that diosgenin-induced apoptosis depends on caspase-3, characterized by decreased mitochondrial membrane potential, nuclear translocation of AIF, and cleavage of poly (ADP-ribose) polymerase (Figure 4). Diosgenin administration prompted p53 activation and cell cycle arrest in many cell lines.[111] Diosgenin triggered apoptosis in Hep-G2 cells via a Bcl-2 protein family-mediated mitochondria/caspase-3-dependent mechanism. Diosgenin significantly produced reactive oxygen species, leading to oxidative stress that triggered apoptosis via the activation of ASK1 (crucial upstream signal) for JNK/p38 MAPK activation in HepG2 cancer cells.[68] A separate

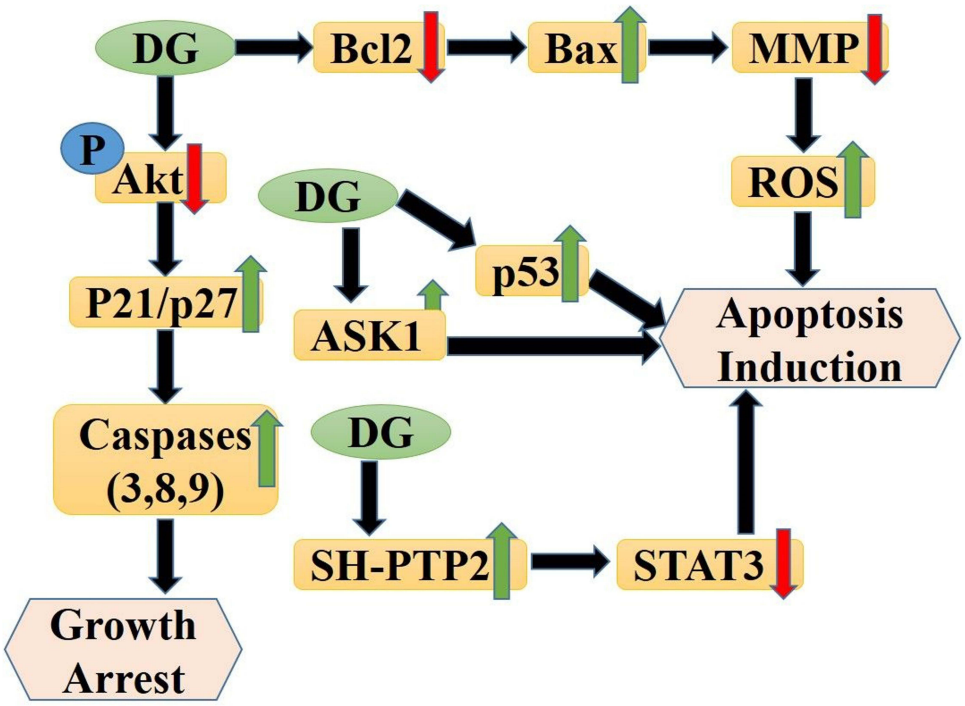

Figure 4 Anticancer effect of diosgenin in hepatocellular carcinoma.
Abbreviations: Bax, Bcl-2-associated X protein; Bcl2, B-cell lymphoma/lymphoma 2, MMP, Mitochondrial membrane potential; ROS, Reactive oxygen species Akt, Protein kinase B, p53, tumor protein p53, ASK1, Apoptosis signal-regulating kinase 1, DG, Diosgenin, SH-PTP2, Src homology two phosphatase 2, STAT3, Signal transducer and activator of transcription 3.

investigation indicated diosgenin's cytotoxic, genotoxic, and mutagenic effects on HepG2 cells. A decline in cell viability was noted in cells treated with diosgenin. The comet assay and CBMN demonstrated a genotoxic effect. Diosgenin treated HepG2 cells revealed elevated micronucleus frequency, cytostatic effect, DNA damage, and cell death.[69]

Recent data indicate that many cell signaling pathways, including the STAT3 signaling route[112] and the Hippo signaling system,[113] contribute to oncogenesis in liver cancer. A study demonstrated that diosgenin decreased TAZ expression in Hep-G2 liver cancer cells, thereby impeding cell growth, inducing apoptosis, and partially suppressing cell migration and invasion through TAZ suppression.[65] Diosgenin has been documented to inhibit the STAT3 signaling pathway and to limit the growth and chemosensitization of human hepatocellular carcinoma cells. Diosgenin stimulated the production of Src homology two phosphatase 2 (SH-PTP2), which was associated with the downregulation of constitutive STAT3 activation and enhanced the apoptotic effects of paclitaxel and doxorubicin.[66] Another study evaluated the chemo-modulatory effects of diosgenin on volasertib, a polo-like kinase 1 inhibitor, and doxorubicin in HepG2 and Huh-7 cells. Diosgenin had favorable chemo-modulatory effects on volasertib and doxorubicin in HCC via downregulating PCNA and PLK1, upregulating caspase-3 and P53 and thereby leading to apoptosis induction.[114] Collectively, these data suggested that diosgenin exhibits a cytotoxic effect on human HCC cells and possesses potential therapeutic benefits for HCC patients.

Gastrointestinal Cancers

Selectively triggering apoptosis in cancer cells is becoming acknowledged as a feasible therapeutic strategy for various malignancies, including colorectal and pancreatic tumors. Diosgenin enhances the sensitivity of HT-29 cells to TRAIL-induced apoptosis via activating the p38 MAPK pathway and promoting DR5 overexpression. Moreover, diosgenin alone, TRAIL alone, or their combination reduced COX-2 expression, and a COX-2 inhibitor further boosted apoptosis induction.[70] Apoptosis was significantly elevated in colon cancer SW480 cells treated with diosgenin. Ki67 expression significantly diminished, but Bax and caspase 3 levels substantially elevated following diosgenin therapy. The nude mice carcinogenesis assay demonstrated that the tumorous volume and mass in the diosgenin treatment group were

significantly reduced compared to the control, with a more pronounced inhibitory effect shown at higher concentrations of diosgenin. Diosgenin proved efficient in suppressing the growth and migration of colon cancer cells while simultaneously increasing apoptosis in malignant cells.

Furthermore, diosgenin administration reduced STAT3 expression in SW480 cells.[71] Diosgenin has been discovered to possess potential antitumor action in colorectal cancer. In colorectal cancer (CRC) cells, diosgenin inhibited cell proliferation and induced apoptosis via modulating p53 and Bcl-2 family protein expression levels, mediating the mitochondrial apoptosis pathway. It suppressed migration and invasion by reducing matrix metalloproteinase-9 (MMP-9) levels and decreased aerobic glycolysis through the downregulation of glucose transporters GLUT3 and GLUT4 and pyruvate carboxylase (PC). Diosgenin inhibited CRC cells through the cAMP/PKA/CREB pathway. The nude mice xenograft tumor model showed that DSG may effectively inhibit the growth of CRC cells in vivo without significant adverse effects.[72] Diosgenin modulated esophageal Eca109 cells by diminishing cancer cell proliferation and lowering p38 protein expression levels within the p-p38 pathway.[74] Diosgenin serves as a precursor to steroid hormones and is crucial to the proliferation of multiple carcinomas, including human colorectal cancer and gastric carcinoma. It impeded the advancement of six cholangiocarcinoma cell lines. In vivo, tumor investigations showed that diosgenin markedly suppressed tumor growth in xenografts in nude mice. The expression of mitosis-promoting factor cyclin B1 diminished concomitantly with the increasing levels of the cell cycle inhibitor p21, leading to the arrest of cholangiocarcinoma cell cycles at the G2/M phase. Diosgenin caused apoptosis by elevating cytosolic cytochrome C levels, cleaved caspase-3, cleaved PARP1, and the Bax/Bcl-2 ratio. The GSK3β/β-catenin pathway participated in the death of cholangiocarcinoma cells[75] (Figure 5).

Treatment with diosgenin reduced cell viability, whereas the combination application of an EZH2 inhibitor and GSK126 resulted in a further considerable decline in AGS and SGC-7901 gastric cancer cells. Additionally, co-administration of diosgenin and GSK126 synergistically enhanced cell proliferation, G0/G1 phase arrest, and apoptosis. At the molecular level, the concurrent administration of diosgenin and GSK126 inhibited Rho/ROCK signaling, resulting in the downregulation of epithelial–mesenchymal transition (EMT)-associated molecules.[73] Diosgenin was employed as a microecological regulator in melanoma-bearing C57BL/6 mice to stimulate antitumor immunity and enhance the effectiveness of immune checkpoint antibodies, thus rendering it more appropriate for malignant tumor treatment. Diosgenin enhanced antitumor immunity and the efficacy of PD-1 antibodies against melanoma through the modulation of gut microbiota.[86] Diosgenin administration in HCT-116 and HT-29 cells induced apoptosis by elevating COX-2 and 5-LOX expression and augmenting leukotriene B4 synthesis.[115] The dependency of MESP1 on the anti-cancer action of

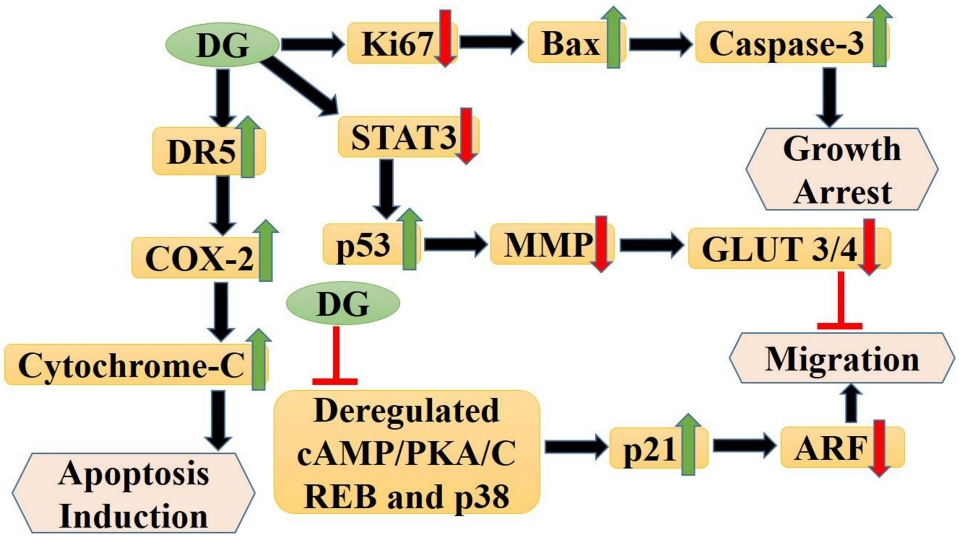

Figure 5 Anticancer effect of diosgenin in Gastrointestinal carcinoma.
Abbreviations: Bax, Bcl-2-associated X protein; MMP, Mitochondrial membrane potential; p53, tumor protein p53, DG, Diosgenin, STAT3, Signal transducer and activator of transcription 3; COX-2, Cyclooxygenase-2; ARF, ADP ribosylation factor; GLUT, glucose transporters; p21, cyclin-dependent kinase inhibitor; DR5, Death Receptor 5.

diosgenin in gastric cancer cells was validated using MESP1 knockdown. MESP1 facilitated the growth of gastric cancer cells by suppressing ARF expression. Diosgenin demonstrated an anti-cancer effect by suppressing MESP1 expression in gastric cancer cells.[116] Diosgenin markedly suppressed the proliferation, colony formation efficiency, migration, and invasion of AGS cells. Diosgenin markedly elevated miR-34a expression in AGS cells while reducing the expression of its target genes E2F1, E2F3, and CCND1. Diosgenin suppressed the proliferation, migration, and invasion of AGS cells, partly via modulating miR-34a and down-regulating the expression of E2F1, E2F3, and CCND1 genes.[117] Diosgenin diminished the invasion and survival capacity of BGC-823 cells treated with cobalt chloride.

Furthermore, combining diosgenin with HIF-1α-specific short hairpin RNA (shRNA) resulted in a more pronounced inhibition of BGC-823 cells. The findings indicated that diosgenin could effectively manage stomach cancer cells in hypoxic conditions, particularly when paired with reduced HIF-1α.[118] Marked suppression of cell growth was noted in diosgenin-treated Patu8988 and Panc-1 cells. Diosgenin administration promoted apoptotic cell death, inhibited cell migration, and caused G2/M phase arrest in pancreatic cancer cells. EZH2 signaling was intricately linked to the antitumor properties of diosgenin in pancreatic cancer cells.[76]

Other Carcinomas (Glioblastoma, Osteosarcoma, Skin Cancer, Ovarian, Optic Nerve Sheath Meningioma and Squamous Cell Carcinoma)

Diosgenin exhibited a significant inhibitory effect on the proliferation of both C6 and T98G cell lines. Diosgenin exhibited anti-tumor properties in glioblastoma cells by promoting differentiation and preventing migration and angiogenesis.[87] Osteosarcoma (OS) is a highly aggressive malignancy affecting young individuals.[119] Diosgenin suppressed cellular proliferation and triggered apoptosis. Furthermore, diosgenin treatment suppressed cell motility and the downregulation of Cdc20 expression in OS cells. Overexpressed Cdc20 negated the inhibitory effects on cell growth and invasion of diosgenin treated cells.[79] Diosgenin suppressed phosphorylated p38 protein (pP38). Diosgenin may be an adjunctive agent for clinically mitigating metastasis in osteosarcoma patients.[80] Thymoquinone and diosgenin suppressed cell growth and elicited cytotoxicity in A431 and Hep2 cells. These drugs triggered apoptosis by elevating the sub-G1 population, enhancing LIVE/DEAD cytotoxicity, promoting chromatin condensation, facilitating DNA laddering, and raising TUNEL-positive cells. An elevated Bax/Bcl-2 ratio, caspase activation, and poly ADP ribose polymerase cleavage were found in the treated cells. These bioactive compounds reduced phosphorylation [Akt and JNK] suppressed cell growth and triggered apoptosis. In a murine xenograft model, a combination of TQ and DG markedly decreased tumor volume and mass while enhancing apoptosis. Thymoquinone and diosgenin, both individually and synergistically, suppressed cell proliferation and promoted apoptosis in squamous cell carcinoma.[82]

Diosgenin suppressed the proliferation, migration, and invasion of optic nerve sheath meningioma cells by eliciting mitochondrial-mediated apoptosis, autophagy, and G0/G1 cell cycle arrest. Diosgenin further diminished the viability of HBL-52 cells by activating autophagy within them. Autophagy was also associated with the elevation of LC3 II and Beclin 1 expression—diosgenin-induced cell cycle arrest in HBL-52 at the sub-G1 phase. Diosgenin also inhibited the migration and invasion of HBL-52 cells. Diosgenin also induced mitochondrial-dependent apoptotic cell death.[83] The chemopreventive activity of diosgenin was investigated in the context of 7.12-dimethylbenz(a)anthracene (DMBA)-induced carcinogenesis in hamster buccal pouches. DMBA-treated rats exhibited morphological alterations characterized by hyperplasia, dysplasia, and well-differentiated squamous cell carcinoma.

Furthermore, the levels of antioxidants and lipid peroxidation byproducts were significantly modified in hamsters treated with DMBA. The oral treatment of diosgenin (80 mg/kg body weight) for DMBA-treated hamsters dramatically diminished the development of oral tumors and rectified the aforementioned biochemical irregularities. Diosgenin may be an effective chemopreventive drug due to its antioxidant properties in DMBA-induced hamster buccal pouch carcinogenesis.[120] Diosgenin and zoledronic acid decreased cell viability and triggered apoptosis in PE/CA-PJ15 OSSC cells. Both drugs blocked cell migration, modified the cell cycle, and exhibited a possible chemotherapeutic impact on the PE/CA-PJ15 OSSC cell line.[81] Diosgenin inhibited cellular proliferation and induced apoptosis in ovarian cancer by upregulating pro-apoptotic markers and downregulating anti-apoptotic mediators. Diosgenin downregulated the expression levels of critical proteins in the PI3K signaling pathway, including PI3K, Akt, mTOR, and GSK3, in

OVCAR-3 and SKOV-3 cells. Diosgenin suppressed the proliferation and migration of OVCAR-3 ovarian cancer cells and promoted death, potentially through the modulation of PI3K signaling.[121] Diosgenin has demonstrated the ability to trigger apoptosis in several cell types, excluding thyroid cells. Its apoptotic effect was investigated in IGF-1-stimulated primary human thyrocytes. Diosgenin triggered apoptosis in human thyrocytes pretreated with IGF-1 in a dose-dependent manner via the activation of caspase cascades. Furthermore, diosgenin suppressed FLIP and activated caspase-8 in the FAS-associated apoptotic pathway. Diosgenin augmented ROS generation and modulated Bax and Bcl-2 expression and activated caspase-9 in the mitochondrial apoptotic pathway. The findings demonstrated that diosgenin triggered apoptosis in IGF-1-stimulated primary human thyrocytes via two caspase-dependent pathways.[85]

Diosgenin Nanoparticles as Novel Nanomaterial Against Various Cancers

Researchers have shown that early identification, diagnosis, and treatment enhance survival rates. Advancements in nanotechnology have displayed numerous potential in prognosis and diagnosis in breast cancer treatments.[122] Nanoformulated camptothecin has also been used as an efficient and safer anticancer agent against various human carcinomas.[123] Inorganic nanoparticles conjugated with tumor-specific ligands have shown wider application in delivering chemotherapeutic (or hormonal) drugs with better tumor selectivity.[124] Iron oxide nanoparticles (IONPs) are widely utilized nanomaterials used in breast cancer management for its superparamagnetic potential. MRI and CTs employing iron-based magnetic nanoparticles represent potential methodologies for the radiological examination of breast cancer.[125] Nanomedicine consisting of iron oxide nanoparticle (IONP) core functionalized with the strong anticancer bioactive compound diosgenin is derived from the medicinal plant *Dioscorea bulbifera*, utilizing a citric acid linker molecule. IONPs were produced via reverse co-precipitation and characterized using high-resolution TEM, field emission scanning electron microscopy, and dynamic light scattering. IONPs-D was the inaugural diosgenin-functionalized new magnetic nanomedicine exhibiting antiproliferative, migration-inhibiting, and apoptosis-inducing characteristics against MCF7 breast cancer cells.[126] Diosgenin-encapsulated PCL-Pluronic nanoparticles (PCL-F68-D-NPs) were synthesized via nanoprecipitation to enhance efficacy in glioblastoma treatment. The synthesized nanoparticles exhibited favorable size distribution, stability, shape, and chemical and mechanical properties. The nanoparticles exhibited elevated encapsulation efficiency, loading efficiency, and yield. The in vitro cytotoxicity of PCL-F68-D-NPs exhibited more toxicity towards U87-MG cells than free Diosgenin.[127] Nanoparticles encapsulating diosgenin were produced using ionic gelation employing three distinct chitosan weight percentages and the polyanion sodium tripolyphosphate (STPP) as the cross-linking agent. Diosgenin was released in a diffusion-controlled manner from chitosan nanoparticles in drug release research. DIO@CS exhibited considerable anticancer efficacy against A431 human skin cancer cells. Mice generated by DMBA exhibited reduced weight growth compared to those treated with DIO@CS NPs. Oral DIO@CS nanoparticles restored cellular antioxidants and reduced histopathological staining with hematoxylin and eosin in breast cancer. Diosgenin nanoformulations offered an innovative treatment for breast cancer.[128]

Diosgenin was encapsulated in liposomes to enhance its solubility and, consequently, its efficacy. Diosgenin-noisome (diosgenin encapsulated in noisome) was synthesized using the thin-film hydration technique and characterized using optical microscopy, dynamic light scattering (DLS), scanning electron microscopy (SEM), and UV–visible spectrophotometry. The results indicated that niosomes enhanced the solubility of naturally generated hydrophobic compounds, improving their anticancer efficacy in HepG2 cells. The loading efficiency of diosgenin was markedly enhanced with a sustainable and regulated release rate.[129] Another investigation assessed the anticancer potential of diosgenin encapsulated within poly-glycerol malate co-dodecanedioate (PGMD) nanoparticles. Diosgenin-encapsulated PGMD nanoparticles (using nanoprecipitation technique) demonstrated a diffusion and dissolution-controlled drug release pattern adhering to Korsmeyer–Peppas kinetic model. Additionally, cytotoxic (in vitro) and morphological investigations confirmed its toxicity against A549 lung cancer cells.[130] Diosgenyl saponin (solid anticancer drug) induced endoplasmic reticulum stress and mitochondria-mediated apoptotic pathways in liver cancer. A fluorophore-conjugated derivative of diosgenin [Glc/CNHphth-diosgenin (GND)] caused ER enlargement, mitochondrial impairment, and autophagosome formation while upregulating IRE-1α for autophagy and apoptosis induction. GND stimulated autophagy to initiate caspase-8-dependent apoptosis. The observations indicated that diosgenyl saponin is a potent anticancer drug that induces endoplasmic reticulum stress and mitochondria-mediated apoptotic pathways in liver cancer.[131] Diosgenin altered the

cancer chemotherapy drug cytarabine (Ara-C) owing to its anti-tumor properties and lipophilicity. Diosgenin altered the biomembrane affinity of Ara-C and effectively substituted cholesterol during liposome production. The DG-Ara-C liposomes demonstrated superior anti-cancer efficacy against leukemia and solid tumor cells compared to free diosgenin or Ara-C. Diosgenin demonstrated potential as a carrier for anti-cancer drugs to enhance bioactivity, as it plays a crucial role in modulating biomembrane affinity, liposome preparation, and the release of hydrophilic Ara-C from lipid vesicles.[23]

The tailored delivery methods that integrate natural products with chemotherapeutic agents effectively eradicate tumors while minimizing toxicity and enhancing efficacy.[132] Doxorubicin (DOX) has shown toxicity, drug resistance, and unfavorable prognosis in liver cancer.[133] A Diosgenin-based liposome encapsulating DOX (Dios-DOX-LP) was formulated for the synergistic treatment of liver cancer, wherein Diosgenin not only substituted cholesterol as the membrane stabilizer to maintain liposomal integrity but also served as a chemotherapeutic adjuvant to DOX for enhanced therapeutic efficacy. Dios-DOX-LP exhibited commendable stability and a gradual release effect. In comparison to commercial DOX liposome (CHOL-DOX-LP), Dios-DOX-LP demonstrated enhanced anti-tumor efficacy both in vitro and in vivo by promoting apoptosis and suppressing tumor cell proliferation, achieving a tumor suppression rate of 78% in tumor-bearing nude mice.[134] Metastasis, a significant obstacle in cancer treatment, is the primary cause of tumor progression and recurrence. The anti-metastasis approach has been regarded as a viable therapy for clinical cancer management.[135] Diosgenin is recognized for its ability to suppress tumor metastasis, while doxorubicin (DOX) is known to cause tumor death. The inhibitory impact of DOX/NPs on tumor proliferation and migration surpassed that of NPs or free DOX. DOX/NPs integrate mitochondria-associated metastasis and apoptosis through a distinctive internalization mechanism of the carrier to combat malignancies. DOX/NPs are effectively concentrated at tumor locations by augmenting the enhanced permeability and retention (EPR) effect compared to free DOX. The in vivo investigation demonstrated that DOX/NPs, devoid of cardiotoxicity, markedly suppressed tumor spreading through a synergistic therapeutic effect while decreasing tumor volume and weight by inducing apoptosis. The nanocarrier DOX/NPs has emerged as a promising approach for synergistically augmenting the efficacy of cancer therapy.[136] A separate study assessed the impact of diosgenin in conjunction with cisplatin on apoptosis in A549 non-small cell lung carcinoma cells. Diosgenin markedly enhanced the cytotoxic effects of cisplatin and substantially elevated the expression levels of γ-H2AX in cells. Melatonin administration resulted in elevated ROS levels and reduced expression of antioxidant enzymes. The co-treatment of DG and cisplatin enhanced cellular cytotoxicity by elevating ROS levels, generating oxidative DNA damage, and diminishing cellular antioxidant defenses, thereby significantly promoting apoptosis in tumor cells.[108]

DMBA-treated tumor-bearing rats (induced with breast cancer) were orally fed diosgenin. There are elevated levels of total cholesterol, liver and kidney biomarkers, phospholipids, phase-I detoxification enzymes, lipid peroxidation markers, triglycerides, free fatty acids, total lipase, low-density lipoprotein, and low-density lipoprotein. It further leads to reduced levels of phase-II detoxification enzymes (enzymatic and non-enzymatic antioxidants), lecithin acyltransferase, high-density lipoprotein, and lipoprotein lipase in kidney, plasma, and liver tissues of DMBA-induced rats, unveiling hepatic histopathological and renal changes. Nano diosgenin (DN@CS-NP) is a potent hepatoprotective and nephroprotective therapeutic agent that significantly affects breast cancer compared to free diosgenin.[137] Diosgenin derivatives synthesized using Pd(II) catalyzed dehydrogenative coupling had an anticancer effect on breast cancer cells by inhibiting their proliferation and promoting death through modulation of the AKT1 pathway.[138] Diosgenin has been documented to impede autophagy in many human carcinomas. Autophagy induction was confirmed via analysis of autophagic flux including autophagosomal accumulation and destruction. Furthermore, autophagy inhibition using chloroquine and 3-methyladenine enhanced diosgenin-induced death, signifying autophagy involvement in diosgenin-treated chronic myeloid leukemia cells. Subsequent research directed that diosgenin-induced autophagy and cytotoxicity were associated with ROS generation and suppressed mTOR signaling pathway.[84] Another study investigated the efficient production of multilayer self-assembled electrostatic oil-in-water Pickering emulsions (PEs) utilizing quaternized nanocellulose (Q-NC) and diosgenin-conjugate alginate (DGN-ALG) particles as stabilizers to create hydrocolloid nanocarriers. The analysis of cellular internalization demonstrated significant cellular uptake. The MTT assay exhibited significant anticancer efficacy in human MCF-7 and A549 cells.[139]

Novel diosgenin analogs were synthesized via Cu(I)-catalyzed alkyne-azide cycloaddition to investigate their structure–activity relationship. Diosgenin and its equivalents showed notable antiproliferative effects against four human cancer cell lines: HBL-100 (breast), A549 (lung), HT-29 (colon), and HCT-116 (colon). Among the produced analogs, Dgn-1, which possesses a simple phenyl R moiety linked via triazole to the parent molecule, was recognized as the most potent analog against the A549 cancer cell line, surpassing the efficacy of the positive control (BEZ-235). Dgn-2 and Dgn-5, possessing o-nitrophenyl and o-cyanophenyl R moieties, respectively, exhibited significant antiproliferative activity against all evaluated human cancer cell lines. The structure–activity relationship (SAR) indicated that analogs enhance antiproliferative activity, including a simple phenyl R moiety or electron-withdrawing ortho-substituted R moieties.[140] Gold nanoparticles (AuNPs) and nanoformulations encapsulating diosgenin (Dio-AuNPs) using green method utilizing algal extract from Dictyosphaerium (sp. strain DHM, LC159306) were used as a reducing agent. The in vitro antiproliferative effects of AuNPs and Dio-AuNPs were assessed on the colorectal (HCT116) and breast (HCC1954) cancer cells utilizing the sulforhodamine B (SRB) proliferation assay. Dio-AuNPs exhibited remarkable potency in the HCT116 and HCC1954 cell lines, respectively. The anticancer efficacy of both diosgenin and AuNPs can be significantly amplified when utilized in conjunction.[141] DGN-conjugated poly(ε-caprolactone)–MPEG copolymers were made, and nanoparticulate formulations were created by encapsulating imatinib (ITB) into DGN-conjugated PCL–MPEG nanoparticles (NPs) using an emulsion solvent evaporation technique. The nanoparticulate formulations exhibited uniform particle size, a low polydispersity index, excellent encapsulation efficiency, substantial drug loading capacity, and excellent colloidal stability. The in vitro release profile was affected by the pH of the simulated medium, demonstrating an initial burst effect followed by a gradual and sustained release over ten days. The in vitro biocompatibility and anticancer efficacy were assessed utilizing human fibroblast (L929), leukemia (K-562), osteosarcoma (SAOS-2), and breast carcinoma (MCF-7) cell lines. The cytotoxicity assay indicated that the IC50 of ITB-loaded DGN-conjugated nanoparticles was lower than that of the free medicines.

Furthermore, DGN-conjugated nanoparticles demonstrated a pronounced synergistic impact by amalgamating two anticancer agents, DGN and ITB. The findings indicate that diosgenin-conjugated polymeric nanoparticles may serve as a promising delivery strategy for cancer therapy.[142] Polylactide-co-glycolide (PLGA)-encapsulated diosgenin nanoparticles (PLGA-DGN NPs) demonstrated significant encapsulation efficiency, loading capacity, excellent colloidal stability, and an initial burst release in an acidic environment. The nanoparticles demonstrated considerable cytotoxic efficacy at their IC50 concentration compared to diosgenin. PLGA-DGN nanoparticles enhanced the cellular uptake of diosgenin in MCF-7 cells and prolonged blood circulation time, presenting an exceptional pharmacokinetic profile. The bio-distribution analysis showed that PLGA-DGN nanoparticles significantly increased diosgenin accumulation in tumor tissue. PLGA-DGN nanoparticles had significant antiangiogenic and antiproliferative effects in a Swiss albino mice tumor xenograft model, evidenced by tumor shrinkage and reduced expression of CD31 and Ki-67. Consequently, PLGA-DGN nanoparticles may serve as a promising anticancer agent, paving the way for additional research.[143] The detained analysis of different types of diosgenin nanoformulations and their anticancer mode of action are summarized in Table 3.

Table 3 Anticancer Potential of Diosgenin Nanoformulations in Several Cancers (With Their Mode of Action)

Diosgenin nanoformulation	Cancer cell/ Animal model	Cancer type	Mode of action	Reference
Poly lactide-co-glycolide (PLGA)-encapsulated diosgenin nanoparticles	MCF-7 cells	Breast Cancer	• Exhibited significant cytotoxic activity • Facilitated cellular internalization of diosgenin	[143]
	Mice tumor xenograft model (Swiss albino mice)	Breast Cancer	• Tumor regression • Downregulation of CD31 and Ki-67 expression	[143]

(*Continued*)

Table 3 (Continued).

Diosgenin nanoformulation	Cancer cell/ Animal model	Cancer type	Mode of action	Reference
Diosgenin functionalized iron oxide nanoparticles	MCF7 cells	Breast cancer	• Antiproliferative • Apoptosis inducing potential	[126]
Diosgenin encapsulated PCL-Pluronic nanoparticles	U87-MG cells	Brain cancer	Displayed: • Higher toxicity • High encapsulation efficiency • Loading efficiency and yield	[127]
Nanoparticles encapsulating diosgenin DIO@CS NPs	A431 cells	Skin cancer	• Anticancer activity • Released diosgenin diffusion-controlled in drug release • Novel skin cancer therapy	[128]
Diosgenin loaded into niosome	HepG2 cells	Hepatocellular cancer	• Increased solubility and efficiency • Increased loading efficiency of diosgenin with sustainable and controllable release rate	[129]
Diosgenin encapsulated polyglycerol malate co-dodecanedioate nanoparticles	A549 cells	Lung carcinoma	• Potential anticancer efficacy • Dissolution controlled drug release pattern	[130]
Fluorophore-appended derivative of diosgenin	Hep-G2 cells	Liver cancer	• Induced ER swelling, mitochondrial damage, and autophagosome • Upregulated IRE-1α levels leading to autophagy induction and activated caspase-8-dependent apoptosis	[131]
Nano diosgenin	DMBA administered tumor-bearing rats	Breast Cancer	• Decreased DMBA • Induced renal and hepatic toxicities	[137]
Quaternized nanocellulose (Q-NC) and diosgenin-conjugate alginate particles	A549 and MCF-7 cells	Lung Cancer and Breast Cancer	• Potent cyto-inhibitor • High cellular uptake	[142]
Gold nanoformulations loaded with diosgenin	HCT116 and HCC1954 cells	Colorectal cancer and Breast cancer	In-vitro antiproliferative activities	[141]
Diosgenin-conjugated PCL–MPEG polymeric nanoparticles	L929, K-562, SAOS-2, and MCF-7 cells	Fibroblast, leukemia, osteosarcoma, breast carcinoma	• High encapsulation efficacy • High drug loading capacity • Better colloidal stability	[139]
CNT functionalized with carboxylic acid (CNTCOOH), loaded with both FUA and DGN	A549, HepG2 and MCF7 cells	Non-small-cell lung cancer, hepatocellular carcinoma, and breast cancer	• Growth inhibition of cancer cells • Apoptosis induction • Inhibition of lncRNA expression	[144]

Another study exhibited significant inhibitory potential for synergistic nanoformulation of diosgenin with incorporated carbon nanotubes functionalized with carboxylic acid or amine against HepG2 cancer cells than MCF7 and A549 cells. The carboxylic acid-functionalized carbon nanotubes (CNTCOOH), loaded with FUA and DG and coated with chitosan-stearic acid, suppressed lncRNA expression and altered microRNAs and proteins.[144]

Conclusion

Diosgenin and its derivatives have demonstrated pharmacological advantages in combating cancer, diabetes, osteoporosis, Alzheimer's disease, and stroke in numerous studies. Diosgenin has demonstrated activity on various molecular targets that are critical in the development and prevalence of multiple human carcinomas. Multitargeting abilities of diosgenin affect numerous molecular targets and signaling pathways simultaneously. Diosgenin possesses a competitive advantage over the majority of commercially available medical products due to this characteristic. Nanocarriers improve solubility, bioavailability, pharmacological efficacy, stability, and decrease toxicity. Nanocarrier-mediated drug delivery satisfies the requirements for targeted drug administration and accumulation, regulated release, and the transport of large molecules. This review emphasizes the significance of diosgenin's multitargeted approach in cancer therapy, such as its potential to reduce toxicity, encapsulation efficiency, loading capacity, excellent colloidal stability, and an initial burst release in an acidic environment compared to conventional treatments and its broad applicability across different cancer types. Additional research is required to mitigate these limitations and elucidate safety and long-term efficacy of diosgenin nanoparticles. Moreover, research exhibiting its nontoxic efficacy strongly validated for its utilization in prospective clinical studies or trials. Diosgenin showed significant potential in the treatment and prevention of various human carcinomas; however, further clinical research is required to validate and establish the effectiveness and safer application of diosgenin.

Abbreviations

NPs, Nanoparticles; Skp2, S-phase kinase-associated protein 2; NEDD-4, Neural precursor cell expressed developmentally down-regulated protein 4; HGF, Hepatocyte growth factor; LXN, Latexin gene; mTOR, Mammalian target of rapamycin; P2Ps, P2 phytosomes; ROS, Reactive oxygen species; MMP, Mitochondrial membrane potential; hTERT, Human telomerase reverse transcriptase; Bax, Bcl-2-associated X protein; Bcl2, B-cell lymphoma/lymphoma 2; DDX3, DEAD box polypeptide 3; STAT3, Signal transducer and activator of transcription 3; GLUT, Glucose transporters; COX-2, Cyclooxygenase-2; shRNA, Short hairpin RNA; IONPs Iron oxide nanoparticles; STPP, Sodium tripolyphosphate; DLS, Dynamic light scattering; SEM, Scanning electron microscopy; PGMD, Poly-glycerol malate co-dodecanedioate; DOX, Doxorubicin; PLGA, Polylactide-co-glycolide.

Data Sharing Statement

No data was used for the as it is a review article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Mabe NW, Perry JA, Malone CF, Stegmaier K. Pharmacological targeting of the cancer epigenome. *Nat Cancer*. 2024;5(6):844–865. doi:10.1038/s43018-024-00777-2
2. Debela DT, Muzazu SG, Heraro KD, et al. New approaches and procedures for cancer treatment: current perspectives. *SAGE Open Med*. 2021;9:20503121211034366. doi:10.1177/20503121211034366
3. Metze K, Adam RL, Kayser G, Kayser K. Pathophysiology of cancer and the entropy concept. In: *Model-Based Reasoning in Science and Technology: Abduction, Logic, and Computational Discovery*. Berlin, Heidelberg: Springer; 2010:199–206.
4. Peixoto da Silva S, Santos JM, Costa e Silva MP, Gil da Costa RM, Medeiros R. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia, Sarcopenia Muscle*. 2020;11(3):619–635. doi:10.1002/jcsm.12528
5. Agarwal G, Carcache PJB, Addo EM, Kinghorn AD. Current status and contemporary approaches to the discovery of antitumor agents from higher plants. *Biotechnol Adv*. 2020;38:107337. doi:10.1016/j.biotechadv.2019.01.004
6. Sauter ER. Cancer prevention and treatment using combination therapy with natural compounds. *Expert Rev Clin Pharmacol*. 2020;13 (3):265–285. doi:10.1080/17512433.2020.1738218
7. Lin SR, Chang CH, Hsu CF, et al. Natural compounds as potential adjuvants to cancer therapy: preclinical evidence. *Br J Pharmacol*. 2020;177 (6):1409–1423. doi:10.1111/bph.14816
8. Hashem S, Ali TA, Akhtar S, et al. Targeting cancer signaling pathways by natural products: exploring promising anti-cancer agents. *Biomed Pharmacother*. 2022;150:113054. doi:10.1016/j.biopha.2022.113054
9. Siddiqui AJ, Jahan S, Singh R, et al. Plants in anticancer drug discovery: from molecular mechanism to chemoprevention. *Biomed Res Int*. 2022;2022(1):5425485. doi:10.1155/2022/5425485
10. Akhtar MF, Saleem A, Rasul A, Baig MMFA, Bin-Jumah M, Daim MMA. Anticancer natural medicines: an overview of cell signaling and other targets of anticancer phytochemicals. *Eur J Pharmacol*. 2020;888:173488. doi:10.1016/j.ejphar.2020.173488
11. Katolkar UN, Surana SJ. Exploring the potential role of phytopharmaceuticals in alleviating toxicities of chemotherapeutic agents. *Curr Protein Pept Sci*. 2024;25(10):753–779. doi:10.2174/0113892037307940240606075208
12. Tariq L, Bhat BA, Hamdani SS, Mir RA. Phytochemistry, pharmacology and toxicity of medicinal plants. *Med Aromatic Plants*. 2021;2021:217–240.
13. Chen Y, Wu J, Yu D, Du X. Advances in steroidal saponins biosynthesis. *Planta*. 2021;254:1–17. doi:10.1007/s00425-021-03732-y
14. Mustafa NH, Sekar M, Fuloria S, et al. Chemistry, biosynthesis and pharmacology of sarsasapogenin: a potential natural steroid molecule for new drug design, development and therapy. *Molecules*. 2022;27(6):2032. doi:10.3390/molecules27062032
15. Srinivasa UM, Naidu MM. Fenugreek (Trigonella foenum-graecum L.) seed: promising source of nutraceutical. *Studi Nat Prod Chem*. 2021;71:141–184.
16. Sun F, Yang X, Ma C, et al. The effects of diosgenin on hypolipidemia and its underlying mechanism: a review. *Diab Metab Syndrome Obes*. 2021;Volume 14:4015–4030. doi:10.2147/DMSO.S326054
17. Zhao H, Zhang X, Zhang B, Qu X. Gastroprotective effects of diosgenin against HCl/ethanol-induced gastric mucosal injury through suppression of NF-κβ and myeloperoxidase activities. *Open Life Sci*. 2021;16(1):719–727. doi:10.1515/biol-2021-0075
18. Mohseni-Moghaddam P, Khanmohammadi M, Roghani M. Literature review on hepatoprotective effects of diosgenin: possible mechanisms of action. *Front Pharmacol*. 2023;14:1226548. doi:10.3389/fphar.2023.1226548
19. Selim S, Al Jaouni S. Anti-inflammatory, antioxidant and antiangiogenic activities of diosgenin isolated from traditional medicinal plant, Costus speciosus (Koen ex. Retz.) Sm. *Nat Product Res*. 2016;30(16):1830–1833. doi:10.1080/14786419.2015.1065493
20. Tak Y, Kaur M, Chitranashi A, et al. Fenugreek derived diosgenin as an emerging source for diabetic therapy. *Front Nutr*. 2024;11:1280100. doi:10.3389/fnut.2024.1280100
21. Gupta DD, Mishra S, Verma SS, et al. Evaluation of antioxidant, anti-inflammatory and anticancer activities of diosgenin enriched Paris polyphylla rhizome extract of Indian Himalayan landraces. *J Ethnopharmacol*. 2021;270:113842. doi:10.1016/j.jep.2021.113842
22. Diab D, Pinon A, Ouk C, et al. Involvement of autophagy in diosgenin-induced megakaryocyte differentiation in human erythroleukemia cells. *Mol Med Rep*. 2021;24(5):746. doi:10.3892/mmr.2021.12386
23. Liao AM, Cai B, Huang JH, et al. Synthesis, anticancer activity and potential application of diosgenin modified cancer chemotherapeutic agent cytarabine. *Food Chem Toxicol*. 2021;148:111920. doi:10.1016/j.fct.2020.111920
24. Zhang C, Niu H, Wan C, et al. Drug D, a diosgenin derive, inhibits L-arginine-induced acute pancreatitis through meditating GSDMD in the endoplasmic reticulum via the TXNIP/HIF-1α pathway. *Nutrients*. 2022;14(13):2591. doi:10.3390/nu14132591
25. Semwal P, Painuli S, Abu-Izneid T, et al. Diosgenin: an updated pharmacological review and therapeutic perspectives. *Oxid Med Cell Longev*. 2022;2022(1):1035441. doi:10.1155/2022/1035441
26. Biswas D, Nazir R, Biswas P, et al. Endophytic sources of diosgenin, a natural steroid with multiple therapeutic values. *S Afr J Bot*. 2020;134:119–125. doi:10.1016/j.sajb.2020.04.009

27. Mondal S. Anticancer potential of biologically active diosgenin and its derivatives: an update. *Current Trad Med*. 2024;10(1):67–80. doi:10.2174/2215083809666230202143136
28. Yezdani U, Khan MG, Kushwah N, Verma A, Khan F. Application of nanotechnology in diagnosis and treatment of various diseases and its future advances in medicine. *World J Pharm Pharm Sci*. 2018;7(11):1611–1633.
29. Mazayen ZM, Ghoneim AM, Elbatanony RS, Basalious EB, Bendas ER. Pharmaceutical nanotechnology: from the bench to the market. *Future J Pharm Sci*. 2022;8(1):12. doi:10.1186/s43094-022-00400-0
30. Murday JS, Siegel RW, Stein J, Wright JF. Translational nanomedicine: status assessment and opportunities. *Nanomed Nanotechnol Biol Med*. 2009;5(3):251–273. doi:10.1016/j.nano.2009.06.001
31. Fan D, Cao Y, Cao M, Wang Y, Cao Y, Gong T. Nanomedicine in cancer therapy. *Signal Transduction Targeted Ther*. 2023;8(1):293. doi:10.1038/s41392-023-01536-y
32. Guo YX, He YX. Nanoparticle-based drug delivery systems: an updated strategy for treating fungal keratitis. *Colloid Interface Sci Commun*. 2024;61:100794. doi:10.1016/j.colcom.2024.100794
33. Chenthamara D, Subramaniam S, Ramakrishnan SG, et al. Therapeutic efficacy of nanoparticles and routes of administration. *Biomater Res*. 2019;23(1):20. doi:10.1186/s40824-019-0166-x
34. Bilia AR, Piazzini V, Risaliti L, et al. Nanocarriers: a successful tool to increase solubility, stability and optimise bioefficacy of natural constituents. *Curr Med Chem*. 2019;26(24):4631–4656. doi:10.2174/0929867325666181101110050
35. Wang D, Wang X. Diosgenin and its analogs: potential protective agents against atherosclerosis. *Drug Des Devel Ther*. 2022;16:2305–2323. doi:10.2147/DDDT.S368836
36. Obidiegwu JE, Lyons JB, Chilaka CA. The Dioscorea Genus (Yam)-an appraisal of nutritional and therapeutic potentials. *Foods*. 2020;9(9):1304. doi:10.3390/foods9091304
37. Jesus M, Martins AP, Gallardo E, Silvestre S. Diosgenin: recent Highlights on Pharmacology and Analytical Methodology. *J Analytical Meth Chem*. 2016;2016:4156293. doi:10.1155/2016/4156293
38. Nigam V. Phytochemistry, anthelmintic study of herbaceous aerial part of Kallstroemia pubescens (G. Don) & review of novel effects of diosgenin: a plant derived steroid. *Int J Current Res Physiol Pharmacol*. 2018;5–9. doi:10.31878/ijcrpp.2018.22.2
39. Yu C, Li Z, Yin H, et al. Green production of diosgenin from Discorea nipponica Makino tubers based on pressurized biphase acid hydrolysis via response surface methodology optimization. *Green Chem Lett Rev*. 2019;12(1):79–88. doi:10.1080/17518253.2019.1579370
40. Cai B, Zhang Y, Wang Z, et al. Therapeutic potential of diosgenin and its major derivatives against neurological diseases: recent advances. *Oxid Med Cell Longev*. 2020;3153082. doi:10.1155/2020/3153082
41. Yang ZHAO, Bing FENG, Li-Ping KANG, et al. Biotransformation of Dichotomin by pectinex BE XXL. *Chinese J Nat Med*. 2009;7(5):381–389.
42. Okawara M, Tokudome Y, Todo H, Sugibayashi K, Hashimoto F. Enhancement of diosgenin distribution in the skin by cyclodextrin complexation following oral administration. *Biol Pharm Bull*. 2013;36(1):36–40. doi:10.1248/bpb.b12-00467
43. Liu P, Xu L, Guo JH, et al. Pharmacokinetic analysis of diosgenin in rat plasma by a UPLC-MS/MS approach. *J Analytical Meth Chem*. 2022;2022:5607347. doi:10.1155/2022/5607347
44. de Souza W, Rodrigues JC. Sterol biosynthesis pathway as target for anti-trypanosomatid drugs. *Interdisciplinary Perspectives Infectious Dis*. 2009;2009:642502. doi:10.1155/2009/642502
45. Chaudhary S, Chikara SK, Sharma MC, et al. Elicitation of Diosgenin production in Trigonella foenum-graecum (Fenugreek) Seedlings by Methyl Jasmonate. *Int J mol Sci*. 2015;16(12):29889–29899. doi:10.3390/ijms161226208
46. Rytting E, Lentz KA, Chen XQ, Qian F, Vakatesh S. Aqueous and cosolvent solubility data for drug-like organic compounds. *AAPS J*. 2005;7(1):E78–E105. doi:10.1208/aapsj070110
47. Manda VK, Avula B, Ali Z, et al. Characterization of in vitro ADME properties of diosgenin and dioscin from Dioscorea villosa. *Planta med*. 2013;79(15):1421–1428. doi:10.1055/s-0033-1336521
48. Okawara M, Hashimoto F, Todo H, Sugibayashi K, Tokudome Y. Effect of liquid crystals with cyclodextrin on the bioavailability of a poorly water-soluble compound, diosgenin, after its oral administration to rats. *Int J Pharm*. 2014;472(1–2):257–261. doi:10.1016/j.ijpharm.2014.06.032
49. Xu T, Zhang S, Zheng L, Yin L, Xu L, Peng J. A 90-day subchronic toxicological assessment of dioscin, a natural steroid saponin, in Sprague-Dawley rats. *Food Chem Toxicol*. 2012;50(5):1279–1287. doi:10.1016/j.fct.2012.02.027
50. Zhang J, Wang X, Yang J, et al. Novel diosgenin derivatives containing 1, 3, 4-oxadiazole/thiadiazole moieties as potential antitumor agents: design, synthesis and cytotoxic evaluation. *Eur J Med Chem*. 2020;186:111897. doi:10.1016/j.ejmech.2019.111897
51. Cai H, Gong L, Liu J, Zhou Q, Zheng Z. Diosgenin inhibits tumor angiogenesis through regulating GRP78-mediated HIF-1α and VEGF/VEGFR signaling pathways. *Die Pharmazie*. 2019;74(11):680–684.
52. He Z, Chen H, Li G, et al. Diosgenin inhibits the migration of human breast cancer MDA-MB-231 cells by suppressing Vav2 activity. *Phytomedicine*. 2014;21(6):871–876. doi:10.1016/j.phymed.2014.02.002
53. Liu Y, Zhou Z, Yan J, Wu X, Xu G. Diosgenin exerts antitumor activity via downregulation of Skp2 in breast cancer cells. *Biomed Res Int*. 2020;2020(1):8072639. doi:10.1155/2020/8072639
54. Khanal P, Patil VS, Bhandare VV, et al. Systems and in vitro pharmacology profiling of diosgenin against breast cancer. *Front Pharmacol*. 2023;13:1052849. doi:10.3389/fphar.2022.1052849
55. Liao WL, Lin JY, Shieh JC, et al. Induction of G2/M phase arrest by diosgenin via activation of Chk1 kinase and Cdc25C regulatory pathways to promote apoptosis in human breast cancer cells. *Int J Mol Sci*. 2019;21(1):172. doi:10.3390/ijms21010172
56. Jagadeesan J, Nandakumar N, Rengarajan T, Balasubramanian MP. Diosgenin, a steroidal saponin, exhibits anticancer activity by attenuating lipid peroxidation via enhancing antioxidant defense system during NMU-induced breast carcinoma. *J Environ Pathol Toxicol Oncol*. 2012;31(2):121–129. doi:10.1615/JEnvironPatholToxicolOncol.v31.i2.40
57. Selim S, Al Jaouni S. Anticancer and apoptotic effects on cell proliferation of diosgenin isolated from Costus speciosus (Koen.) Sm. *BMC Complementary Alternative Med*. 2015;15:1–7. doi:10.1186/s12906-015-0836-8
58. Chen PS, Shih YW, Huang HC, Cheng HW. Diosgenin, a steroidal saponin, inhibits migration and invasion of human prostate cancer PC-3 cells by reducing matrix metalloproteinases expression. *PLoS One*. 2011;6(5):e20164. doi:10.1371/journal.pone.0020164

59. Zhang J, Xie JJ, Zhou SJ, et al. Diosgenin inhibits the expression of NEDD4 in prostate cancer cells. *Am J Transl Res*. 2019;11(6):3461.
60. Nie C, Zhou J, Qin X, et al. Diosgenin-induced autophagy and apoptosis in a human prostate cancer cell line. *Mol medrep*. 2016;14 (5):4349–4359. doi:10.3892/mmr.2016.5750
61. Sikka S, Shanmugam MK, Siveen KS, et al. Diosgenin attenuates tumor growth and metastasis in transgenic prostate cancer mouse model by negatively regulating both NF-κB/STAT3 signaling cascades. *Eur J Pharmacol*. 2021;906:174274. doi:10.1016/j.ejphar.2021.174274
62. Chang HY, Kao MC, Way TD, Ho CT, Fu E. Diosgenin suppresses hepatocyte growth factor (HGF)-induced epithelial–mesenchymal transition by down-regulation of Mdm2 and vimentin. *J Agri Food Chem*. 2011;59(10):5357–5363. doi:10.1021/jf200598w
63. Peng Y, Tang R, Ding L, et al. Diosgenin inhibits prostate cancer progression by inducing UHRF1 protein degradation. *Eur J Pharmacol*. 2023;942:175522. doi:10.1016/j.ejphar.2023.175522
64. Li Y, Wang X, Cheng S, et al. Diosgenin induces G2/M cell cycle arrest and apoptosis in human hepatocellular carcinoma cells. *Oncol Rep*. 2015;33(2):693–698. doi:10.3892/or.2014.3629
65. Chen Z, Xu J, Wu Y, et al. Diosgenin inhibited the expression of TAZ in hepatocellular carcinoma. *Biochem Biophys Res Commun*. 2018;503 (3):1181–1185. doi:10.1016/j.bbrc.2018.07.022
66. Li F, Fernandez PP, Rajendran P, Hui KM, Sethi G. Diosgenin, a steroidal saponin, inhibits STAT3 signaling pathway leading to suppression of proliferation and chemosensitization of human hepatocellular carcinoma cells. *Cancer Lett*. 2010;292(2):197–207. doi:10.1016/j.canlet.2009.12.003
67. Yu H, Liu Y, Niu C, Cheng Y. Diosgenin increased DDX3 expression in hepatocellular carcinoma. *Am J Transl Res*. 2018;10(11):3590.
68. Kim DS, Jeon BK, Lee YE, Woo WH, Mun YJ. Diosgenin induces apoptosis in HepG2 cells through generation of reactive oxygen species and mitochondrial pathway. *Evidence-Based Complementary Alternative Med*. 2012;2012(1):981675. doi:10.1155/2012/981675
69. Cruz MS, Navoni JA, da Costa Xavier LA, et al. Diosgenin induces genotoxic and mutagenic effects on HepG2 cells. *Food and Chemical Toxicology*. 2018;120:98–103. doi:10.1016/j.fct.2018.07.011
70. Lepage C, Léger DY, Bertrand J, Martin F, Beneytout JL, Liagre EB. Diosgenin induces death receptor-5 through activation of p38 pathway and promotes TRAIL-induced apoptosis in colon cancer cells. *Cancer Lett*. 2011;301(2):193–202. doi:10.1016/j.canlet.2010.12.003
71. Lai Z, Wang H, Tang X, Zhang L, Wang T, Cheng J. Study on the mechanism of diosgenin targeting STAT3 to inhibit colon cancer proliferation and migration. *Dis Markers*. 2022;2022(1):7494887. doi:10.1155/2022/7494887
72. Li SY, Shang J, Mao XM, et al. Diosgenin exerts anti-tumor effects through inactivation of cAMP/PKA/CREB signaling pathway in colorectal cancer. *Eur J Pharmacol*. 2021;908:174370. doi:10.1016/j.ejphar.2021.174370
73. Liu S, Rong G, Li X, et al. Diosgenin and GSK126 produce synergistic effects on epithelial–mesenchymal transition in gastric cancer cells by mediating EZH2 via the Rho/ROCK signaling pathway. *Onco Targets Ther*. 2020;Volume 13:5057–5067. doi:10.2147/OTT.S237474
74. Ding W, Jiang Y, Jiang Y, et al. Role of SB203580 in the regulation of human esophageal cancer cells under the effection of Diosgenin. *Int J Clin Exp Med*. 2015;8(2):2476.
75. Mao XM, Zhou P, Li SY, et al. Diosgenin suppresses cholangiocarcinoma cells via inducing cell cycle arrest and mitochondria-mediated apoptosis. *Onco Targets Ther*. 2019;Volume 12:9093–9104. doi:10.2147/OTT.S226261
76. Guo W, Chen Y, Gao J, et al. Diosgenin exhibits tumor suppressive function via down-regulation of EZH2 in pancreatic cancer cells. *Cell Cycle*. 2019;18(15):1745–1758. doi:10.1080/15384101.2019.1632624
77. Rahmati-Yamchi M, Ghareghomi S, Haddadchi G, Milani M, Aghazadeh M, Daroushnejad H. Fenugreek extract diosgenin and pure diosgenin inhibit the hTERT gene expression in A549 lung cancer cell line. *Mol biol rep*. 2014;41:6247–6252. doi:10.1007/s11033-014-3505-y
78. Xu L, Xu D, Li Z, Gao Y, Chen H. Synthesis and potent cytotoxic activity of a novel diosgenin derivative and its phytosomes against lung cancer cells. *Beilstein J Nanotechnol*. 2019;10(1):1933–1942. doi:10.3762/bjnano.10.189
79. Long C, Chen J, Zhou H, et al. Diosgenin exerts its tumor suppressive function via inhibition of Cdc20 in osteosarcoma cells. *Cell Cycle*. 2019;18(3):346–358. doi:10.1080/15384101.2019.1568748
80. Huang H, Nie C, Qin X, Zhou J, Zhang L. Diosgenin inhibits the epithelial-mesenchymal transition initiation in osteosarcoma cells via the p38MAPK signaling pathway. *Oncol Lett*. 2019;18(4):4278–4287. doi:10.3892/ol.2019.10780
81. López EPF, Wang QT, Wei W, Jornet PL. Potential chemotherapeutic effects of diosgenin, zoledronic acid and epigallocatechin-3-gallate on PE/CA-PJ15 oral squamous cancer cell line. *Arch Oral Biol*. 2017;82:141–146. doi:10.1016/j.archoralbio.2017.05.023
82. Das S, Dey KK, Dey G, et al. Antineoplastic and apoptotic potential of traditional medicines thymoquinone and diosgenin in squamous cell carcinoma. *PLoS One*. 2012;7:e46641. doi:10.1371/journal.pone.0046641
83. Zhu X, Chen Z, Li X. Diosgenin inhibits the proliferation, migration and invasion of the optic nerve sheath meningioma cells via induction of mitochondrial-mediated apoptosis, autophagy and G0/G1 cell cycle arrest. *J BUON*. 2020;25(1):508–513.
84. Jiang S, Fan J, Wang Q, et al. Diosgenin induces ROS-dependent autophagy and cytotoxicity via mTOR signaling pathway in chronic myeloid leukemia cells. *Phytomedicine*. 2016;23(3):243–252. doi:10.1016/j.phymed.2016.01.010
85. Mu S, Tian X, Ruan Y, et al. Diosgenin induces apoptosis in IGF-1-stimulated human thyrocytes through two caspase-dependent pathways. *Biochem Biophys Res Commun*. 2012;418(2):347–352. doi:10.1016/j.bbrc.2012.01.024
86. Dong M, Meng Z, Kuerban K, et al. Diosgenin promotes antitumor immunity and PD-1 antibody efficacy against melanoma by regulating intestinal microbiota. *Cell Death Dis*. 2018;9(10):1039. doi:10.1038/s41419-018-1099-3
87. Khathayer F, Ray SK. Diosgenin as a novel alternative therapy for inhibition of growth, invasion, and angiogenesis abilities of different glioblastoma cell lines. *Neurochem Res*. 2020;45(10):2336–2351. doi:10.1007/s11064-020-03093-0
88. Zhang W, Cao L, Sun Z, et al. Skp2 is over-expressed in breast cancer and promotes breast cancer cell proliferation. *Cell Cycle*. 2016;15 (10):1344–1351. doi:10.1080/15384101.2016.1160986
89. Li C, Du L, Ren Y, et al. SKP2 promotes breast cancer tumorigenesis and radiation tolerance through PDCD4 ubiquitination. *J Exp Clin Cancer Res*. 2019;38:1–15.
90. Hecht F, Pessoa CF, Gentile LB, Rosenthal D, Carvalho DP, Fortunato RS. The role of oxidative stress on breast cancer development and therapy. *Tumor Biol*. 2016;37:4281–4291. doi:10.1007/s13277-016-4873-9
91. Holze C, Michaudel C, Mackowiak C, et al. Oxeiptosis, a ROS-induced caspase-independent apoptosis-like cell-death pathway. *Nat Immunol*. 2018;19(2):130–140. doi:10.1038/s41590-017-0013-y
92. Ali A, Kulik G. Signaling pathways that control apoptosis in prostate cancer. *Cancers*. 2021;13(5):937. doi:10.3390/cancers13050937

93. Liu W, Meng Y, Zong C, Zhang S, Wei L. Autophagy and tumorigenesis. *Autophagy*. 2020;2020:275–299.
94. Rangel M, Kong J, Bhatt V, Khayati K, Guo JY. Autophagy and tumorigenesis. *FEBS J*. 2022;289(22):7177–7198. doi:10.1111/febs.16125
95. Ye X, Wang L, Shang B, Wang Z, Wei W. NEDD4: a promising target for cancer therapy. *Curr Cancer Drug Targets*. 2014;14(6):549–556. doi:10.2174/1568009614666140725092430
96. Shorning BY, Dass MS, Smalley MJ, Pearson HB. The PI3K-AKT-mTOR pathway and prostate cancer: at the crossroads of AR, MAPK, and WNT signaling. *Int J mol Sci*. 2020;21(12):4507.
97. Pungsrinont T, Kallenbach J, Baniahmad A. Role of PI3K-AKT-mTOR pathway as a pro-survival signaling and resistance-mediating mechanism to therapy of prostate cancer. *Int J mol Sci*. 2021;22(20):11088. doi:10.3390/ijms222011088
98. Sadrkhanloo M, Paskeh MDA, Hashemi M, et al. STAT3 signaling in prostate cancer progression and therapy resistance: an oncogenic pathway with diverse functions. *Biomed Pharmacother*. 2023;158:114168. doi:10.1016/j.biopha.2022.114168
99. Fu J, Su X, Li Z, et al. HGF/c-MET pathway in cancer: from molecular characterization to clinical evidence. *Oncogene*. 2021;40 (28):4625–4651. doi:10.1038/s41388-021-01863-w
100. Chen FZ, Zhao XK. Ubiquitin-proteasome pathway and prostate cancer. *Oncol Res Treatment*. 2013;36(10):592–596. doi:10.1159/000355166
101. Varkaris A, Corn PG, Gaur S, Dayyani F, Logothetis CJ, Gallick GE. The role of HGF/c-Met signaling in prostate cancer progression and c-Met inhibitors in clinical trials. *Expert Opin Invest Drugs*. 2011;20(12):1677–1684. doi:10.1517/13543784.2011.631523
102. Dobija-Kubica K, Zalewska-Ziob M, Bruliński K, et al. Telomerase activity in non-small cell lung cancer. *Kardiochirurgia i Torakochirurgia Polska/Polish J Thoracic Cardiovasc Surg*. 2016;13(1):15–20.
103. Guterres AN, Villanueva J. Targeting telomerase for cancer therapy. *Oncogene*. 2020;39(36):5811–5824. doi:10.1038/s41388-020-01405-w
104. Erdagi SI, Yildiz U. Synthesis of diosgenin derivatives by A and B ring modifications and low-valent titanium (Ti0)-catalysed McMurry coupling reactions and designing to create novel biological agents. *J Mol Struct*. 2022;1256:132511. doi:10.1016/j.molstruc.2022.132511
105. Wang W, Chen Z, Chen X, et al. DG-8d, a novel diosgenin derivative, decreases the proliferation and induces the apoptosis of A549 cells by inhibiting the PI3k/Akt signaling pathway. *Steroids*. 2021;174:108898. doi:10.1016/j.steroids.2021.108898
106. Sun M, He L, Fan Z, Tang R, Du J. Effective treatment of drug-resistant lung cancer via a nanogel capable of reactivating cisplatin and enhancing early apoptosis. *Biomaterials*. 2020;257:120252. doi:10.1016/j.biomaterials.2020.120252
107. da Silva MF, de Lima LVA, de Oliveira LM, et al. Regulation of cytokinesis and necroptosis pathways by diosgenin inhibits the proliferation of NCI-H460 lung cancer cells. *Life Sci*. 2023;330:122033. doi:10.1016/j.lfs.2023.122033
108. Wang Q, Zhang L, Xiao Y, Ghaemnezhad A. Diosgenin promotes cisplatin-induced apoptosis through oxidative DNA damage in A549 non-small cell lung cells. *Cell Biol Int*. 2022;46(10):1571–1576. doi:10.1002/cbin.11862
109. Gao M, Chen L, Yu H, Sun Q, Kou J, Yu B. Diosgenin down-regulates NF-κB p65/p50 and p38MAPK pathways and attenuates acute lung injury induced by lipopolysaccharide in mice. *Int Immunopharmacol*. 2013;15(2):240–245. doi:10.1016/j.intimp.2012.11.019
110. Secchi M, Lodola C, Garbelli A, Bione S, Maga G. DEAD-box RNA helicases DDX3X and DDX5 as oncogenes or oncosuppressors: a network perspective. *Cancers*. 2022;14(15):3820. doi:10.3390/cancers14153820
111. Corbiere C, Liagre B, Terro F, Beneytout JL. Induction of antiproliferative effect by diosgenin through activation of p53, release of apoptosis-inducing factor (AIF) and modulation of caspase-3 activity in different human cancer cells. *Cell Res*. 2004;14(3):188–196. doi:10.1038/sj.cr.7290219
112. Jia J, Zhou X, Chu Q. Mechanisms and therapeutic prospect of the JAK-STAT signaling pathway in liver cancer. *mol Cell Biochem*. 2024;1–17. doi:10.1007/s11010-024-04983-5
113. Liu Y, Wang X, Yang Y. Hepatic Hippo signaling inhibits development of hepatocellular carcinoma. *Clin Mol Hepatol*. 2020;26(4):742. doi:10.3350/cmh.2020.0178
114. Yousef EH, El-Mesery ME, Habeeb MR, Eissa LA. Diosgenin potentiates the anticancer effect of doxorubicin and volasertib via regulating polo-like kinase 1 and triggering apoptosis in hepatocellular carcinoma cells. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2024;397:1–12.
115. Lepage C, Liagre B, Cook-Moreau J, Pinon A, Beneytout JL. Cyclooxygenase-2 and 5-lipoxygenase pathways in diosgenin-induced apoptosis in HT-29 and HCT-116 colon cancer cells. *Int j Oncol*. 2010;36(5):1183–1191. doi:10.3892/ijo_00000601
116. Gu L, Zheng H, Zhao R, Zhang X, Wang Q. Diosgenin inhibits the proliferation of gastric cancer cells via inducing mesoderm posterior 1 down-regulation-mediated alternative reading frame expression. *Hum Exp Toxicol*. 2021;40(12_suppl):S632–S645. doi:10.1177/09603271211053292
117. Ya L, Ruibai L, Fengqin S, et al. Anti-cancer effect of diosgenin through regulating miR-34a and its target genes in gastric cancer. *J Beijing Univ Trad Chin Med*. 2020;43(2):1.
118. Mao ZJ, Tang QJ, Zhang CA, et al. Anti-proliferation and anti-invasion effects of diosgenin on gastric cancer BGC-823 cells with HIF-1α shRNAs. *Int J mol Sci*. 2012;13(5):6521–6533. doi:10.3390/ijms13056521
119. Moukengue B, Lallier M, Marchandet L, et al. Origin and therapies of osteosarcoma. *Cancers*. 2022;14(14):3503. doi:10.3390/cancers14143503
120. Rajalingam K, Sugunadevi G, Arokia Vijayaanand M, Kalaimathi J, Suresh K. Anti-tumour and anti-oxidative potential of diosgenin against 7, 12-dimethylbenz (a) anthracene induced experimental oral carcinogenesis. *Pathol Oncol Res*. 2012;18:405–412. doi:10.1007/s12253-011-9460-1
121. Fang F, Zhang X, Fang Y. Diosgenin inhibits proliferation and migration of ovarian cancer cells and induce apoptosis via upregulation of PTEN. *Chem Biol Drug Des*. 2024;103(3):e14459. doi:10.1111/cbdd.14459
122. Mosleh-Shirazi S, Abbasi M, Reza Moaddeli M, et al. Nanotechnology advances in the detection and treatment of cancer: an overview. *Nanotheranostics*. 2022;6(4):400. doi:10.7150/ntno.74613
123. Namasivayam SKR, Haveela E, Samrat K, et al. Production, nanoformulation, and potential anticancer effect of camptothecin metabolites from biomass of Aspergillus Niger. *Biomass Convers Biorefin*. 2024;14(15):18005–18018. doi:10.1007/s13399-023-03861-2
124. Huang H, Feng W, Chen Y, Shi J. Inorganic nanoparticles in clinical trials and translations. *Nano Today*. 2020;35:100972. doi:10.1016/j.nantod.2020.100972
125. Hosseinkazemi H, Samani S, O'Neill A, et al. Applications of iron oxide nanoparticles against breast cancer. *J Nanomater*. 2022;2022 (1):6493458. doi:10.1155/2022/6493458
126. Ghosh S, More P, Derle A, et al. Diosgenin functionalized iron oxide nanoparticles as novel nanomaterial against breast cancer. *J nanosci nanotechnol*. 2015;15(12):9464–9472. doi:10.1166/jnn.2015.11704

127. Rabha B, Bharadwaj KK, Baishya D, Sarkar T, Edinur HA, Pati S. Synthesis and characterization of diosgenin encapsulated poly-ε-caprolactone -pluronic nanoparticles and its effect on brain cancer cells. *Polymers*. 2021;13(8):1322. doi:10.3390/polym13081322
128. Kala K, Sivalingam S, Devi Y, Devi Y. Encapsulation of Diosgenin in chitosan nanoparticles with enhanced in vitro and in vivo anticancer activity in Female Sprague Dawley rats. *Surf Interfaces*. 2023;41:103158. doi:10.1016/j.surfin.2023.103158
129. Hajizadeh MR, Parvaz N, Barani M, et al. Diosgenin-loaded niosome as an effective phytochemical nanocarrier: physicochemical characterization, loading efficiency, and cytotoxicity assay. *DARU J Pharma Sci*. 2019;27:329–339. doi:10.1007/s40199-019-00277-0
130. Sharma N, Singhal M and Kumari RM, et al. Diosgenin loaded polymeric nanoparticles with potential anticancer efficacy. *Biomolecules*. 2020;10(12). doi:10.3390/biom10121679), 1679.
131. Meng X, Dong H, Pan Y, et al. Diosgenyl saponin inducing endoplasmic reticulum stress and mitochondria-mediated apoptotic pathways in liver cancer cells. *J Agri Food Chem*. 2019;67(41):11428–11435. doi:10.1021/acs.jafc.9b05131
132. Anwar DM, El-Sayed M, Reda A, Fang JY, Khattab SN, Elzoghby AO. Recent advances in herbal combination nanomedicine for cancer: delivery technology and therapeutic outcomes. *Expert Opin Drug Delivery*. 2021;18(11):1609–1625. doi:10.1080/17425247.2021.1955853
133. Al-Malky HS, Al Harthi SE, Osman AMM. Major obstacles to doxorubicin therapy: cardiotoxicity and drug resistance. *J Oncol Pharm Pract*. 2020;26(2):434–444. doi:10.1177/1078155219877931
134. Chen L, Lan J, Li Z, et al. A novel diosgenin-based liposome delivery system combined with doxorubicin for liver cancer therapy. *Pharmaceutics*. 2022;14(8):1685. doi:10.3390/pharmaceutics14081685
135. Fares J, Fares MY, Khachfe HH, Salhab HA, Fares Y. Molecular principles of metastasis: a hallmark of cancer revisited. *Signal Transduction Targeted Ther*. 2020;5(1):28. doi:10.1038/s41392-020-0134-x
136. Wei Z, Wang H, Xin G, et al. A pH-sensitive prodrug nanocarrier based on diosgenin for doxorubicin delivery to efficiently inhibit tumor metastasis. *Int j Nanomed*. 2020;Volume 15:6545–6560. doi:10.2147/IJN.S250549
137. Vengaimaran M, Dhamodharan K, Sankaran M. Nano diosgenin abates DMBA induced renal and hepatic toxicities: biochemical and histopathological evaluation on the Breast Cancer Model. *Curr Bioact Compd*. 2023;19(4):47–67.
138. Dharani S, Kalaiarasi G, Ravi M, Raj NS, Lynch VM, Prabhakaran R. Diosgenin derivatives developed from Pd (II) catalysed dehydrogenative coupling exert an effect on breast cancer cells by abrogating their growth and facilitating apoptosis via regulating the AKT1 pathway. *Dalton Trans*. 2022;51(17):6766–6777. doi:10.1039/D2DT00514J
139. Erdagi SI, Yildiz U. Diosgenin-conjugated PCL–MPEG polymeric nanoparticles for the co-delivery of anticancer drugs: design, optimization, in vitro drug release and evaluation of anticancer activity. *New J Chem*. 2019;43(17):6622–6635. doi:10.1039/C9NJ00659A
140. Fazili KM, Fazili KM, Bhat KA, Ara T, Ara T. Synthesis and biological evaluation of novel 3-O-tethered triazoles of diosgenin as potent antiproliferative agents. *Steroids*. 2017;118:1–8. doi:10.1016/j.steroids.2016.11.003
141. Amina SJ, Iqbal M, Faisal A, et al. Synthesis of diosgenin conjugated gold nanoparticles using algal extract of Dictyosphaerium sp. and in-vitro application of their antiproliferative activities. *Mater Today Commun*. 2021;27:102360. doi:10.1016/j.mtcomm.2021.102360
142. Erdagi SI, Ngwabebhoh FA, Yildiz U. Pickering stabilized nanocellulose-alginate: a diosgenin-mediated delivery of quinalizarin as a potent cyto-inhibitor in human lung/breast cancer cell lines. *Mater Sci Eng C*. 2020;109:110621. doi:10.1016/j.msec.2019.110621
143. Dey SK, Pradhan A, Roy T, Das S, Chattopadhyay D, Choudhury SM. Biogenic polymer-encapsulated diosgenin nanoparticles: biodistribution, pharmacokinetics, cellular internalization, and anticancer potential in breast cancer cells and tumor xenograft. *J Drug Delivery Sci Technol*. 2022;76:103743. doi:10.1016/j.jddst.2022.103743
144. AbouAitah K, Abdelaziz AM, Higazy IM, et al. Functionalized Carbon Nanotubes for Delivery of Ferulic Acid and Diosgenin Anticancer Natural Agents. *ACS Appl Bio Mater*. 2024;7(2):791–811. doi:10.1021/acsabm.3c00700