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Diosgenin: A review of exploring its Potential as an Anti-cancer agent

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ABSTRACT

Diosgenin, a natural phytosteroid in various plant sources, has garnered attention for its potential anti-inflammatory and anti-cancer attributes. This review comprehensively examines the anticancer and anti-inflammatory properties of diosgenin by analysing pertinent research. Diosgenin exhibits various biological effects, including hypolipidemia, hypoglycemia, and potent antioxidant activity. Studies have demonstrated its capacity to hinder cancer cell proliferation, trigger apoptosis, and impede metastasis in diverse cancer types. Mechanistically, diosgenin modulates pivotal signalling pathways governing cell cycle regulation, differentiation, and apoptosis. Beyond its anticancer properties, diosgenin exhibits notable anti-inflammatory attributes, selectively engaging molecules critical to the inflammation cascade and influencing cellular mechanisms encompassing invasion, migration, proliferation, and metastasis in cancerous cells. It effectively inhibits pro-inflammatory cytokines and signalling pathways, including NF-κB and MAPK, thus mitigating inflammation-driven cancers. Notably, diosgenin exhibits promise in prostate and breast cancer, where it restrains invasion and migration of prostate cancer cells, suppresses pro-inflammatory cytokines, and downregulates matrix-degrading enzymes. To sum up, diosgenin stands out as a natural compound boasting dual capabilities, with both anti-inflammatory and anti-cancer properties. Its capacity to regulate signalling pathways associated with inflammation and tumourigenesis positions it as a promising candidate for the development of anti-carcinogenic therapeutics. Nonetheless, further in-depth research is essential to fully unravel the underlying mechanisms and evaluate diosgenin's clinical potential in the realm of cancer therapy.

Keywords: *Diosgenin; Anti-inflammatory; Anticancer; Signaling pathway*

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1. INTRODUCTION

Diosgenin, a phytosteroid derived from the sapogenin class of glycosides, represents a naturally occurring bioactive compound with diverse pharmacological benefits. It is primarily sourced from *Dioscorea* species (wild yams), as well as other plants such as *Trigonella foenum-graecum* (fenugreek), *Costus speciosus*, *Smilax menispermoidea*, *Aletris*, and *Trillium* (Semwal et al., 2022; Sethi et al., 2018a; C. H. Yan et al., 2015a). The chemical structure of Diosgenin features a steroidal framework, which underpins its biological activities and contributes to its efficacy in various therapeutic contexts. Traditionally, Diosgenin has played a significant role in herbal medicine, being utilized in the synthesis of steroidal drugs, particularly corticosteroids and contraceptives. In modern pharmacology, its utility has expanded, showcasing a wide array of biological effects such as anti-inflammatory, hypoglycemic, hypolipidemic, and anti-proliferative properties (Semwal et al., 2022; Sethi et al., 2018a; C. H. Yan et al., 2015a).

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With more than 19.3 million new cases and 10 million fatalities recorded in 2020 alone, cancer continues to rank among the world's top causes of death (Sathishkumar et al., 2022). The limitations of conventional cancer treatments, including drug resistance, off-target toxicity, and high costs, underscore the urgency for exploring safer and more effective alternatives. Natural compounds, such as Diosgenin, are gaining traction due to their multifaceted mechanisms of action and ability to target various hallmarks of cancer without significant side effects. Diosgenin, specifically, has shown promise in inducing apoptosis, inhibiting cell proliferation, and suppressing metastasis across various cancer types in preclinical studies (X. M. Mao et al., 2019).

The current interest in Diosgenin stems from its ability to regulate critical signaling pathways involved in inflammation and cancer. Key pathways such as nuclear factor-kappa B (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3) are pivotal in modulating the inflammatory milieu that often underlies cancer development (Ren et al., 2023a). Diosgenin's inhibition of these pathways, along with its antioxidant properties and ability to induce programmed cell death (apoptosis) in cancer cells, underscores its potential as a therapeutic agent.

This review aims to provide a comprehensive analysis of Diosgenin's anti-inflammatory and anti-cancer properties, with a focus on its mechanisms of action, preclinical and clinical evidence, and future therapeutic potential. By synthesizing current knowledge, this review seeks to highlight the relevance of Diosgenin in the development of novel strategies for cancer therapy, particularly in addressing inflammation-driven cancers and enhancing treatment efficacy through natural compound-based interventions (Semwal et al., 2022; Sethi et al., 2018a).

2. REVIEW METHODOLOGY

For the execution of this comprehensive study, a thorough analysis of pertinent research including pharmacological properties of cancer such as concerning the anti-cancer and anti-inflammatory properties of diosgenin was conducted. The search was conducted across various scientific databases, including PubMed, Google Scholar, DOAJ, Medline, and Scopus, employing specific keywords: "Diosgenin," "Diosgenin/pharmacology," "Diosgenin/therapeutic use," "Humans," "Anti-inflammatory agents/pharmacology," "Inflammation and cancer," "Anti-inflammatory activity of diosgenin," "Mechanism of inflammation and cancer," "Mechanism of anti-cancer activity of diosgenin," "Saponins/toxicity," "steroids," and "Signal Transduction/drug effects." The inclusion criteria encompassed studies elucidating the molecular mechanisms and experimental evidence of diosgenin's anti-cancer and anti-inflammatory effects. The salient findings were then succinctly summarized and presented in tables and visual representations.

3. CHEMICAL STRUCTURE AND PROPERTIES

Diosgenin is a biologically active steroidal sapogenin with a spirostanol skeleton, making it a precursor molecule for synthesizing several steroid hormones, including corticosteroids and sex hormones. Its structure consists of a 27-carbon framework with a spiroketal unit at C-22 and C-26 and a hydroxyl group at C-3, conferring unique biological activity(Patel & Savjani, 2015a). The physicochemical properties of Diosgenin, such as its low aqueous solubility and moderate stability under physiological conditions, have been highlighted as critical factors influencing its pharmacological applications. These properties necessitate the development of innovative formulations to enhance its bioavailability and stability in clinical settings(Mishra et al., 2020) Figure 1.

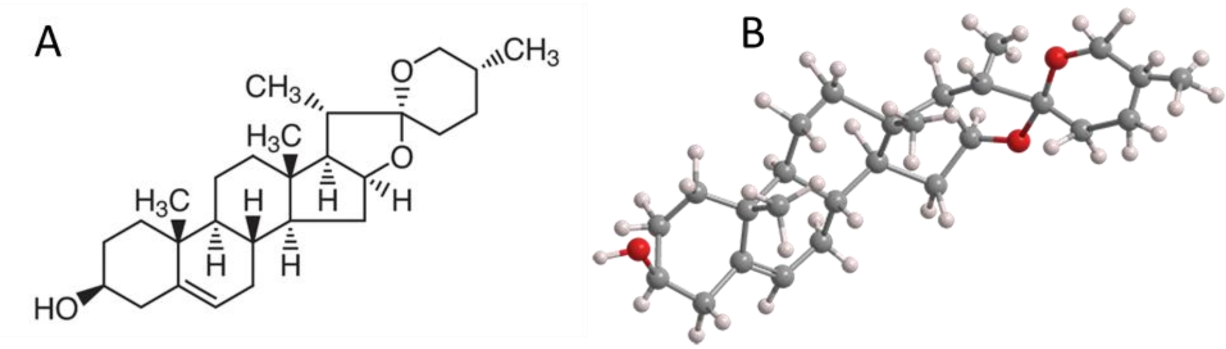

Figure 1. Chemical structure of Diosgenin (A) and its 3D form (B).

3.1 Sources of Diosgenin

Diosgenin is predominantly extracted from plants of the *Dioscorea* genus (wild yams) and *Trigonella foenum-graecum* (fenugreek). Almost 137 species of this genus contain diosgenin (Cai et al., 2020; Kang et al., 2011); Table 1 discussed all the possible sources of diosgenin. These sources are rich in saponins, which serve as precursors for Diosgenin production. Extraction typically involves acid or enzymatic hydrolysis of the glycosides present in the plant, followed by purification using chromatographic techniques. Advanced methods, such as supercritical fluid extraction and green solvents, have been proposed to improve yield and sustainability in Diosgenin extraction processes (Arya et al., 2023). Diosgenin, as a component of fenugreek seed extract, occurs alongside other bioactive compounds, including flavonoids, coumarins, and alkaloids. This diverse biochemical composition underpins the extract's wide range of pharmacological effects, as demonstrated by in vitro and in vivo studies(C. H. Yan et al., 2015b).

Table 1. Diosgenin isolated from different plant species sources.

SN	Botanical Name	Family	References
1	Asparagus officinalis (*Asparagus*)	Asparagaceae	(Poonam & Sahoo, 2015)
2	*Costus speciosus*	Costaceae	(Selim & AL Jaouni, 2015)
3	*Dioscorea villosa (Yam)*	Dioscoreaceae	(Raju & Rao, 2012)
4	*Dioscorea bulbifera*	Ranunculaceae,	(Kirtikar & Basu, 2011)
5	*Helicteres isora* L.	Malvaceae	(Deshpande & Bhalsing, 2014)
6	*Helleborus orientalis*	Ranunculaceae	(Malik & Mujumdar, 2014)
7	*Paris polyphylla*	Melanthiaceae	(S. Gupta et al., 2019)
8	*Rhizoma polgonation*	Asparagaceae	(P. S. Chen et al., 2011)
9	*Smilax china* L.	Smilacaceae	(Yin et al., 2015)
10	*Trigonella foenum-graecum*	Fabaceae	(Arya & Kumar, 2021a)
11	*Trillium govanianum*	Melanthiaceae	(Rawat & Singh, 2020)
12	*Tribulus terrestris* L.	Zygophyllaceae	(S. Wang et al., 2017)

3.2 Pharmacokinetics and Bioavailability

The pharmacokinetics of Diosgenin, encompassing absorption, distribution, metabolism, and excretion (ADME), plays a significant role in its therapeutic potential. After oral administration, Diosgenin exhibits poor aqueous solubility, leading to suboptimal absorption in the gastrointestinal tract. Studies have demonstrated that diosgenin is primarily absorbed in the small intestine through passive diffusion. Its metabolism involves hepatic enzymes, producing metabolites that can modulate biological pathways related to inflammation, apoptosis, and cancer progression (Y. Chen et al., 2015; Wu et al., 2019). In vivo metabolism studies have identified diosgenin's conversion into hydrophilic metabolites through hydroxylation and glucuronidation, facilitating its excretion. This rapid metabolism contributes to its short half-life in systemic circulation(Manda et al., 2013). However, its low systemic bioavailability and rapid elimination limit its efficacy. Strategies to address these challenges include the development of nanoformulations, such as liposomes, nanoparticles, and solid lipid carriers. These approaches enhance its solubility, stability, and targeted delivery. For instance, Diosgenin-loaded nanoparticles have demonstrated improved pharmacokinetics, with enhanced bioavailability and sustained release, thereby increasing its therapeutic efficacy in preclinical cancer models (Das et al., 2012). Encapsulation techniques, particularly polymeric systems, have also shown promise in protecting Diosgenin from enzymatic degradation while ensuring controlled release. Diosgenin demonstrates moderate plasma protein binding, allowing it to be distributed to target tissues. Studies using labeled diosgenin in animal models have shown preferential accumulation in organs such as the liver, lungs, and kidneys. This distribution pattern is consistent with its therapeutic effects in liver and lung cancers (Yin et al., 2015).

4. MECHANISMS OF ANTI-CANCER ACTION

Diosgenin exerts its anti-cancer effects through multiple mechanisms, targeting essential cellular processes and signaling pathways involved in cancer progression. These include the induction of apoptosis, inhibition of cell proliferation, and suppression of cancer cell migration and invasion, each mediated by specific molecular and biochemical pathways.

4.1 Induction of Apoptosis

Apoptosis, also known as programmed cell death, serves as a vital mechanism for the removal of cancerous cells. Diosgenin significantly enhances this process via both intrinsic and extrinsic pathways. Apoptosis in eukaryotic cells is closely associated with caspases, which are cysteinyl aspartate-specific proteinases from the interleukin-1beta-converting enzyme family and contain cysteine. They also contribute to the regulation of cell development, differentiation, and apoptosis (Fan et al., 2005). Research indicates that Diosgenin promotes mitochondrial-mediated apoptosis through the upregulation of pro-apoptotic proteins, including Bax and various caspases (caspase-3, caspase-9, and cleaved PARP1), while concurrently downregulating anti-apoptotic proteins such as Bcl-2. The alteration in the Bax/Bcl-2 ratio promotes the release of cytochrome c from mitochondria, leading to apoptosome formation and the activation of the caspase cascade (Mao et al., 2019).

Additionally, Diosgenin has been shown to enhance the expression of death receptor proteins, such as Fas and TRAIL receptors, thereby initiating extrinsic apoptotic signaling pathways (Zhang et al., 2019). These dual apoptotic mechanisms underscore its potential to selectively target cancer cells. The primary signalling pathways associated with apoptosis encompass the PI3K/Akt pathway, in which Diosgenin inhibits Akt phosphorylation, consequently enhancing apoptotic signals. Diosgenin may induce apoptosis in K562, bladder cancer, rectal cancer, and glioblastoma neoplasm cells by significantly upregulating the protein levels of Bid and p53, while downregulating the protein levels of Bcl-xL and Survivin RNA (D. D. Gupta et al., 2021; Khathayer & Ray, 2020; Li et al., 2021) (Figure 2).

4.2 Inhibition of Cell Proliferation

Diosgenin disrupts the tightly regulated cell cycle in cancer cells, thereby inhibiting their proliferation. It induces cell cycle arrest at key checkpoints, including the G1 and G2/M phases, by modulating the activity of cyclins and cyclin-dependent kinases (CDKs) coupled with the upregulation of p21 (Raju & Rao, 2012). Diosgenin has been reported to downregulate cyclin D1 and CDK4/6, which are essential for G1 phase progression, and cyclin B1, which is critical for G2/M transition (Liao et al., 2019). These effects effectively halt the replication of cancer cells, providing an opportunity for repair mechanisms or apoptosis to take over. Furthermore, Diosgenin has been implicated in the inhibition of the Wnt/β-catenin signaling pathway, which plays a pivotal role in maintaining cancer cell proliferation and stemness. By reducing β-catenin nuclear translocation, Diosgenin diminishes the transcription of proliferative genes such as c-Myc and cyclin D1 (Abdolmaleki et al., 2024). Reactive oxygen species (ROS) generation is another critical mechanism through which diosgenin inhibits cell proliferation. Increased oxidative stress leads to DNA damage and the activation of tumor suppressor pathways like p53, p21, p16, and cdc25 which promotes apoptosis and inhibits cell growth (Abdolmaleki et al., 2024; Khathayer & Ray, 2020; X.-M. Mao et al., 2019a). Diosgenin targets several oncogenic signaling pathways, including PI3K/Akt and NF-κB, which are crucial for cancer cell survival and proliferation. By inhibiting these pathways, diosgenin reduces the proliferative capacity of cancer cells while enhancing apoptosis (Sethi et al., 2018b) (Figure 2).

4.3 Suppression of Cancer Cell Migration and Invasion

The ability of cancer cells to migrate, invade surrounding tissues, and form distant metastases is a hallmark of malignancy. Diosgenin effectively suppresses these processes by targeting key molecules involved in metastasis. It downregulates the expression of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are enzymes responsible for degrading the extracellular matrix, a prerequisite for invasion(Chang et al., 2011).

Additionally, Diosgenin modulates epithelial-to-mesenchymal transition (EMT) markers, such as reducing the expression of mesenchymal markers (e.g., N-cadherin, vimentin) and enhancing epithelial markers (e.g., E-cadherin), thereby reversing EMT and reducing metastatic potential (Gu et al., 2021; Huang et al., 2019). The suppression of angiogenesis, a critical process for tumor growth and metastasis, is another mechanism by which Diosgenin exerts its effects. It inhibits VEGF expression and downregulates VEGFR-mediated pathways, including the MAPK and Akt signaling cascades (Figure 2).

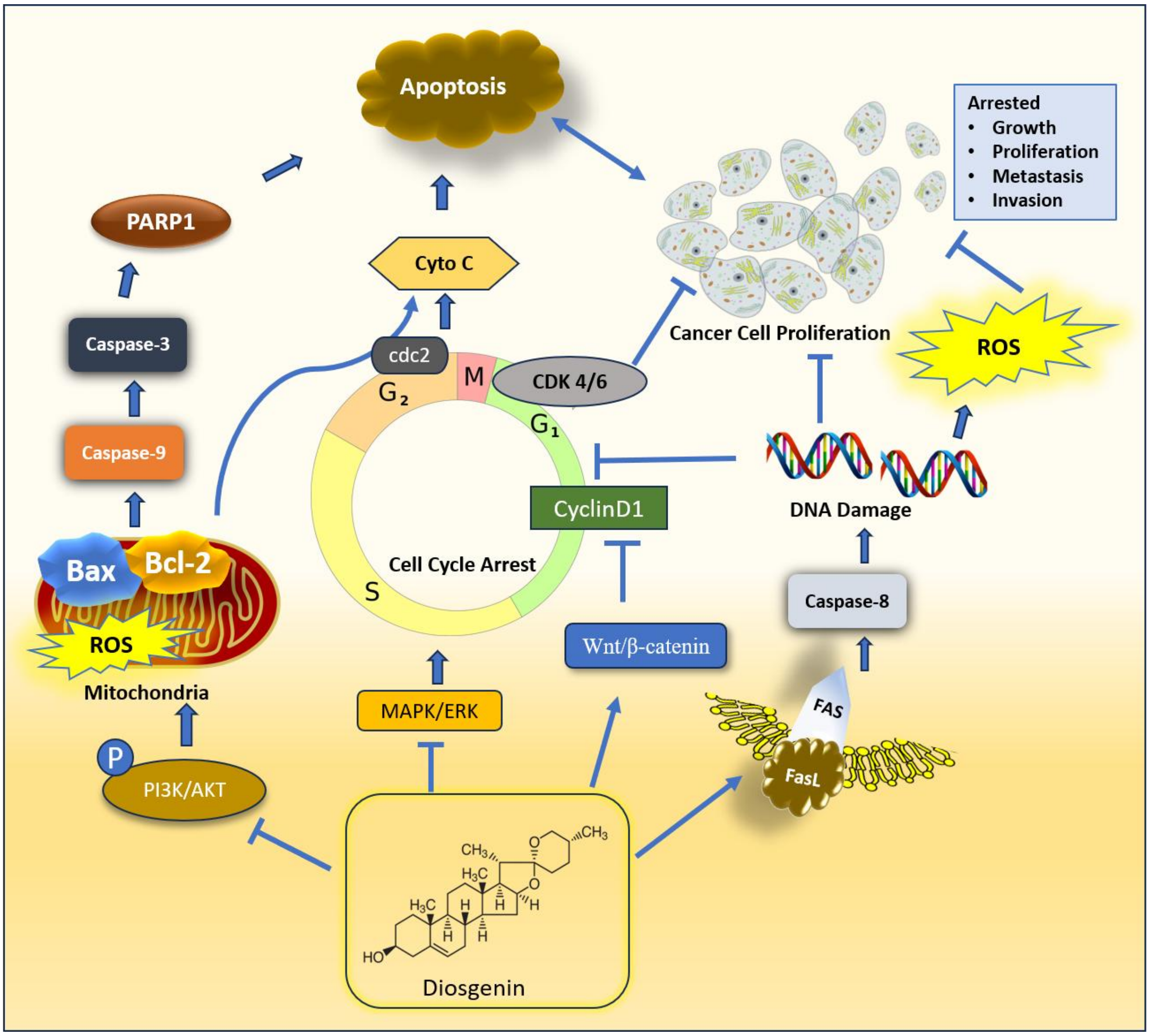

Figure 2. Anti-cancer mechanism of Diosgenin.

4.4 Modulation of Signaling Pathways

Diosgenin demonstrates anti-cancer potential through the modulation of key signalling pathways associated with cellular proliferation, apoptosis, inflammation, and metastasis. The pathways encompass PI3K/Akt/mTOR, NF-κB, and additional regulatory cascades. The PI3K/Akt/mTOR pathway plays a critical role in cellular growth, metabolism, and survival, frequently exhibiting hyperactivation in cancerous conditions. Diosgenin inhibits this pathway through the reduction of Akt and mTOR phosphorylation, which suppresses tumor-promoting signals. Diosgenin significantly inhibits the PI3K/Akt pathway in breast cancer cells, resulting in decreased pro-survival signalling, reduced proliferation, and increased apoptosis (Patel et al., 2020). Furthermore, studies in glioblastoma cells revealed that Diosgenin decreased mTOR activation, impairing cancer cell metabolism and tumor progression (Chang et al., 2011; Y. Chen et al., 2015). This pathway's inhibition highlights Diosgenin's role in downregulating cancer-associated cellular processes.

NF-κB functions as a transcription factor that modulates genes associated with inflammation, cell survival, and immune responses. In cancer, NF-κB frequently exhibits constitutive activation, promoting inflammation-driven tumour proliferation. Diosgenin inhibits NF-κB activation through the suppression of IκB kinase (IKK) phosphorylation, thereby obstructing NF-κB translocation to the nucleus. This leads to the downregulation of pro-inflammatory cytokines, including IL-6 and TNF-α, which are associated with inflammation-driven cancers such as colorectal and pancreatic cancers (Ren et al., 2023b). The capacity of diosgenin to target NF-κB is linked to diminished tumour angiogenesis and metastasis (Figure 3).

Diosgenin inhibits the MAPK/ERK signaling cascade, which is pivotal in cell cycle progression and differentiation. This pathway's suppression leads to reduced tumorigenic activity and increased apoptosis in hepatocellular carcinoma cells (Das et al., 2012). By decreasing β-catenin nuclear translocation, Diosgenin interrupts the transcription of genes linked to cancer proliferation, such as cyclin D1 and c-Myc, particularly in colon cancer cells (Abdolmaleki et al., 2024). Diosgenin downregulates STAT3 phosphorylation, inhibiting cancer cell survival and immune evasion mechanisms in multiple myeloma and other cancers (Lai et al., 2022).

4.5 Oxidative Stress and Antioxidant Effects

Cancer cells often exhibit elevated reactive oxygen species (ROS) levels, leading to oxidative stress that drives DNA damage, mutations, and tumor progression. Diosgenin mitigates oxidative stress by neutralizing ROS and enhancing cellular antioxidant defense mechanisms. It upregulates the expression of antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase while reducing lipid peroxidation(Gong et al., 2010; Manivannan et al., 2013). These effects protect normal cells from oxidative damage while selectively inducing oxidative stress in cancer cells, triggering apoptosis.

In lung cancer models, Diosgenin reduced ROS-mediated DNA damage and suppressed tumor growth by modulating Nrf2, a key regulator of antioxidant responses (Hao & Gao, 2022). Additionally, its ability to modulate mitochondrial ROS production has been linked to the induction of mitochondrial-mediated apoptosis in various cancers.

4.6 Anti-inflammatory Effects

Chronic inflammation is a recognised factor in tumour initiation, progression, and metastasis. Cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) are key inflammatory mediators that contribute to the establishment of a tumor-promoting microenvironment. Diosgenin effectively mitigates inflammation through the modulation of specific mediators. Research indicates that N-(phenyl)methyl substitution at the 27th position of Diosgenin improves its anti-inflammatory activity in SH-SY5Y cell lines. This modification reduces the production of nitric oxide (NO), amyloid beta (Aβ), and reactive oxygen species (ROS). Computational docking analyses indicate that this substitution demonstrates a strong binding affinity for Aβ42, inducible nitric oxide synthase (iNOS), and pro-inflammatory cytokines, highlighting its significant anti-inflammatory, antioxidant, and anti-Aβ properties (Yang et al., 2020). A derivative of Diodgenin, synthesised by combining ibuprofen (2-(4-isobutylphenyl)-propionic acid) with DG via a 6-aminohexanoic acid linker at the 27th position, has shown significant anti-inflammatory effects in both in vitro and in vivo inflammatory models. This combination demonstrates the potential of DG derivatives to improve therapeutic outcomes in inflammation-related conditions (Xin et al., 2013).

COX-2 overexpression is frequently observed in cancers such as colorectal, gastric, and breast cancer, contributing to prostaglandin production and tumor-promoting inflammation. Diosgenin inhibits COX-2 expression and activity, leading to decreased prostaglandin synthesis and a reduction in tumor-supportive inflammation (Tsukayama et al., 2021).

IL-6 and TNF-α are cytokines that promote chronic inflammation and cancer cell survival. Diosgenin downregulates the expression of these cytokines by inhibiting NF-κB and STAT3 signaling, effectively breaking the link between inflammation and tumor progression (De Simone et al., 2015). These effects have been demonstrated in preclinical models of liver and pancreatic cancers. In addition to direct effects on inflammatory mediators, Diosgenin has been shown to modulate the tumor microenvironment, reducing the infiltration of inflammatory immune cells such as macrophages and neutrophils, which are known to support tumor growth and angiogenesis (Figure 3).

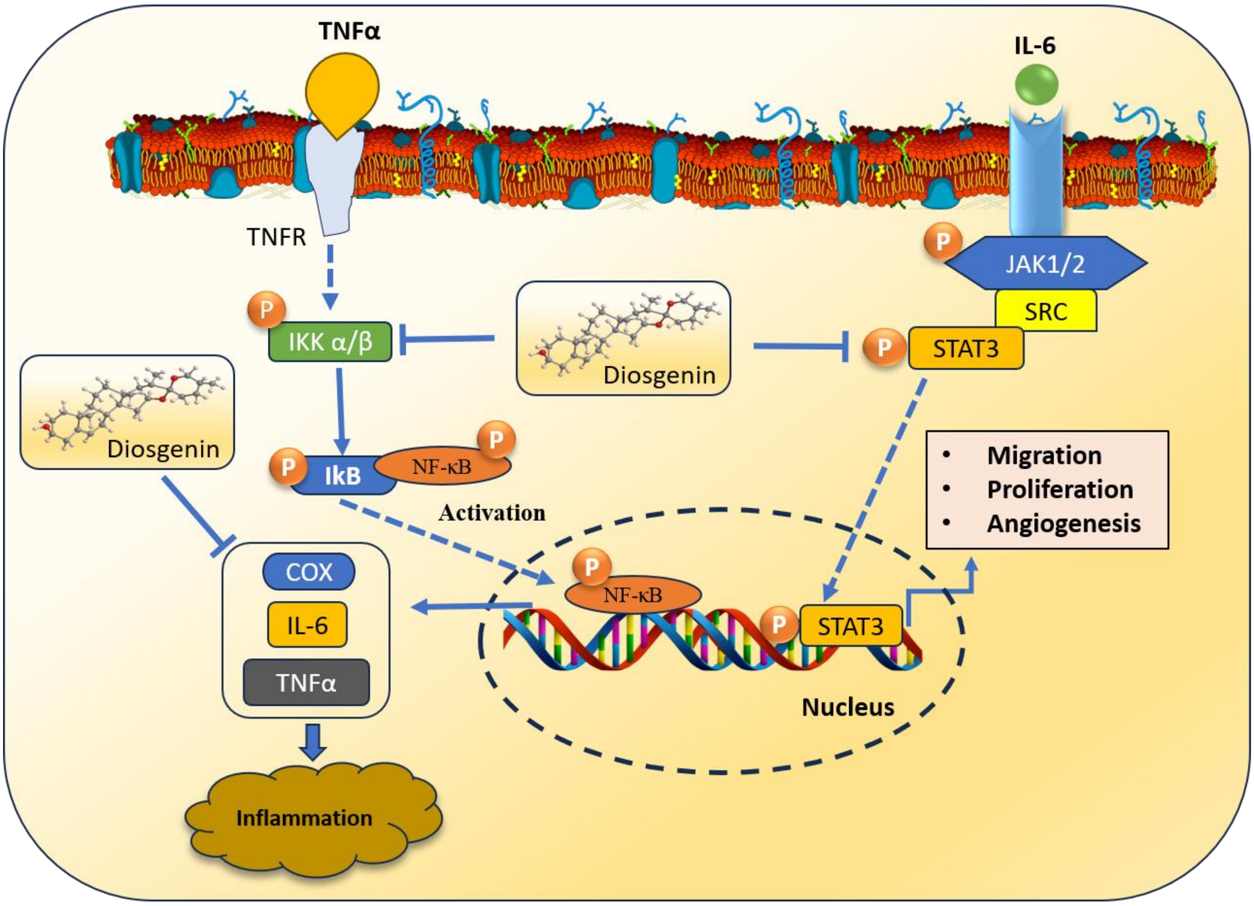

Figure 3. Modulation of Signaling Pathways through diosgenin.

5. PRECLINICAL STUDIES ON DIOSGENIN'S ANTI-CANCER POTENTIAL

5.1 *In-vitro* Studies

- **Effect of Diosgenin on Prostate cancer cell lines**

Chen et al. investigated the molecular pathways through which diosgenin averts metastasis. The results of their study demonstrated that diosgenin had inhibitory effects on the invasion and migration of androgen-independent prostate cancer cells, particularly PC3, in a dose-dependent way, without causing any harmful effects at the tested dosages (Chen et al., 2016). The mRNA expression of tissue inhibitor of metalloproteinase-2 (TIMP-2) was increased by Diosgenin, while the mRNA levels of matrix metalloproteinases (MMPs) -2, -9, -7, and extracellular inducer of matrix metalloproteinase (EMMPRIN) were simultaneously reduced. The observed impact was facilitated by the modulation of crucial enzymes implicated in the degradation of the extracellular matrix and invasion of the stroma, notably matrix metalloproteinase (MMP)-2 and MMP-9. Moreover, diosgenin exhibited a reduction in the transcriptional activity of various crucial signalling pathways, such as NF-kB, ERK, JNK, PI3K/AKT, VEGF, and TIMP-2. It also impacted extracellular regulated kinase (ERK), Janus kinase (JNK), and phosphatidyl-inositol-3 kinase/protein kinase B (PI3K/AKT) (Chen et al., 2011).

In another study, diosgenin was used as a parent compound to synthesize 1α-hydroxysolasodine; it showed significant anti-cancer activity against prostate cancer (PC3), cervical carcinoma (HeLa), and hepatocellular carcinoma (HepG2) cells (P. Liu et al., 2022).

The study conducted by Nie et al. investigated the impact of diosgenin on cellular proliferation, programmed cell death (apoptosis), and the process of autophagy in the DU145 cell line derived from human prostate cancer. This research contributes valuable insights into the therapeutic potential of diosgenin for the treatment of prostate cancer. The findings of their study demonstrated that diosgenin effectively suppressed the proliferation of DU145 cells by the induction of apoptosis and autophagy. The underlying mechanism of this effect is believed to include the suppression of the PI3K/Akt/mTOR signalling pathway. Moreover, diosgenin has exhibited the capacity to impede autophagy, resulting in an elevation of apoptosis and consequently augmenting its therapeutic effectiveness. The utilization of diosgenin in combination has demonstrated efficacy in enhancing its anticancer properties through the inhibition of autophagy (Nie et al., 2016).

Sun et al. conducted a study to investigate the effects of diosgenin on PC3 human prostate cancer cells, specifically examining changes in intracellular calcium concentration (Ca^{2+}i) and cytotoxicity. Diosgenin, in concentrations ranging from 250 to 1000 M, led to an elevation in Ca^{2+}i, an effect that could be reversed by the removal of extracellular calcium. Moreover, diosgenin induction increased in Ca^{2+}i which were attenuated when phospholipase C was inhibited using U73122. Diosgenin also stimulated Mn^{2+} influx, indicating its ability to induce calcium entry. Notably, diosgenin-induced Ca^{2+} influx could be diminished by nifedipine, econazole, SKF96365, PMA, and GF109203X. Cell viability was found to decrease in a concentration-dependent manner when exposed to diosgenin in concentrations ranging from 250 to 600 µM. However, cytosolic calcium chelation using BAPTA/AM failed to prevent the cytotoxic effects induced by diosgenin. In essence, diosgenin led to calcium-independent cytotoxicity in PC3 cells while simultaneously elevating Ca^{2+}i levels, an effect potentiated when combined with both Ca^{2+} release and Ca^{2+} influx. These findings suggest the potential of diosgenin as a novel therapeutic approach in the treatment of human prostate cancer (Sun et al., 2020).

- **Effect of Diosgenin on Breast cancer cell lines**

A study was undertaken by Srinivas et al. with the aim of elucidating the molecular processes that underlie the chemotherapeutic effects of Diosgenin. The researchers showed that this naturally occurring chemical can inhibit the Akt-mediated NF-κB and MAPK signalling pathways, leading to the induction of apoptosis in cells of breast cancer (BCa). In this research investigation, BCa cells were exposed to transfection using PCB6+, Myr-Akt26, or NF-κB-luciferase, and subsequently treated with Diosgenin. The findings of the study indicate that Diosgenin exhibits strong anti-cancer properties by effectively suppressing pro-survival signalling pathways, including Akt, Raf/MEK, and NF-κB. Consequently, this leads to the induction of apoptosis in both estrogen receptor-positive (ER+) and estrogen receptor-negative (ER-) breast cancer (BCa) cells. The anti-cancer impact of Diosgenin was shown in MCF-7 and MDA 231 cells, as evidenced by the downregulation of pro-survival proteins such as X-linked inhibitor of apoptosis protein (XIAP), B-cell leukemia/lymphoma 2 protein (Bcl-2), and survivin. In the MCF Her-2 cell line, the expression of Bcl-2 was observed to be downregulated in a similar manner upon treatment with Diosgenin. It is crucial to emphasize that Diosgenin shown significant variations in cytotoxicity when comparing MCF-10A and BCa cells. Specifically, it selectively suppressed the viability of BCa cells while having no impact on the viability of MCF-10A, which are normal breast epithelial cells (Srinivasan et al., 2009). The authors, He et al., presented noteworthy results concerning the influence of Diosgenin on the migratory behavior of MDA-MB-231 cells, as observed through real-time monitoring. In Her-2 positive breast cancer cells, diosgenin inhibited the expression of AKT, mTOR, JNK and their associated pro-survival signaling pathways, and induced apoptosis in these cells (Chiang et al., 2007).

Diosgenin prominently reduced actin polymerization, phosphorylation of guanine nucleotide exchange factor 2 (Vav2), and activation of Cdc42. These observations underscore Diosgenin's anti-metastatic properties (He et al., 2014). Furthermore, Bhuvanalakshmi et al. documented that Diosgenin effectively inhibited cancer stem cells (CSCs) derived from three different breast cancer cell lines, namely MDA-MB-231, T47D and MCF7. This inhibition was achieved through the induction of apoptosis and a reduction in CSC-related phenotypes. Importantly, the study revealed that the loss of sFRP4 function had a detrimental impact on the CSC population, resulting in their enrichment and reduced responsiveness to Diosgenin treatment. The observed CSCs demonstrated heightened levels of β-catenin and reduced expression of glycogen synthase kinase-3 (GSK3), together with a total absence of epithelial markers that are typically associated with CSCs (Bhuvanalakshmi et al., 2017). In the study conducted by Liao et al., a notable decrease in the mitochondrial membrane potential was detected in breast cancer cells following the administration of Diosgenin. Furthermore, it was shown that Diosgenin has a significant impact on cellular apoptosis by suppressing the production of the anti-apoptotic protein Bcl-2. As a result, a release of cytochrome c occurred, so initiating the activation of the caspase signalling cascade. The inhibitory effect of diosgenin on human breast cancer cell lines is attributed to its ability to regulate the Cdc25C-Cdc2-cyclin B pathway and induce mitochondria-mediated paraptosis. The user's content does not contain any information to rework in an academic manner.

In a separate investigation conducted by Khanal et al., the researchers elucidated the underlying mechanism via which diosgenin exerts its effects on breast cancer, employing a diverse range of biological methodologies. Diosgenin demonstrated the greatest affinity for the IGF1R among the tested compounds. It displayed strong intermolecular interactions and exhibited the lowest amount of free binding energy with IGF1R when compared to MDM2 and SRC. The compound diosgenin demonstrated the most pronounced cytotoxic effects when tested against MCF7 cell lines. Moreover, it was observed that diosgenin exhibited the lowest inhibitory constant in MCF7 cell lines during H2O2-induced oxidative stress. The growth of estrogen receptor-positive MCF-7 breast cancer cells was inhibited by the activation of caspase 3 and the upregulation of p53 tumour suppressor gene activity induced by diosgenin. Additionally, diosgenin suppressed the function of BCL2 in estrogen receptor-negative MDA-MB-231 triple-negative breast cancer cells(Khanal et al., 2023; Srinivasan et al., 2009).

- **Effect of Diosgenin on lung and gastric cancer cell lines**

Numerous studies have provided evidence of the anti-tumour properties of Diosgenin across different types of cancer cells. Nevertheless, a significant dearth of research exists about the examination of the influence of Diosgenin on LXR-α and its corresponding target ABCA1 in cells afflicted with lung cancer. To bridge this knowledge gap, Ganesan et al. undertook a study that explored the involvement of Diosgenin in the proliferation of lung cancer cells by examining its impact on LXR-α and ABCA1 induction. Their findings revealed that Diosgenin effectively reduced the proliferation of A549 cells by up-regulating LXR-α, ABCA1, Bax, caspase-3, while concurrently inhibiting the synthesis of BCL-2 (Ganesan & Arockiam, 2019). A separate investigation conducted by Xu L et al. documented the potent cytotoxic effects of a chemical referred to as P2 on A549 and PC9 cells, which are human non-small-cell lung cancer cells. In addition, it was shown that P2P exhibited increased antiproliferative efficacy through the stimulation of apoptosis and inhibition of cell cycle progression in lung cancer cells, as evidenced by previous research (L. Xu et al., 2019). The study conducted by Gu et al. aimed to investigate the role of mesoderm posterior 1 (MESP1) in the growth of gastric cancer cells. The analysis conducted by the researchers unveiled a significant upregulation of MESP1 expression in human gastric cancer tissues. The downregulation of MESP1 in gastric cancer cells resulted in upregulated expression of ARF and subsequently induced apoptosis. Importantly, the anti-cancer effects associated with MESP1 knockdown were mitigated when ARF was also knocked down. Therefore, it was determined that Diosgenin effectively suppressed the expression of ARF, thereby impeding the growth of gastric cancer cells through the activation of mesoderm posterior 1 (MESP1) [21]. According to a study conducted by Gupta et al., Diosgenin exhibited significant antioxidant activity in vitro, as well as anti-inflammatory activity in vivo and substantial anti-cancer benefits. The observed outcomes were distinguished by the suppression of proliferation in MCF-7 breast cancer cells (Gupta et al., 2021). Table 2 discussed the cancer models and diosgenin effects on *in vitro* studies.

Table. 2 *In vitro* anti-cancer effects of Diosgenin

Cancer model	Cell lines	Cellular and molecular targets	Reference
Human prostate cancer	PC-3 cells	Possible PI3K, ERK, and JNK signalling pathway phosphorylation block	(Chen et al., 2016; Nie et al., 2016; Sun et al., 2020)
		Inhibits MMP-2	
		Inhibits NF-κB	
	DU145	PI3K/Akt/mTOR	(Nie et al., 2016)
Breast cancer	MCF7 cell lines	upregulates the p53 tumour suppressor gene	(Bhuvanalakshmi et al., 2017; Ganesan & Arockiam, 2019; He et al., 2014; Khanal et al., 2023; Liao et al., 2019; Nie et al., 2016; Srinivasan et al., 2009)
	MDA-MB-231	Inhibits BCL2 synthesis	
	SKBR3	Prevents cell migration	
Lung cancer	A549 cell	Inhibits proliferation of A549 cell	(L. Xu et al., 2019)
		Up-regulation of LXR-α, ABCA1, Bax, caspase-3	
		Inhibits BCL-2 synthesis	
	A549 and PC9 cells	Induces apoptosis	(Gu et al., 2021)
		Lung cancer cell proliferation inhibition	
Gastric cancer	MGC-803 and BGC-823 and GC cells	Inhibits ARF expression	(S. Gupta et al., 2019; Raju et al., 2004b)
		Inhibits gastric cancer cell MESP1 expression	
Laryngeal Cancer	TU212 and Hep-2 cells	Cause apoptosis and DNA damage	(Ren et al., 2023b)
		Raise reactive oxygen species.	
Breast	MCF-7	Apoptosis, G1/S arrest	(Srinivasan et al.,

Cancer			2009)
Colon Cancer	HCT116	ROS generation, cell cycle arrest	(Arya & Kumar, 2021b)
Osteosarcoma	1547 cells	Inhibits cell proliferation Induces apoptosis	(Moalic et al., 2001)
Leukemia	HL-60	Mitochondrial dysfunction, caspase activation	(Guo et al., 2008)
Prostate cancer	PC3 cells	Inhibits the NF-κB signalling pathway Inhibits matrix metalloproteinases. Impedes cellular invasion and migration	(J. Chen et al., 2016; Sethi et al., 2018b)
Human Laryngocarcinoma Human Melanoma	HEp-2 cells M4Beu cells	Halted cell proliferation Induces caspase-3 dependent apoptosis p53 upregulation	(Corbiere et al., 2004)
Epithelial Carcinoma	A431 & A549	Apoptosis through mitochondrial dependent pathway	(Wang et al., 2022)

5.2 *In vivo* Studies

A multitude of in vivo research have cumulatively shown persuasive evidence concerning the significant inhibitory effects of Diosgenin on tumour growth. In a recent study, the objective was to evaluate the efficacy of dietary fenugreek seed and its principal steroidal saponin ingredient, Diosgenin, in mitigating azoxymethane-induced rat colon carcinogenesis throughout both the initiation and promotion phases. The research investigation was centered on objectives pertaining to preneoplastic colonic lesions or aberrant crypt foci (ACF). Furthermore, the study investigated the ways via which Diosgenin impedes the growth of tumours in HT-29 human colon cancer cells. Male F344 rats, at the age of 7 weeks, were exposed to experimental diets comprising of either 0% or 1% fenugreek seed powder (FSP), or 0.05% or 0.1% Diosgenin for a duration of one week prior to the administration of an azoxymethane injection at a dosage of 15 mg/kg body weight. This methodology facilitated the evaluation of the test agent's influence throughout both the commencement and subsequent phases. Concurrently, in vitro tests were undertaken to examine the effects of Diosgenin on cell proliferation and apoptosis induction in the HT-29 human colon cancer cell line, with a focus on its dose-dependent modulation. Additionally, HT-29 cells treated with Diosgenin demonstrated a partial suppression of Bcl-2 and an elevation in caspase-3 protein levels. The collective findings of this study indicate that Diosgenin, which is the main bioactive ingredient found in fenugreek, shows potential as a new preventive agent for colon cancer. It is worth mentioning that the administration of Diosgenin during the promotional stage in a rat colorectal tumour model led to an additional decrease in azoxymethane (AOM)-induced colonic aberrant crypt foci formation (Raju et al., 2004a).

The chemo-protective properties of Diosgenin against human breast cancer were established by Jagadeesan et al. Significantly, Diosgenin demonstrated a pronounced cytotoxicity, leading to a considerable decrease in the proliferation of MCF-7 cells that was dependent on the dosage administered. The administration of Diosgenin resulted in a rise in LDH activity, subsequently causing a reduction in GSH activity inside MCF-7 cells. In addition, the administration of Diosgenin shown significant efficacy in reducing the elevated levels of lipid peroxidation found in rats with breast cancer generated by N-Nitroso-N-Methylurea (NMU). It is noteworthy to acknowledge that NMU is a carcinogenic agent that exhibits a high degree of specificity towards the mammary gland, mostly due to its lack of involvement in metabolic activation. The antioxidant activity of Diosgenin was found to be crucial in counteracting the abnormalities in lysosomal enzymes and providing defense against oxidative stress-induced macromolecular damage and free radical production (Jagadeesan et al., 2013).

Malisetty et al. assessed the ability of Diosgenin to suppress azoxymethane (AOM)-induced rat colon cancer. The primary objective of the study was to evaluate the chemo-preventive efficacy of Diosgenin against the development of colonic adenocarcinomas. To identify the underlying mechanism by which Diosgenin inhibits tumour growth, this study investigated markers associated with cell proliferation and death in both colonic cancers and normal-appearing crypts. In the present investigation, male F344 rats were originally administered the AIN-76A diet as a control regimen upon reaching the age of 7 weeks. Following this, one week later, the rats were administered subcutaneous injections of AOM at a dosage of 15 mg/kg body weight, once weekly for a duration of 2 weeks. Alternatively, an equal volume of sterile saline (vehicle) was administered. The treatment of Diosgenin led to a notable decrease in the occurrence of both invasive and non-invasive colon cancers, resulting in a significant reduction of up to 60% ($p < 0.0004$). Furthermore, rats fed a diet containing Diosgenin exhibited substantially lower colon tumour multiplicity (adenocarcinomas/rat), showing a reduction of 68% ($p < 0.0001$). Notably, compared to animals fed the control diet, there was a substantial increase in BrdU labelling ($p < 0.005$) and a decrease in PCNA labelling ($p < 0.001$) observed in the colonic crypts and tumours of animals fed the Diosgenin-containing diet. Diosgenin, a naturally occurring steroidal saponin found in fenugreek, was found to possess significant chemo-preventive effects against colon cancer. This groundbreaking evidence paves the way for further developments involving Diosgenin and its potential utilization in human clinical trials (Malisetty et al., 2005).

A study was undertaken by Miyoshi et al. to assess the effects of reduced dosages of Diosgenin and Sanyaku on colon cancer generated by AOM/dextran sodium sulfate (DSS) in mice. The findings of their study indicated that administering Diosgenin at lower doses of 20, 100, and 200 mg/kg body weight in a mouse model of AOM/dextran sodium sulfate-induced colon aberrant crypt foci did not result in a reduction in the mass of adenocarcinoma. Nevertheless, a notable decrease in the number of tumours was found across all three administered doses(Miyoshi et al., 2011). Vengaimaran and colleagues conducted a research investigation aimed at examining a new treatment pathway utilizing Nano Diosgenin (DG). The primary objective was to determine the specific metabolic enzymes accountable for the anti-breast cancer properties of Nano Diosgenin. The initiation of breast cancer was achieved with the administration of a solitary injection of 7,12-Dimethyl Benz(a)anthracene (DMBA) at a dosage of 25 mg per kilogram of body weight. Rats carrying tumours produced by DMBA were administered oral dosages of DG (10 mg/kg body weight) and DG encapsulated chitosan nanoparticles (DG@CS-NP) (5 mg/kg body weight) in a timely manner following the initial manifestation of the tumour. After the experimental procedure, biochemical assessments were performed. The study findings revealed that Nano DG had a substantial effect on normalizing the levels of glycolytic enzymes, pentose phosphate pathway enzymes, gluconeogenic enzymes, and mitochondrial enzymes in breast, liver, and kidney tissues, hence restoring them towards their baseline levels. According to the findings, it can be inferred that Diosgenin, administered at a dosage of 10 mg/kg body weight, demonstrates a significant level of aerobic glycolysis activity. This characteristic renders it a potentially viable option for the manipulation of metabolic processes in the context of chemotherapy-induced reprogramming (Vengaimaran et al., 2023). A separate investigation conducted by Vengaimaran et al. examined the therapeutic efficacy of Diosgenin encapsulated Chitosan nanoparticles (DG@CS-NP) in relation to the development of mammary carcinogenesis in female Sprague Dawley rats. This assessment examined the impact of the intervention on hormone levels, cellular proliferation, inflammatory reactions, and programmed cell death. The experiment involved the administration of 7,12-dimethylbenz(a)anthracene (DMBA) through subcutaneous injections near the mammary gland of female Sprague Dawley rats. The purpose of this procedure was to promote the development of mammary tumours in the rats. The dosage of DMBA administered was 25 mg per kilogram of body weight. Rats that had developed tumours through the induction of DMBA were subjected to oral administration of DG@CS-NP at a dosage of 5 mg/kg body weight, in order to observe and assess the progression of tumour growth. The utilization of architectural immunohistochemistry was employed in order to evaluate the expression levels of ER, PR, PCNA, Cyclin D1, NF-κB, TNF, Bcl-2, Caspase-3, and p53 in the rats that were exposed to experimental settings. The molecular docking research provided additional evidence for the interaction between diosgenin and the proteins. The administration of DG@CS-NP to rats resulted in a significant decrease in the levels of ER, PR, PCNA, Cyclin D1, NF-κB, TNF-α, and Bcl-2, while there was a notable increase in the expressions of Caspase-3 and p53, as demonstrated by the study. The observed expression patterns in DMBA-treated rats were found to be contrary. The findings were further substantiated by conducting molecular docking studies, which emphasized the robust interaction between Diosgenin and targets associated with breast cancer. The therapeutic benefits of diosgenin are achieved through the modulation of hormonal fluctuations, reduction of inflammation and cell growth-associated protein expression, and induction of apoptosis by inhibiting molecules that prevent cell death [28]. An independent investigation aimed to assess the anticancer properties of steroid saponins derived from the rhizome of Paris polyphylla var. yunnanensis. The study aimed to clarify the structure-activity relationships of these steroid saponins through in vitro and in vivo experiments. The MTT experiment utilized the mouse lung adenocarcinoma cell line LA795 to evaluate cytotoxicity. The AnnexinV-FITC/PI flow cytometry method was employed to assess apoptosis. The research focused on evaluating the inhibitory effects of Diosgenin-3-α-L-arabinofuranosyl (1→4)-[α-L-rhamnopyranosyl (1→2)]. The effects of diosgenin, the primary steroid saponin and glycopyranoside found in Paris polyphylla, on the development of LA795 lung adenocarcinoma in T739 inbred mice were examined. The study indicated that Diosgenin exhibited a notable inhibitory effect on tumour growth. Notable decreases in tumour weights were recorded in the groups receiving Diosgenin at doses of 100 mg/kg and 200 mg/kg via oral administration. The observed inhibitory ratios for tumour growth were 29.44% and 33.94% in the respective cases. The study conducted by Yan et al. (Yan et al., 2009), observed that the administration of Diosgenin to inbred T739 mice resulted in a significant reduction in the development rate of mouse LA795 lung adenocarcinoma tumours, with a decrease of approximately 33.94%. Table 3 discussed the anti-cancer effects of cancer types and model used with doses.

Table 3. Anti-cancer effects of diosgenin on In-vivo studies.

Cancer Type	Model Type	Dose (mg/kg)	Outcome	Reference
Breast Cancer	Xenograft (MCF-7 and MDA-MB-231)	10	Significant reduction in tumor volume	(Srinivasan et al., 2009)
Colon Cancer	AOM-induced adenocarcinoma in rat	15	Tumor reduction and multiplicity by 68%	(Malisetty et al., 2005)
Colon Cancer	LA795 lung adenocarcinoma	25	Tumor growth inhibition of 33.94%	(Yan et al., 2009)
DMBA- hamster model	OSCC	80	Inhibit growth of oral tumors	(Rajalingam et al., 2012)
Hepatocellular	Rat tumor model	40	Improved survival by 40%	(Chen et al., 2018)

5.3 Synergistic Effects

- **Combination Therapy with Chemotherapeutic Agents:**

The combination of Diosgenin with conventional chemotherapeutic agents has revealed synergistic effects, improving overall therapeutic outcomes. Diosgenin enhanced the efficacy of doxorubicin in MCF-7 cells by reducing drug resistance through downregulation of P-glycoprotein (Khan et al., 2018). In a lung cancer model, combining Diosgenin with cisplatin improved tumor suppression by 30% compared to cisplatin alone, with reduced systemic toxicity (Patel & Savjani, 2015b). Diosgenin has been shown to potentiate the effects of drugs like doxorubicin and paclitaxel. In breast cancer models, diosgenin enhanced the cytotoxicity of paclitaxel by upregulating pro-apoptotic markers and downregulating NF-κB signaling (Sethi et al., 2018b).

- **Combination with Other Phytochemicals:**

Diosgenin has also shown synergistic interactions with other plant-derived compounds, such as curcumin and resveratrol. Diosgenin and curcumin combination enhanced apoptosis in prostate cancer cells by co-targeting the PI3K/AKT and Wnt/β-catenin pathways (Gupta et al., 2020). Resveratrol and Diosgenin co-treatment resulted in significant reductions in metastatic markers in breast cancer cells (Sharma et al., 2021). Diosgenin has demonstrated synergistic effects when combined with curcumin and quercetin. In prostate cancer cells, the combination led to a significant reduction in cell viability compared to individual treatments, attributed to enhanced ROS production and mitochondrial dysfunction (Vlk et al., 2020). Figure 4 explains the efforts taken for Diosgenin drug delivery systems and drug and phytochemical combinations.

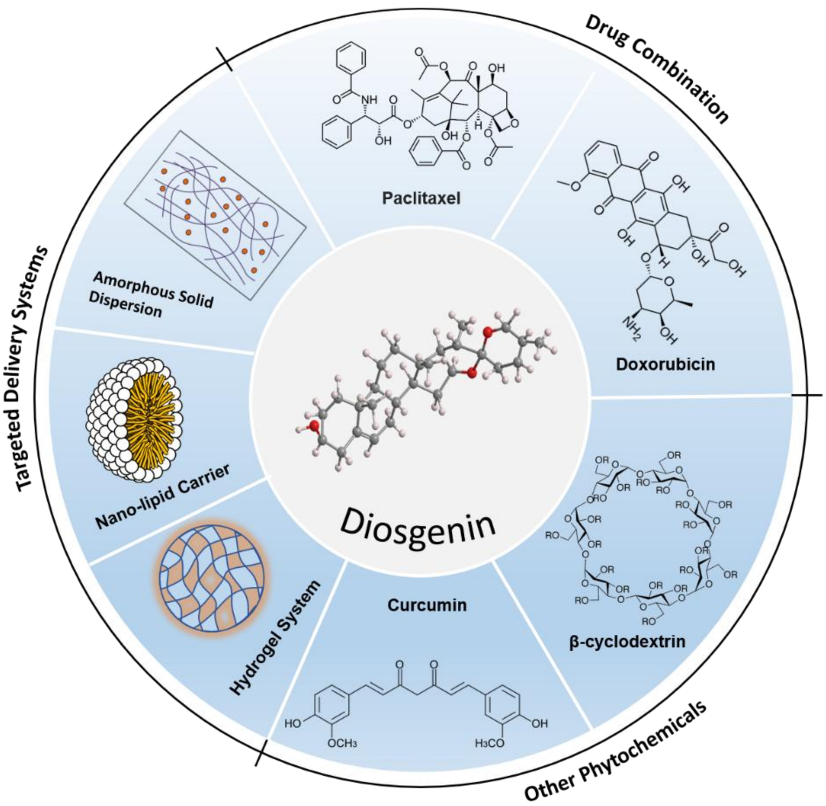

Figure 4. Diosgenin drug delivery systems and drug and phytochemical combination efforts.

6. CLINICAL EVIDENCE AND TRIALS

A randomized clinical trial involving 64 patients diagnosed with tumor cachexia (ages 35–75 years) evaluated the effects of Shenling Baizhu Powder (参苓白术散, SLP) administered over four weeks. The study demonstrated that SLP, in combination with nutritional support, significantly improved the Karnofsky Performance Score and reduced the expression of inflammatory cytokines, including TNF-α, TWEAK, and Fn14. These findings suggest that the anti-cachexia effects of SLP may be attributed to its ability to modulate these cytokines (Dey et al., 2012).

In a pharmacokinetic study involving 24 cancer patients, diosgenin exhibited poor oral absorption with a time to peak concentration (T_{max}) of approximately five hours and an extended half-life (t1/2) averaging 30 hours. Higher doses of diosgenin were associated with decreased bioavailability, displaying nonlinear pharmacokinetics at doses ranging from 1,200 to 2,400 mg. However, a single oral dose within the range of 600–2,400 mg demonstrated good safety and tolerability in clinical settings (Gao, 2009).

Another study included 34 cancer patients who were randomly divided into five groups to assess the safety and tolerability of diosgenin. The results indicated that doses ranging from 400 to 2,600 mg did not result in significant adverse drug reactions. Based on these findings, diosgenin doses equivalent to 2–13 tablets (200 mg per tablet) fall within the safety range for clinical practice (D. Wang, 2009).

Despite substantial evidence from in vitro and in vivo studies, large-scale, randomized controlled trials (RCTs) evaluating Diosgenin's efficacy in cancer patients are conspicuously lacking. Current clinical research is limited to observational and exploratory studies, which do not provide the robust evidence needed for regulatory approval. Furthermore, studies investigating its interaction with standard chemotherapeutic agents and its potential role as an adjuvant therapy are necessary. Such data will be essential for designing effective combination therapies and integrating Diosgenin into clinical oncology (Gupta et al., 2021).

7. TOXICITY AND SAFETY PROFILE

Diosgenin has garnered attention for its selective anticancer properties, particularly in breast cancer. A pivotal study conducted by Srinivasan et al. (2009) demonstrated that diosgenin selectively modulates the AKT signaling pathway to inhibit the survival of breast cancer cells while sparing normal breast epithelial cells (MCF-10A). This finding underscores diosgenin's potential as a targeted therapeutic agent with minimal off-target effects on healthy cells. Such selective toxicity is a significant advantage in cancer therapy, where preserving normal tissue function is paramount (Srinivasan et al., 2009).

Complementing preclinical findings, a clinical study conducted by Tohda et al. (2017) evaluated the safety profile of a diosgenin-rich yam extract in a placebo-controlled, randomized, double-blind crossover trial involving 28 healthy volunteers aged 20–81 years. Over the 12-week administration period, no adverse effects were reported, indicating that diosgenin is well-tolerated in humans. This evidence reinforces its suitability for further clinical exploration (Tohda et al., 2017).

However, despite these promising findings, there remains a dearth of comprehensive studies assessing the toxicity and potential adverse effects of diosgenin. Limited investigations, such as those by Lee et al. (2017), Liu et al. (2022), and Xu et al. (2022), have explored diosgenin's safety, but the data are insufficient to draw definitive conclusions (Lee et al., 2017; P. Liu et al., 2022; M. L. Xu et al., 2022). Rigorous toxicity studies, including long-term assessments and evaluations in diverse populations, are essential to fully elucidate diosgenin's safety profile and to mitigate risks associated with its therapeutic use. Expanding this body of research is critical for advancing diosgenin as a reliable therapeutic agent.

8. CHALLENGES AND FUTURE PERSPECTIVES

The low bioavailability of diosgenin and dioscin presents a significant challenge, impeding the potential for these compounds to be developed for clinical trials. Dioscin has recently been formulated into a nanostructured lipid carrier (NLC) for drug delivery, enhancing drug load potency and stability, as well as improving the bioavailability and solubility of dioscin (Jiao et al., 2017). Limited research has addressed the enhancement of diosgenin's bioavailability, including the synthesis of liquid crystals in conjunction with β-cyclodextrin, which demonstrated improved bioavailability of diosgenin when used together (Okawara et al., 2014). Diosgenin nanocrystals were synthesized in a separate study, resulting in enhanced dissolution and oral bioavailability (C. Z. Liu et al., 2017). Researchers have synthesized soluplus-mediated diosgenin amorphous solid dispersions (ASDs), resulting in a fivefold increase in diosgenin bioavailability(Liu et al., 2020). Further research on the bioavailability and solubility of these compounds across various patient populations is necessary.

Future research should focus on advanced drug delivery systems, derivatives with enhanced potency, robust clinical trials, and personalized medicine strategies. The poor bioavailability of Diosgenin is a critical barrier to its therapeutic application. Novel delivery systems, such as nanoparticles and liposomes, offer a promising solution by improving its solubility, stability, and targeted delivery. The advancement of Diosgenin derivatives has created new opportunities for application in cancer therapy. Structural modifications, including N-substitutions and conjugation with chemotherapeutic agents, have shown increased anticancer activity and enhanced pharmacokinetic profiles both in vitro and in vivo. Despite these challenges, the positive preclinical results, especially concerning anti-inflammatory, antioxidant, and neuroprotective effects, justify ongoing research efforts.

9. CONCLUSION

In summary, the growing amount of data indicates that diosgenin, a naturally occurring substance with a variety of pharmacological characteristics, has great potential as an anticancer drug. Its multi-targeted mechanism, impacting diverse biological processes, as evidenced by several in-vitro and in-vivo studies conducted across different cancer types including modulation of cell cycle regulators, pro-apoptotic proteins, and oncogenic pathways, makes it a promising candidate for combination therapies with conventional chemotherapeutics. The collective evidence indicates that Diosgenin has the potential to selectively target and regulate critical signalling pathways, specifically those involving MAPK, p53, AKT, and NF-κB, which play a crucial role in the therapy of cancer. Moreover, the inhibitory effect of Diosgenin on cancer is ascribed to its dual functionality as an antioxidant and anti-inflammatory agent, along with its propensity to cause apoptosis in cancerous cells. Understanding the pharmacokinetics and bioavailability of diosgenin is critical for its clinical translation. While poor solubility and rapid metabolism pose challenges, advancements in drug delivery systems such as nanoparticles and prodrugs hold promise for overcoming these limitations.

10. AUTHOR CONTRIBUTIONS

Ashwini Narayan contributed towards writing the manuscript, where she referred articles on Diosgenin to understand its anti-inflammatory effects and collated the information from the public domain contributed by various scientists across the scientific community. Dr. B.S. Priya and Dr. Souparnika H.Manjunath analyzed and reviewed the draft. Dr. Nanjunda Swamy S supervised and supported the entire process.

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12. CONFLICT OF INTEREST

None.

REFERENCES

[1] Cancer prevalence remains a global concern, with millions of new cases and deaths reported annually. The regional disparities in incidence rates underscore the urgent need for targeted treatment strategies.[1] Cancer not only impacts adults but also affects