REVIEW ARTICLE

Saponins as anticancer agents: Delving into their mechanisms of action

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Abstract

Background: Cancer is a complex global disease driven by various biological processes that promote excessive cell growth, evade growth-inhibiting factors, facilitate replication, evade cell death, stimulate blood vessel formation, and initiate invasion and metastasis. The burden of cancer is increasing rapidly, with breast and prostate cancers being prevalent. Early detection and intervention are crucial to reducing morbidity and mortality rates. Natural products, especially saponins derived from medicinal plants, have gained attention due to their potential in cancer treatment, offering low toxicity and high efficacy. **Purpose:** This article aims to compile and analyze data on specific saponins derived from plants, elucidating their mechanisms of action in exerting anticancer effects. **Study Design:** This study involves a comprehensive review of existing literature on the anticancer properties of saponins. Various classes of saponins, including cycloartanes, dammaranes, oleananes, spirostanes, furostanes, and alkaloidal saponins, are explored for their potential to combat cancer. **Methods:** The study involves a literature review of scientific articles, studies, and research papers published on the anticancer properties of saponins. Mechanisms of action, effects on cell proliferation, apoptosis induction, cell cycle arrest, and modulation of signaling pathways are assessed for each saponin class. **Results:** Saponins exhibit diverse pharmacological functions, including anti-carcinogenic, anti-inflammatory, anti-viral, antimicrobial, antioxidant, and antitumor effects. Different classes of saponins demonstrate efficacy against various cancer types through mechanisms such as apoptosis induction, cell cycle arrest, and inhibition of angiogenesis. Specific saponins such as ginsenosides, tubeimosides, saikosaponins, and solanine have shown promising results in inhibiting cancer cell growth and promoting apoptosis through intricate cellular pathways. **Conclusion:** Saponins derived from plants hold significant promise as potential therapeutic agents against cancer due to their multifaceted pharmacological properties. The diverse mechanisms of action exhibited by various saponin classes make them valuable candidates for further research and drug development. Harnessing the potential of saponins may pave the way for innovative and targeted anticancer treatments, offering hope in the fight against this global health challenge.

Key words: Angiogenesis, anticancer, apoptosis, cancer, proliferation, saponins

INTRODUCTION

Cancer is a multifaceted global disease that manifests through various biological processes, including maintaining signals for excessive cell growth, avoidance of growth-inhibiting factors, facilitation of unlimited replication, evasion of cell demise, stimulation of new blood vessel formation, and initiation of invasion and metastasis. Furthermore, cancer cells reprogram energy metabolism and evade immune destruction, contributing to the complexity of the disease.[1] As evidenced by population-based cancer registries, cancer has emerged as a significant global health concern, projected to affect over 40% of the population.[2] The burden of cancer is rapidly escalating, with an estimated 1.2 million new cases and 400,000 deaths projected for 2020, compared to 2018.[3] This surge in cancer cases has profound implications for countries worldwide, presenting a formidable challenge to global public health. Notably, breast and prostate cancers prevail, displaying the highest frequency and fatality rates among females and males, respectively.[1] Tragically, numerous cancer-linked deaths result from belated diagnoses.[1] However, prompt detection

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and timely treatment can significantly reduce morbidity and mortality rates, emphasizing the critical nature of early intervention.

Numerous strategies have been explored to combat cancer, including chemotherapy, surgery, and radiotherapy. Despite the effectiveness of chemotherapy, patients frequently encounter various side effects, such as asthenia, fatigue, anorexia, and increased vulnerability to infections. Moreover, the non-selectivity and toxicity of Food and Drug Administration-approved anticancer drugs have presented considerable limitations in the management of cancer.[4] Therefore, there is a need to discover novel drugs that are effective against cancer yet have fewer side effects and are accessible. Natural products are proving to be valuable for cancer treatment, primarily due to their low toxicity and high efficacy.[5] These beneficial compounds are predominantly derived from medicinal plants, which hold the potential for the identification and development of novel drugs to treat diseases and cancer. By exploring the vast diversity of plant species, scientists have been able to discover and isolate bioactive compounds with therapeutic properties. These bioactive substances, often referred to as secondary metabolites, have been used since ancient times in traditional medicine and continue to be a valuable source of novel drug leads today.[6] Through careful extraction and analysis of these secondary metabolites, we can identify their biological activities and explore their potential in treating various diseases. The objective of this article is to compile data concerning certain saponins derived from plants and elucidate their mechanisms of action in exerting anticancer effects.

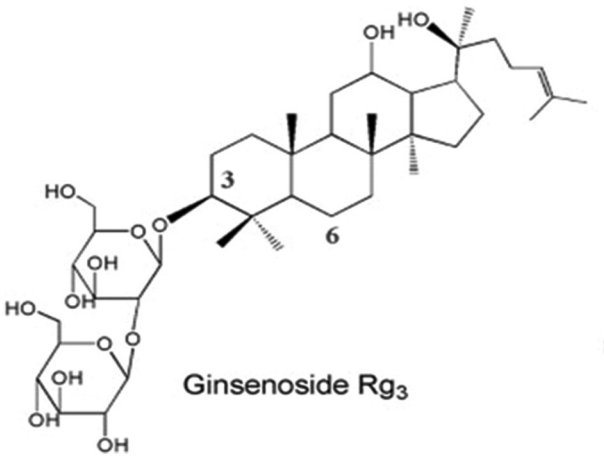

Figure 1: Structure of ginsenoside

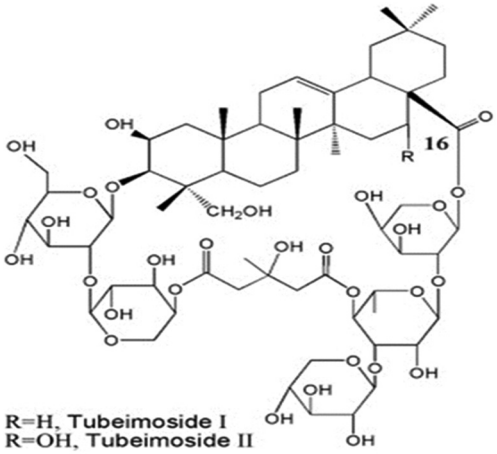

Figure 2: Structure of tubeimosides

SAPONIN

Saponins are a class of secondary metabolites found in various natural sources, particularly in plants and marine organisms. They are high-molecular-weight glycosides and consist of a polycyclic aglycone attached to one or more sugar-side chains. This aglycone segment, also referred to as sapogenin, exists as either a steroid (C27) or a triterpene (C30) compound.[7] The foaming characteristic of saponins arises from the interaction between a hydrophobic (fat-soluble) sapogenin and a hydrophilic (water-soluble) sugar component when agitated in watery solutions, which is the reason behind their designation as "saponins." These unique properties make saponins excellent surfactants, enabling them to lower the surface tension of water and form stable foams. One of the main natural sources of saponins in the human diet is lentils.[8] Lentils are known to contain significant amounts of saponins, which contribute to their emulsifying and foaming properties.[8] Saponins are found in a wide range of plant families, but some of the most common groups of medicinal plants from which saponins are isolated include Fabaceae, Compositae,

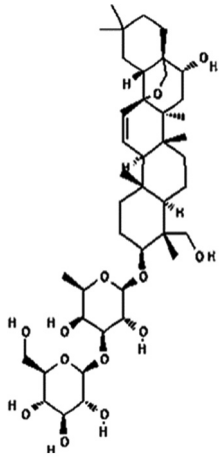

Figure 3: Structure of saikosaponin D

Liliaceae, Quillajaceae, Sapindaceae, and Dioscoreaceae. Saponins are classified according to their basic units based on their sapogenin framework: triterpenoid saponins and steroidal saponins.[9] Triterpenoid saponins are derived from triterpenes, which are comprised of six isoprene units

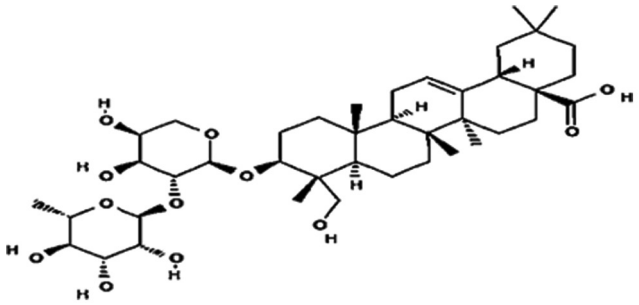

Figure 4: Structure of Alpha-hederin

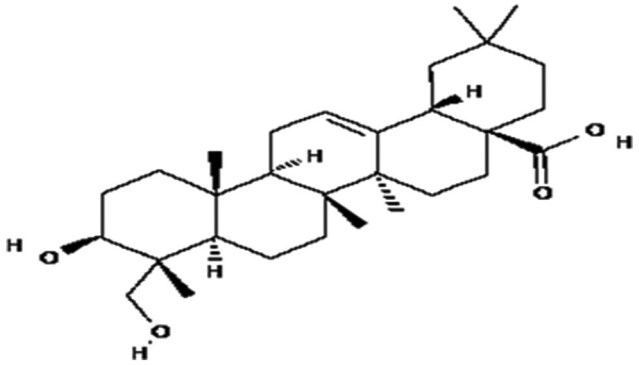

Figure 5: Structure of hederagenin

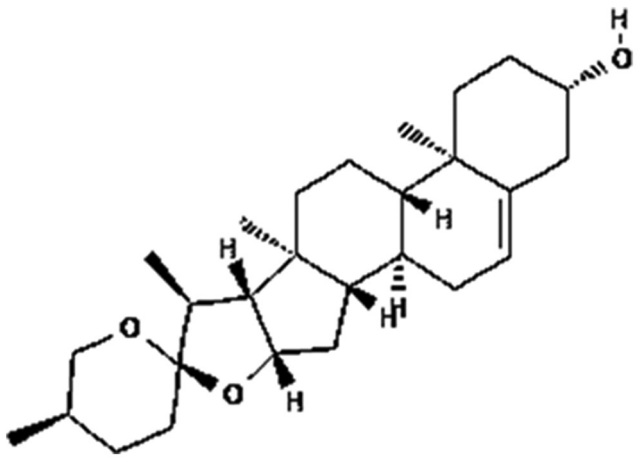

Figure 6: Structure of diosgenin

and have a triterpenoid backbone (triterpene aglycone). Steroidal saponins, on the other hand, have a steroidal nucleus as their basic unit (steroidal aglycone). This classification system encompasses more than eleven discernible saponin classes, namely tirucallanes, hopanes, lanostanes, lupanes, oleananes, cycloartanes, dammaranes, taraxasteranes, cucurbitanes, ursanes, and steroidal. Remarkably, among these distinct saponin categories, compelling evidence suggests the pronounced antitumor efficacy of certain subclasses, specifically cycloartanes, dammaranes, oleananes, lupanes, and steroids [Table 1], in effectively combating a diverse range of cancer types.[10]

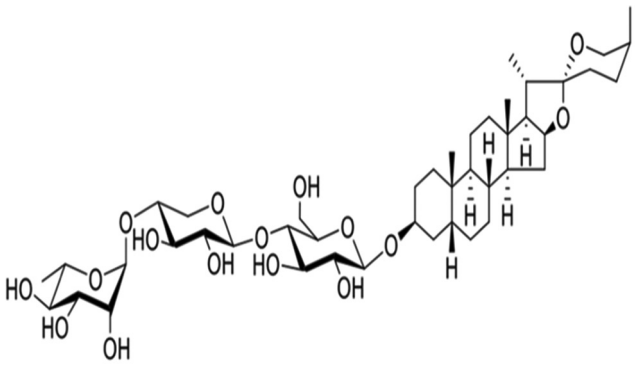

Figure 7: Structure of Aspiletrein A

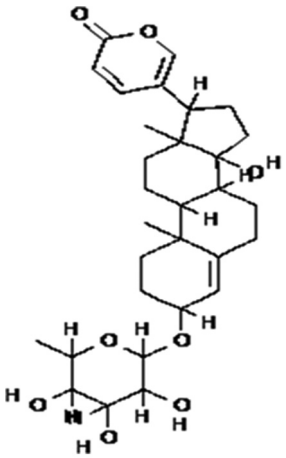

Figure 8: Structure of Proscillaridin A

Saponins have garnered extensive research attention due to their multifaceted pharmacological attributes.[11] According to empirical investigations, saponins exhibit a diverse array of pharmacological functions encompassing anti-carcinogenic, anti-inflammatory, anti-viral, antimicrobial, antioxidant, cytotoxic, phytotoxic, antitumor, antispasmodic, antidiabetic, anti-angiogenic, and anthelmintic properties.[11-13] Furthermore, saponins have demonstrated immunoregulatory effects and have been associated with cardioprotective attributes. Notably, saponins have demonstrated considerable promise in the domain of anticancer activity, thereby inciting substantial interest in cancer research endeavors.[4] These bioactive compounds have displayed encouraging outcomes in impeding tumor proliferation and initiating apoptosis (programmed cell death) in cancerous cells, thereby accentuating their potential in the development of novel therapeutic agents and pharmaceuticals. Remarkably, triterpenoid saponins, a specific subclass within the saponin repertoire, have emerged as a focal point of study due to their potent pro-apoptotic and anticancer effects.[13] It is recognized that saponins elicit anticancer responses chiefly through apoptosis induction, cell death promotion, angiogenesis inhibition, anti-proliferative effects, and mitigation of multidrug resistance.[4,14]

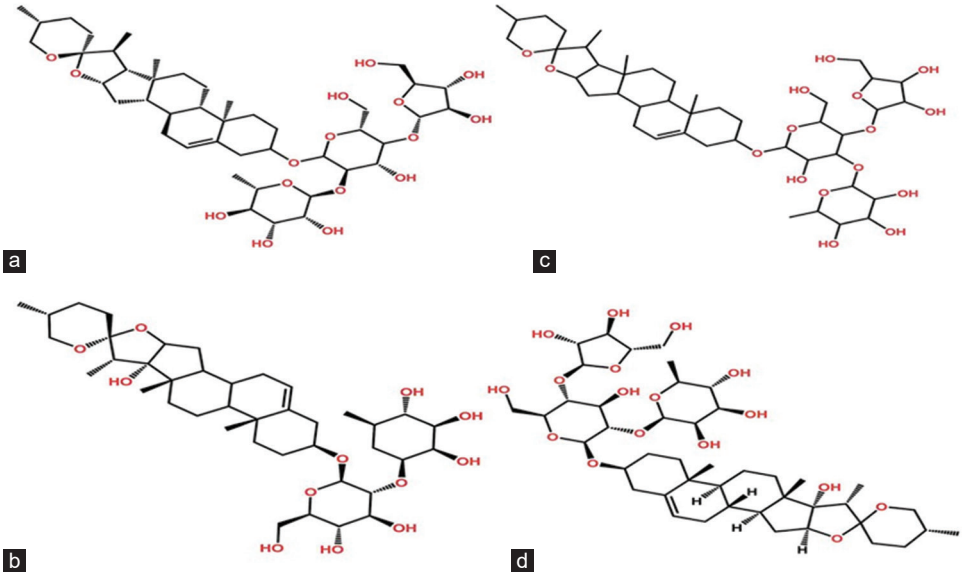

Figure 9: Structure of polyphyllin I (a), polyphyllin II (b), polyphyllin VI (c), and polyphyllin H (d)

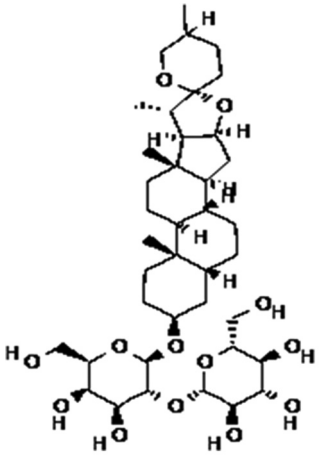

Figure 10: Structure of timosaponin AIII

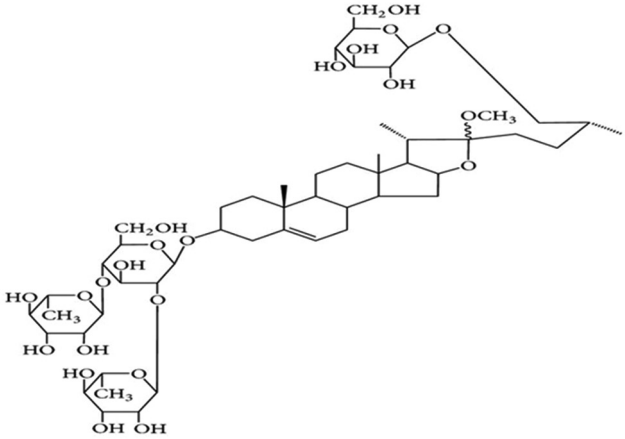

Figure 11: Structure of methyl protodioscin

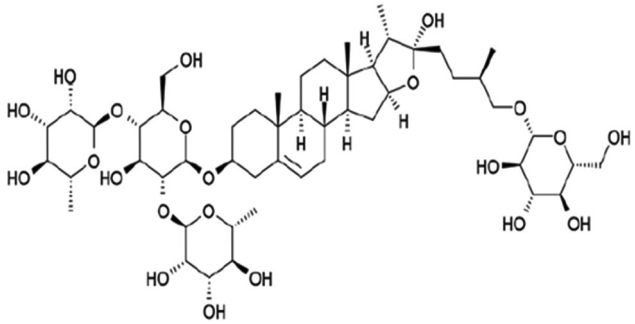

Figure 12: Structure of protodioscin

DAMMARANES

Ginsenosides

Ginsenosides, Rg3 [Figure 1] inhibits the growth of human lung cancer cells (A549 and PC9) *in vitro*. This effect is achieved by curbing cell proliferation and viability within both A549 and PC9 cells while stimulating apoptosis in A549 and SK-MES-1 cells. Furthermore, ginsenosides, Rg3, also orchestrates the arrest of G1-phase cells and modulates the expression of proteins linked to metastasis (E-cadherin, N-cadherin, Vimentin, and Snail) within lung cancer cells, thereby impeding the metastatic progression of these cells.[15,16] Furthermore, ginsenosides, Rh2 and Rd, have inhibitory actions against the proliferation of gastric SGC-7901 cells, and when combined with protopanaxadiol, Ginsenoside Rh2 effectively inhibits proliferation and triggers cytoplasmic vacuolization in gastric cancer HGC-27 cells by the upregulating LC3II and p62 expression, ultimately leading to mitochondrial impairment, disruption of lysosomal function, and a blockage of autophagic flow.[17] In addition, ginsenoside Rg1 has been found to induce apoptosis through the generation of reactive oxygen species (ROS) and suppress the invasion and migration within breast cancer cell populations.[18]

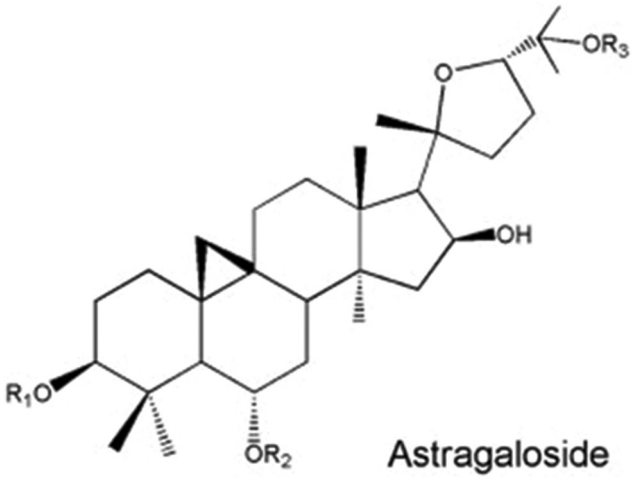

Figure 13: Structure of astragaloside

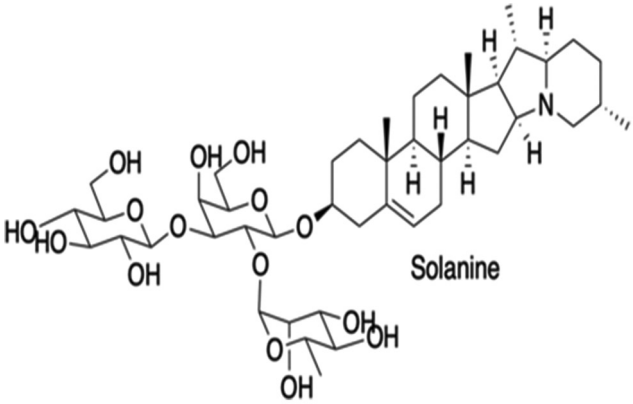

Figure 14: Structure of solanine

OLEANANES

Tubeimosides

Tubeimoside I as shown in Figure 2, exhibited effectiveness against breast cancer cells (MDA-MB-231 cells and MDA-MB-231 xenograft mice model) as well as prostate carcinoma (DU145 cells) when tested *in vivo*.[19] Its action on breast cancer cells involves the suppression of Nuclear Factor-kappa B DNA binding activity to the C-X-C Motif Chemokine Receptor 4 (CXCR4) promoter. This effectively inhibits the expression of CXCR4, leading to a reduction in breast tumor metastasis. Furthermore, in prostate cancer DU145 cells, Tubeimoside I induces mitochondrial apoptosis by triggering an increase in ROS generation, causing mitochondrial dysfunction and endoplasmic reticulum (ER) stress. This process is characterized by the modulation of B-cell Lymphoma 2 (Bcl-2) family protein expression, cleaved caspase-3 levels, and the activation of Apoptosis signal-regulating kinase 1 (ASK-1) along with its downstream targets p38 and c-Jun N-terminal Kinase (JNK).[20,21] In addition, Tubeimoside II induces cell cycle arrest and apoptosis in

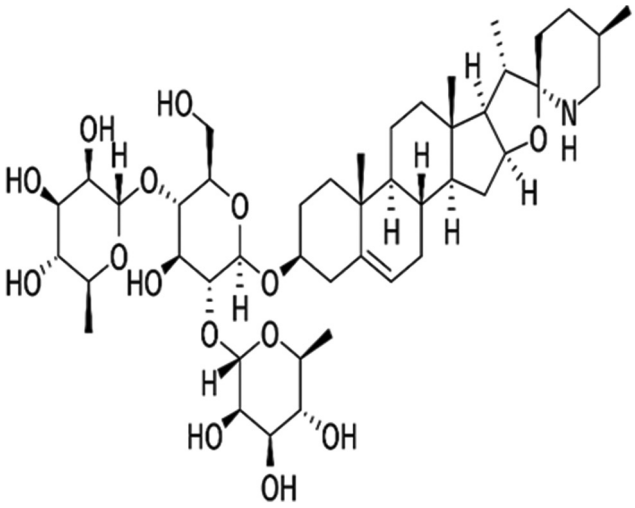

Figure 15: Structure of solamargine

glioblastoma cells (U87MG). Specifically, it prompts cell cycle arrest at the S phase, with a gradual increase observed at higher concentrations, ultimately leading to an accelerated sub-G1 peak.[22]

Saikosaponin

Saikosaponin A triggers the activation of extracellular signal-regulated kinase (ERK) alongside its downstream transcriptional machinery, resulting in the expression of p15 (INK4b) and p16 (INK4a), which in turn induces growth inhibition in HepG2 cells.[10] In hepatoma HuH-7 cells and breast cancer MCF-7 and MDA-MB-231 cell lines, Saikosaponin A induces G0/G1 arrest.[23] In addition, Saikosaponin A induces cell death in hepatocellular carcinoma (HCC) cells by causing the cleavage of Bid and poly-ADP ribose polymerase (PARP), and triggering the activation of caspase-2 and caspase-8 leading to the conformational activation of Bcl-2-Associated X Protein (BAX), and decreasing the levels of inhibitors of apoptosis (IAP) family proteins.[23]

Saikosaponin D [Figure 3] demonstrates a dose-dependent decrease in cell proliferation in Hep G2 and Hep 3B cells. This effect is evident in both p53-positive Hep G2 cells and p53-negative Hep 3B cells, whereas Saikosaponin D reduces cell proliferation and induces apoptosis.[10] It also triggers apoptosis in human breast cancer MDA-MB-231 cells by activating the p38 mitogen-activated protein kinase (MAPK) signaling pathway, resulting in a significant increase in p-p38 expression levels.[24] In cases of liver cancer, Saikosaponin D prompts autophagy by reducing mammalian target of rapamycin (mTOR) phosphorylation and suppressing the p- signal transducer and activator of transcription 3(STAT3)/C/EBPβ signaling pathway, which controls COX2 expression, subsequently leading to apoptosis.[25] Moreover, Saikosaponin D inhibits the proliferation of human hepatoma

cell lines (PLC/PRF/5 and HepG2) and human pancreatic cancer cell lines BxPC-3 by restraining cell growth and DNA synthesis.[23]

Alpha-hederin

Alpha-hederin as demonstrated in Figure 4, induces alterations in the cell membrane, resulting in cytoplasmic vacuolization that leads to cell death, observed in both cancer cells (melanoma) and non-cancerous cells (mouse 3T3 fibroblasts).[26] In the context of human ovarian cancer cells (SKOV-3 Cells), Alpha-hederin triggers apoptosis by reducing the Mitochondrial Membrane Potential, impeding the Bcl-2 signaling cascade response through Bcl-2 protein dephosphorylation, initiating G0/G1 cell cycle arrest, and activating caspase-9 and caspase-3/7.[26,27] Notably, Alpha-hederin exhibits similar effects in human colorectal cancer cells, inhibiting the proliferation of HCT116 and HCT8 cells by inducing apoptosis through the activation of the mitochondrial apoptosis pathway and concurrently suppressing autophagy both *in vitro* and *in vivo* through the activation of AMP-activated protein kinase (AMPK)/mTOR signaling.[27]

Hederagenin

Hederagenin as illustrated in Figure 5, hinders the proliferation of human LoVo colon cells through the reduction of mitochondrial membrane potential, down-regulation of Bcl-2, B-cell lymphoma-extra large, and Survivin mRNA levels, and the modulation of Bcl and caspase family pathways, ultimately resulting in apoptosis.[28] In addition, it triggers apoptosis in breast cancer cells (MDA-MB-231 and MCF-7) by decreasing mitochondrial Apaf-1 and Cyto C levels, while simultaneously enhancing the activities of caspase-3 and-9.[29]

STEROIDAL SAPONIN

Spirostanes

Diosgenin

In Figure 6, diosgenin has been documented to influence diverse stages of tumorigenesis, encompassing processes like tumor cell proliferation, apoptosis, epithelial-mesenchymal transition, cell migration, and angiogenesis.[30] In particular, diosgenin exerts notable inhibition on the cell viability and motility of breast cancer cells (MCF-7 and MDA-MB-231), instigating apoptosis by curbing S-phase kinase-associated protein expression in breast cancer cells.[31,32] Furthermore, diosgenin induces growth inhibition, prompts cell cycle arrest, and triggers apoptosis in breast cancer cell lines MCF-7 and Hs578T.[30,31] In prostate cancer cells, diosgenin (1–10 μmol/L) effectively curtails the HGF-induced escalation of vimentin and MDM2 levels, and E-cadherin in HK-2 cells.[30] In addition, at a concentration of 10 μmol/L, diosgenin impedes the invasion of gastric cancer BGC-823 cells in a hypoxic-mimicking, a process facilitated by the expression and secretion of proteolytic enzymes such as matrix metalloproteinases (MMPs) that degrade extracellular matrix components.[30]

Aspiletrein A

Aspiletrein A [Figure 7] induces apoptosis through the activation of cell death pathways, involving the accumulation of ROS that subsequently trigger AMPK activation, resulting in the inhibition of mTOR in Non-Small-Cell Lung Cancer Cells (NSCLC) (Witayateeraporn *et al*., 2022). Moreover, it facilitates apoptosis in lung cancer cells by augmenting the ratio of proapoptotic Bax to antiapoptotic Bcl-2 and concurrently reducing the levels of the antiapoptotic protein Mcl-1.[33]

Table 1: Saponin classification, structure and sources

Saponin subclass	Compounds	Sources	References
Dammaranes	Ginsenosides	*Panax ginseng, Panax quinquefolius*	[55]
Oleananes	Tubeimosides	*Bolbostemma paniculatum*	[22]
	Saikosaponin	*Bupleurum scorzonerifolium*, Radix bupleuri	[24,56]
	Alpha-hederin and Hederagenin	*Hedera helix, Chenopodium quinoa, Kalopanax pictus, Nigella sativa, Clematis ganpiniana*	[26,27,57]
Spirostanes	Diosgenin	*Dioscorea* species, Fenugreek (*Trigonella foenum graecum*)	[18,58]
	Aspiletrein A	*Aspidistra letreae*	[59]
	Proscillaridin A	*Drimia maritima, Urginea maritima,* and *Convallaria species*	[33]
	Polyphyllins	*Paris polyphylla, Rhizoma paridis*	[39,42]
	Timosaponin AIII	*Anemone flaccida, Anemone raddeana, Anemarrhena asphodeloides*	[55]
Furostanes	Protodioscin and Methyl protodioscin	*Tribulus terrestris, Asparagus cochinchinensis, Dioscorea collettii, Polygonatum sibiricum*	[60,61]
Cycloartanes	Astragaloside	*Astragalus membranaceus*	[49]
Alkaloidal	Solamargine, Solanine	*Solanum melongena, Solanum tuberosum, Solanum incanum*	[52,62,63]

Proscillaridin A

Proscillaridin A, as depicted in Figure 8, triggers a cascade of events leading to apoptosis in A549 lung adenocarcinoma cells, encompassing the activation of JNK, disruption of mitochondrial function, induction of ER stress (characterized by elevated levels of phosphorylated eukaryotic translation initiation factor 2α or p-eIF2α and activating transcription factor), and suppression of the STAT3 signaling pathway (accomplished by diminishing STAT3 phosphorylation at tyrosine 705).[34] In addition, Proscillaridin A impedes cell proliferation and prompts apoptosis in NSCLC tumors carrying various prevalent driver gene mutations. This effect is achieved by obstructing the phosphorylation of epidermal growth factor receptor (EGFR) at tyrosine residue 1173 in EGFR mutant cell lines and elevating *in vitro* Ca2+ levels, facilitated by the inhibition of *in vitro* Na+/K+ ATPase.[35] Furthermore, the compound curtails JAK2/STAT3 signaling and synergistically enhances the anticancer potency of doxorubicin in prostate cancer cells.[36]

Polyphyllin

Polyphyllin G, also known as polyphyllin VII, exhibits the capability to hinder cell viability and proliferation in diverse human nasopharyngeal cancer cell types (such as HONE-1 and NPC-039 cells). This inhibition is achieved by instigating autophagy through the activation of Protein Kinase B (AKT), p38 MAPK, and JNK signaling pathways. Moreover, Polyphyllin G prompts apoptosis by activating the ERK pathway.[37] In addition, it elicits cell apoptosis and enforces G1 phase cell cycle arrest in human colorectal cancer cells (HT-29 and SW-620). The apoptotic process is facilitated in a caspase-3-dependent manner.[38] In HepG2 cells, Polyphyllin G triggers autophagic cell death. This is accomplished by suppressing the PI3K/AKT/mTOR pathway, along with the activation of the JNK pathway. Consequently, Bcl-2 phosphorylation is initiated, leading to Beclin-1 dissociation from the Beclin-1/Bcl-2 complex, ultimately culminating in autophagy induction.[39]

Polyphyllin I and its analogues as illustrated in Figure 9, induce cytotoxicity in lung cancer (A549 cells) and human colorectal adenocarcinoma cell line (HT-29 cells). This effect is driven by mitochondrial dysfunction (resulting in decreased MMP) and disruption of intracellular Ca2+ homeostasis. This disruption activates mitochondrial dehydrogenase and stimulates oxidative phosphorylation, resulting in cellular apoptosis.[40] Notably, Polyphyllin VI elevates ROS levels in lung cancer cells (A549) and the human non-small cell lung carcinoma cell line (H1299 cells). This increase is achieved by upregulating the NF-κB signaling pathway, ultimately triggering apoptosis.[41]

In ovarian cancer, Polyphyllin II thwarts the phosphorylation of several intracellular proangiogenic kinases, including extracellular signal-related kinases, AKT kinases, focal adhesion kinases, and Src family kinases, by obstructing VEGF receptor 2 activation in endothelial cells. This inhibitory action curtails angiogenesis in an ovarian cancer mouse model and significantly retards the growth of ovarian cancers.[42]

Timosaponin AIII (TSAIII)

TSAIII, as depicted in Figure 10, exerts inhibitory effects on the growth of human colorectal cancer cells HCT-15 by inducing cell cycle arrest at both the G0/G1 and G2/M phases.[15] Furthermore, in pancreatic cancer cells, TSAIII exhibits the ability to hinder proliferation, bring about cell cycle arrest specifically at the G1 phase, and facilitate caspase-dependent apoptosis through the modulation of the PI3K/AKT signaling pathway.[43] In the context of promyelocytic leukemia HL60 cells, TSAIII induces apoptosis via a caspase-dependent mechanism, amplified by the enhancement of JNK1/2 and p38 MAPK phosphorylation level.[44] Moreover, in breast cancer cells, TSAIII orchestrates cell cycle arrest at the G2/M phase, concurrently activating the ATM/Chk2 and p38 MAPK signaling pathways. This intricate cascade culminates in apoptosis induction.[45]

Furostanes Saponin

Methyl protodioscin (MPD)

MPD [Figure 11] demonstrates significant anticancer properties by impeding proliferation and triggering apoptosis across various cancer cell lines, including HepG2 liver cancer, A549 lung cancer, cervical cancer, osteosarcoma, and pancreatic cancer cells.[46] In addition, MPD exerts a downregulating effect on the expression of c-Myc – a gene responsible for driving uncontrolled proliferation – in pancreatic cancer cells MIA PaCa-2 and PANC-1. This reduction in c-Myc, a gene pivotal for perpetual proliferation, contributes to the suppression of glycolysis, effectively impeding the progression of pancreatic cancer.[47] In the realm of cervical cancer, MPD orchestrates multiple effects: suppressing proliferation, and causing cell cycle arrest by orchestrating the modulation of survivin, Cyclin B1, and CDK1 mRNA levels, while simultaneously augmenting p53, p21, and Wee1 expression. These intricate adjustments ultimately result in dose-dependent apoptosis induction in Hela cells.[47]

Protodioscin

In Human HCC, Protodioscin as shown in Figure 12, displayed the capability to curtail cell viability and hinder proliferation, ultimately prompting apoptosis. This apoptotic response was brought about through the disruption of mitochondrial membrane potential and the induction of ER stress. Notably, this stress induction is linked to the release and accumulation of Ca2+ within the mitochondria. These effects were consistently observed across various HCC cell lines, namely Huh-7, HepG2, PLC/PRF/5, SK-Hep-1, and HA22T/VGH.[48]

CYCLOARTANES

Astragaloside-IV (AS-IV)

AS-IV, as illustrated in Figure 13, demonstrates prominent anticancer effects encompassing several key mechanisms, including the arrest of the cell cycle at the G0/G1 phase. It further triggers apoptosis induction by initiating both ER stress and the mitochondrial-dependent apoptotic pathway. Moreover, it facilitates autophagy induction and hampers cell proliferation and invasion[49] AS-IV has been demonstrated to curtail cell proliferation in three distinct NSCLC cell lines – namely, A549, NCIH1299, and HCC827 – achieved through the reduction of bcl2 and the elevation of Bax and caspase 3 levels.[50] In addition, AS-IV prompts cytotoxicity and impedes the proliferation of HCC cells by arresting them in the G1 phase and activating both the caspase-8 dependent extrinsic and caspase-9 dependent intrinsic apoptotic pathways.[51]

ALKALOIDAL SAPONIN

Solanine

Within human HCC HepG2 cells, Solanine as highlighted in Figure 14, induces the generation of ROS, diminishes the presence of the proliferation-linked protein HDAC1, a protein linked to proliferation, and enhances the expression and kinase activity of ASK1 and TBP-2. These proteins activate the JNK and p38 signaling pathways, ultimately driving apoptosis.[52] In addition, Solanine exhibits a suppressive impact on extrahepatic metastasis by reducing microRNA-21 expression within exosome-treated A549 lung cancer cells.[53]

Solamargine

Solamargine, as expressed in Figure 15 induces apoptosis in human cholangiocarcinoma QBC939 cells by modulating the protein expression of Bcl-2 and XIAP mRNA levels, while enhancing the protein expression of Bax, caspase 3, cleaved-caspase 3, caspase 7, and cleaved PARP, thereby facilitating the apoptotic process.[54] In gastric cancer cells, Solamargine decreases the phosphorylation of ERK 1/2 in the MAPK pathway. In addition, it elevates the expression of lncNEAT1_2 and LncPINT by inhibiting Erk1/2 MAPK signaling, leading to increased cleavage of caspase-7 and PARP and ultimately promoting apoptosis.[24,52] Solamargine inhibits the growth of human NSCLC by impacting the phosphatidylinositol 3-kinase/Akt (PI3-K/Akt) signaling pathway both *in vitro* and *in vivo*, as well as inhibiting E-prostanoid receptor 4 (EP4) mRNA.[30] The inhibition of Akt phosphorylation by GA reduces the expression of transcription factors SP1 and NK-κB subunit p65, which in turn suppresses the expression of the Prostaglandin E2 (PGE2) EP4 protein. This has implications for the modulation of processes such as growth and metastasis, which are associated with the protein family that includes PGE2.[52]

CONCLUSION

The exploration of saponins and their mechanism of anticancer effects have provided valuable insights into the potential of these natural compounds in the battle against cancer. The multifaceted nature of cancer, with its complex array of biological processes and challenges, demands innovative approaches to treatment. While traditional chemotherapy has been effective, its limitations in terms of non-selectivity, toxicity, and side effects underscore the need for alternative therapeutic options.

Plant-based compounds like saponins offer a promising avenue for the development of novel anticancer drugs. The diverse sources of saponins, ranging from various plant species to marine organisms, provide a rich pool for the discovery of bioactive compounds with therapeutic potential. Saponins exhibit unique properties due to their complex structure, which includes hydrophobic and hydrophilic components. These properties enable them to interfere with multiple cellular processes crucial for cancer development and progression. The discussed saponin classes—dammaranes, oleananes, spirostanes, furostanes, cycloartanes, and alkaloidal — have demonstrated remarkable anticancer activities through different mechanisms. From inducing apoptosis and cell cycle arrest to modulating signaling pathways and inhibiting angiogenesis, each class of saponin presents its own distinct approach to combating cancer.

In the face of the global cancer burden, the exploration of saponins opens new possibilities for the development of targeted and effective therapeutic interventions. The extensive research highlighted in this review sheds light on the potential of saponins as a valuable resource in the pursuit of improved cancer treatments. As science continues to unravel the intricate mechanisms underlying cancer, saponins emerge as a promising avenue for the design of novel drugs with enhanced efficacy, fewer side effects, and greater accessibility. By harnessing the power of nature, saponins offer a beacon of hope in the ongoing fight against cancer, providing a glimpse into a future where effective treatments bring relief to patients and communities worldwide.

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AUTHOR CONTRIBUTORSHIP

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