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Review

Chemical study and medical application of saponins as anti-cancer agents

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ABSTRACT

Saponins are a group of naturally occurring plant glycosides, characterized by their strong foam-forming properties in aqueous solution. The presence of saponins has been reported in more than 100 families of plants out of which at least 150 kinds of natural saponins have been found to possess significant anti-cancer properties. There are more than 11 distinguished classes of saponins including dammaranes, tirucallanes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes and steroids. Due to the great variability of their structures, saponins always display anti-tumorigenic effects through varieties of antitumor pathways. In addition, there are a large amount of saponins that still either remain to be trapped or studied in details by the medicinal chemists. This article reviews many such structures and their related chemistry along with the recent advances in understanding mechanism of action and structure–function relationships of saponins at the molecular and cellular levels. These aglycones have been described and their classification and distribution have been listed in the review. Some special saponins with strong antitumor effects have also been exhibited. Ginsenosides, belonging to dammaranes, have been found beneficial targeted on inhibition of tumor angiogenesis by suppressing its inducer in the endothelial cells of blood vessels, and then on prevention of adhering, invasion, and metastasis of tumor cells. Dioscin, one of the steroidal saponins, and its aglycone diosgenin also have been extensively studied on its antitumor effect by cell cycle arrest and apoptosis. Other important molecules discussed include oleanane saponins such as avicins, platycodons, saikosaponins, and soysaponins along with tubeimosides.

Contents

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1. Introduction

Saponins are common in a variety of higher plants and usually found in roots, tubers, leaves, blooms or seeds. Based on the carbon skeletons, saponins were classified into triterpenes and steroids. Their glycone parts were mostly oligosaccharides, arranged either in a linear or branched fashion, attached to hydroxyl groups through an acetal linkage [1].

Modern research found that saponins have antitumor effect on many cancer cells. Several saponins inhibit tumor cell growth by cell cycle arrest and apoptosis with IC50 values up to 0.2 mM. Meanwhile, saponins in combination with conventional tumor treatment strategies, result in improved therapeutic success. Furthermore, a much clearer understanding of how the various saponin structures are related to each other is obtained with the use of the classification presented [2]. The objective of this review is to provide a timely update on the sources, classification, and applications of saponins with special focus on their mechanism of antitumor effect and structure–function relationship.

2. Source and classification

The percentage of saponins has been reported in more than 100 families of plants, out of which at least 150 kinds of natural saponins have been found to possess significant anticancer properties (Tables 1 and 2).

The steroidal saponins are mainly found in *Agavaceae*, *Dioscoreaceae*, *Liliaceae*, *Solanaceae*, *Scrophulariaceae*, *Amaryllidaceae*, *Leguminosae* and *Rhamnaceae*; while triterpene saponins are predominantly present in *Acanthopanax*, *Leguminosae*, *Araliaceae*, *Scrophulariaceae*, *Campanulaceae* and *Caryophyllaceae*. There are more than 11 mainly distinguished classes of saponins including dammaranes, tirucallanes, lupanes, hopanes, oleananes, taraxasteranes, ursanes, cycloartanes, lanostanes, cucurbitanes, and steroidals. Among

Notes to Table 1:
[a]Ara α-L-arabinofuranosyl, Fuc β-D-fucosyl, Gal β-D-galactosyl, Gla α-galactosidase, Glc β-D-glucopyranosyl, Rha α-L-rhamnopyranosyl, Xyl β-D-xylosyl.
[b]Human promyelocytic acute myelogenous leukemia: HL-60.
Human chronic myelogenous leukemia cells: K562, THP-1, U937.
Lymphocytic leukemia cell: P388.
Murine leukemic: L1210, P388.
Human oral squamous cell carcinoma: HSC-2.
Central nervous system (CNS) cancer line; U251.
Nasopharynx: CNE-2Z, KB.
Non-small cell lung cancer (NSCLC): A549, LA795, LL/2.
Human breast ductal carcinoma: BT-549.
Breast adenocarcinoma: Bcap37, MCF7, MDA-MB-231, NCI-ADR-RES.
Human gastric adenocarcinoma: MK-1.
Stomach cancer cells: SGC-7901.
Pancreas carcinoma: MIA PaCa-2.
Hepatoma: BEL-7402, HA22T, SK-Hep-1.
Colon carcinoma: Colo-205, 26-L5, DLD-1, HT-29, KM-12.
Laryngeal epidermoid: Hep-2.
Human oral epidermoid carcinoma: KB.
Glioblastoma: U251MG, U373, U87MG.
Malignant melanoma: A375, B16BL6, B16F10, H1477, HTB-140, LOX, MALME-3M, M14, M4 Beu, SK-MEL.
Glioma: GBM8401/TSGH.
Human fibrosarcoma: HT-1080.
Non-cancer mouse 3T3 fibroblasts; human skin fibroblasts: HSFs.
Human monocytic: THP-1.
Renal carcinoma cell: 786-0 and UO-31.
Human ovary carcinoma: A2780, HO-8910, OVCAR3, SK-OV-3.
Ovarian teratocarcinoma: PA 1.
Uterine cervix cancer: HeLa.
Prostatic adenocarcinoma: PC 3.
References cited in this table [3–43].

these saponins, cycloartanes, dammaranes, oleananes, lupanes and steroids showed strong antitumor effect on kinds of cancers.

3. Mechanisms of the antitumor effect of saponins

Some special saponins with strong antitumor effects have been exhibited.

3.1. Cycloartanes

Cycloartane saponins displayed slight anti-cancer effect but they could be used as chemotherapeutic agent in the treatment of tumors. For example, total Astragalus saponins (AS) (Fig. 1 and Table 3) [58] possess antitumor properties in human colon cancer cells and tumor xenografts. They down-regulated expression of the HCC tumor marker α-fetoprotein and suppressed HepG2 cell growth by inducing apoptosis and

Table 1
The steroid saponins in the natural plants.

Family	Species	Saponins[a]	Kinds of cancer[b]	Ref.
Agavaceae	*Agave utahensis*		HL-60	[3]
	Agave fourcroydes	Chlorogenin hexasaccharide	HeLa	[4]
Alliaceae	*Allium macrostemon Bunge*	26-*O*-Glc-5α-furost-25(27)-ene-3β,22,26-tetraol-3-*O*-Glc(1→2)[Glc(1→3)]-Glc(1→4)-Gal	SF-268	[5]
		26-*O*-Glc-5β-furost-20(22)-25(27)-dien-3β,12β,26-triol-3-*O*-Glc(1→2) Gal	NCI-H460, SF-268	
		Macrostemonoside O, P, Q and R	HepG2, MCF-7, NCI-H460, SF-268, R-HepG2	[6]
	Allium leucanthum C. Koch	Leucospiroside A	A549, DLD-1	[7]
Asclepiadaceae	*Cynanchum auriculatum*	Wilfoside C1N and wilfoside C3N	A549	[8]
	Myriopteron extensum	Extensumsides A	Eight cancer cell lines	[9]
Asparagaceae	*Asparagus racemosus Willd*	Asparanin A	HepG2	[10]
	Asparagus filicinus	Filiasparosides A-D Aspafiliosides A and B	A549, MCF-7	[11]
	Asparagus oligoclonos	Aspaoligonins A and B Asparanin A	Five human tumor cell lines	[12]
	Asparagus gobicus	3-*O*-[Xyl(1-4)-Glc(1-2)-Glc]- (25S)-5β-spirostan-3β-ol	HO-8910, Bel-7402	[13]
Dioscoreaceae	*Dioscorea collettii* var. *hypoglauca*	Methyl protodioscin (NSC-698790)	HepG2	[14–16]
		Methyl protogracillin (NSC-698792)	KM12,U251,MALME-3M&M14,7 86-0&UO-31,MDA-MB-231	[17]
		Protoneodioscin, protodioscin, protoneogracillin, protogracillin,	K562	[18]
		Prosapogenin A of dioscin, dioscin and gracillin	K562	[19]
		Prosapogenin B of dioscin	K562	[20]
	Dioscorea futschauensis R.Kunth	(25S)-spirost-5-en-3β,27-diol-3-*O*-[Rha(1→2)-Glc(1)→3]-Glc, prosapogenin A of dioscin, dioscin and gracilin	ts-FT210	[21]
	Dioscorea panthaica	dioscoreside E, protodioscin	Many	[22]
		dioscoresides C, D, pseudoprotodioscin, pregnadienolone 3-*O*-β-gracillimatriose, pregnadienolone 3-*O*-β-chacotrioside	A375, L929, HeLa	[23]
Dracaenaceae	*Dracaena draco*	Icodeside	HL-60, A-431	[24]
		Draconins A-C	HL-60	[25]
	Nam ginseng (roots and rhizomes of Dracaena angustifolia)	Namonins A, B	26-L5, HT-1080, B-16 BL6	[26]
Liliaceae	*Paris polyphylla* var. *yunnanensis*	Diosgenyl saponins, pennogenyl saponins	Lung, liver cancer	[27,28]
	Paris formosana Hayata	Formosanin C	HT-29	[29]
	Anemarrhena asphodeloides	Timosaponin A-III	HeLa	[30]
	Polygonatum sibiricum	Neosibiricosides A-D,	MCF-7	[31]
	Sansevieria ehrenbergii	Sansevistatin 1, 2	P388	[32]
	Camassia cusickii	TGHS-1, TGHS-2	L1210	[33]
Convallariaceae	*Smilacina atropurpurea*	Smilacinoside A, funkioside D, aspidistrin	K562	[34]
		Atropurosides B, F; dioscin	SK-MEL, KB, BT-549, SK-OV-3, HepG2, non-cancerous Vero cells	[35]
	Convallaria majalis L.	Convallamaroside	Human kidney tumor cells	[36]
Solanaceae	*Solanum torvum*	Torvosides M	Human cancer cell lines	[37]
	Solanum nigrum	Degalactotigonin	HepG2, NCI-H460, MCF-7, SF-268	[38]
	Solanum indicum L.	protodioscin, methyl protodioscin, methyl protoprosapogenin A of dioscin, dioscin	Colo-205, KB, HeLa, HA22T, Hep-2, GBM8401/TSGH, H1477	[39]
	Cestrum nocturnum	(25R)-2α,17α-dihydroxyspirost-5-en-3β-yl *O*-Glc-(1→2)-*O*-[Xyl-(1→3)] -*O*-Glc-(1→4)-Gal	HSC-2 cells and normal Human gingival fibroblasts	[40]
Zygophyllaceae	*Tribulus parvispinus*	(25R)-26-*O*-Glc-5-furostan-3β,22α,26-triol 3-*O*-{Gal-(1→2)-*O*-[Xyl -(1→3)]-*O*-Glc-(1→4)-Gal} Gitonin	U937, MCF7, and HepG2	[41]
	Tribulus terrestris	Saponins	SK-MEL, KB, BT-549, SK-OV-3	[42]
	Balanites aegyptiaca kernels	Balanitin-6 and -7	A549, U373	[43]

modulating an ERK-independent NF-κB signaling pathway [113]. In addition, AS could be used as an adjuvant in combination with other orthodox chemotherapeutic drugs to reduce the side effects of the latter compounds [114]. It would target at NSAID-activated gene (NAG-1) to reduce the additive effects when used along with PI3K-Akt inhibitors. The information obtained could facilitate future development of a novel target-specific chemotherapeutic agent with known molecular pathways [115].

3.2. Dammaranes

Most dammarane saponins showed anti-cancer effect. The naturally occurring compound OSW-1 (Fig. 2) is found in the bulbs of *Ornithogalum saudersiae* and is highly cytotoxic against tumor cell lines. Nonmalignant cells were statistically significantly less sensitive to OSW-1 than cancer cells, with concentrations that cause a 50% loss of cell viability 40–150-fold greater than those observed in malignant cells. Electron microscopy and biochemical analyses revealed that OSW-1 damaged the mitochondrial membrane and cristae in both human leukemia and pancreatic cancer cells, leading to the loss of transmembrane potential, increase of cytosolic calcium, and activation of calcium-dependent apoptosis [116].

3.3. Oleananes

Oleananes own most kinds of saponins in the nature. Their antitumor effect worked through various pathways, such as anti-cancer, anti-metastasis, immunostimulation, chemoprevention and so forth. Avicins, tubeimoside, saikosaponins, platycodigenins, soybean saponin and *Pulsatilla koreana* saponins showed anti-cancer effect through different signaling transductions. In addition, all of them except tubeimoside and *Pulsatilla koreana* saponins displayed immunostimulation. Saikosaponins, platycodigenins and soybean saponin also have anti-metastatic activity. The detailed mechanisms of saponins listed as following.

Avicins (Fig. 3), derived from the Cactus plant *Acacia victoriae* found in Australia's deserts [117], can dephosphorylate Stat3 in a variety of human tumor cell lines and lead to a decrease in the transcriptional activity of Stat3, which regulated proteins such as c-myc, cyclin D1, Bcl2, survivin and VEGF [69]. Avicins D and G, as the main components of avicins, induced growth inhibition of human T lymphocytes, promoted apoptosis [118] and triggered autophagic cell death [119]. Meanwhile, they decreased respiratory activity [120] and induced ATP efflux after inhibition of the voltage dependent anion channel in the outer mitochondrial membrane [121].

Tubeimoside I (Fig. 4), one of the triterpenoid saponins from the bulb of *Bolbostemma paniculatum* (Maxim) *Franquet*, appears to be a promising agent for cancer chemoprevention [122]. It exerts cytotoxicity in HeLa cells through both mitochondrial dysfunction and ER stress cell death pathways [69]. As an anti-microtubule agent, it can bind to the colchicine binding site of tubulin [123].

Saikosaponin A (Fig. 5) activates ERK together with its downstream transcriptional machinery mediated p15(INK4b) and p16(INK4a) expression that led to HepG2 growth inhibition [124]. It inhibited the proliferation or viability of the MDA-MB-231 and MCF-7 cells in a dose-dependent manner and caused an obvious increase in the sub-G1 population of cell cycles [125]. Treatment with saikosaponin D (Fig. 5) decreased the cell proliferation of Hep G2 and Hep 3B cells in a dose-dependent manner. It therefore decreased the cell proliferation and inducted apoptosis both in p53-positive Hep G2 and p53-negative Hep 3B cells [126]. In addition, it inhibited the proliferation of A549 by inducing apoptosis and blocking cell cycle progression in the G1 phase [127].

Notes to Table 2:
[a]Ara α-L-arabinofuranosyl, Fuc β-D-fucosyl, Gal β-D-galactosyl, Gla α-galactosidase, Glc β-D-glucopyranosyl, Rha α-L-rhamnopyranosyl, Xyl β-D-xylosyl.
[b]Human promyelocytic acute myelogenous leukemia: HL-60.
Human chronic myelogenous leukemia cells: K562, THP-1, U937.
Lymphocytic leukemia cell: P388.
Murine leukemic: L1210, P388.
Human oral squamous cell carcinoma: HSC-2.
Central nervous system (CNS) cancer line; U251.
Nasopharynx: CNE-2Z, KB.
Non-small cell lung cancer (NSCLC): A549, LA795, LL/2.
Human breast ductal carcinoma: BT-549.
Breast adenocarcinoma: Bcap37, MCF7, MDA-MB-231, NCI-ADR-RES.
Human gastric adenocarcinoma: MK-1.
Stomach cancer cells: SGC-7901.
Pancreas carcinoma: MIA PaCa-2.
Hepatoma: BEL-7402, HA22T, SK-Hep-1.
Colon carcinoma: Colo-205, 26-L5, DLD-1, HT-29, KM-12.
Laryngeal epidermoid: Hep-2.
Human oral epidermoid carcinoma: KB.
Glioblastoma: U251MG, U373, U87MG.
Malignant melanoma: A375, B16BL6, B16F10, H1477, HTB-140, LOX, MALME-3M, M14, M4 Beu, SK-MEL.
Glioma: GBM8401/TSGH.
Human fibrosarcoma: HT-1080.
Non-cancer mouse 3T3 fibroblasts; human skin fibroblasts: HSFs.
Human monocytic: THP-1.
Renal carcinoma cell: 786-0 and UO-31.
Human ovary carcinoma: A2780, HO-8910, OVCAR3, SK-OV-3.
Ovarian teratocarcinoma: PA 1.
Uterine cervix cancer: HeLa.Prostatic adenocarcinoma: PC 3.
Macrophage-like cell line, J-774.1.
References cited in this table [30,44–112].

Table 2
Triterpenoid saponins in plants.

Family	Species	Saponin[a]	Kinds of cancer[b]	Ref.
Amaranthaceae	*Alternanthera philoxeroides*	Philoxeroidesides A-D	SK-N-SH, HL60	[44]
		Achyranthoside H methyl ester	MCF-7, MDA-MB-45	[45]
Apiaceae (Umbelliferae)	*Achyranthes fauriei*	Chikusetsusaponin IV a	SK-Hep-1	[46]
	Physospermum verticillatum	Saikosaponin a Buddlejasaponin IV, songarosaponin D	COR-L23	[47]
	Bupleurum rotundifolium	Rotundifoliosides A-J Rotundiosides A, F, G, J-Y	MK-1, HeLa, B16F10	[48]
Araliaceae	*Hedera colchica K. Koch*	Hederacolchisid A1	DLD-1, PA 1, A549, MCF7, PC 3, M4 Beu vs normal human fibroblasts	[49]
	Hedera helix	α-hederin	B16, 3T3 fibroblasts	[50]
	Meryta denhamii	Echinocystic acid as the aglycone	J774.A1, HEK-293, and WEHI-164	[51]
Asteraceae	*Ixeris sonchifolia*	Ixeris saponins B, C	A375, L929, and HeLa	[52]
	Silphium radula Nutt.	Urs-12-ene-3β,6β-triol-3-Gal-(1→2)-Glc	MDA-MB-231	[53]
	Viguiera decurrens	Monodesmoside oleanolic acid saponins	P388, COLON	[54]
	Solidago virgaurea L. *Heteropappus altaicus (Willd.) Novopokr.* *H. biennis (Ldb.) Tamamsch.* *Helianthus annuus* L.	*O*-glycosylation pattern at carbon atom 3 and 28 of the sapogenin Acylglycosidic carbohydrate sequence 1-fucose-2 <1- rhamnose-4 <1-xylose-3 <1-rhamnose of these bisdesmosides Echinocystic acid glycosides the acylglycosidic carbohydrate sequence 1-arabinose-2<1-rhamnose-4<1-glucose	YAC-1, P-815	[55]
Campanulaceae	*Platycodon grandiflorum*	3-*O*-Glc-2β,12α,16α,23,24-pentahydroxyoleanane- 28(13)-lactone 3-*O*-Glc-(1→3)-Glc-2β,12α,16α,23α- tetrahydroxyoleanane-28(13)-lactone Platycodin D	ECA- 109 U937, THP-1, K562	[56] [57–59]
Caprifoliaceae	*Lonicera macranthoides*	Macranthoside B	Many	[60]
	Dianthus versicolor	dianversicosides A-G	Many	[61]
Caryophyllaceae	*Vaccaria segetalis*	3-*O*-[Gal-(1→2)-Glc] quillaic acid 28-*O*-Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Fuc-(1→4)]-Fuc VacA-549 caroside E, vaccaroside G, vaccaroside B, segetoside H and segetoside I	LNcap, P-38,	[30]
	Gypsophila oldhamiana	Gypoldoside A Jenisseensosides A, B, C, D	Many Human colon tumor cells	[62] [63]
Chenopodiaceae	*Chenopodium quinoa*	3-[(*O*-Glc-(1→3)-Ara)oxy]-23- oxo-olean-12-en- 28-oic acid Glc, 3-[(*O*-Glc-(1→3)-Ara)oxy]-27-oxo-olean-12-en-28-oic acid Glc, 3-*O*-Ara serjanic acid 28-*O*-Glc ester, 3-*O*-Glc serjanic acid 28-*O*-Glc ester	HeLa Caco-2	[64] [64]
Combretaceae	*Terminalia tropophylla H. Perrier*	Terminaliaside A	A2780	[65]
Cucurbitaceae	*Gymnocladus chinensis Baillon*	GC-1	Hepatoma cells	[66]
	Gynostemma pentaphyllum	Gypenoside (Gyp) XLIX (23S)-3β,20ξ,21ξ-trihydroxy-19-oxo-21,23-epoxydammar-24-ene 3-*O*-[Rha(1)][Xyl(1→3)]-Ara (23S)-21ξ-*O*-ethyl-3β,20ξ,21-trihydroxy-19-oxo-21,23-epoxydammar-24-ene 3-*O*-[Rha(1→2)][Xyl(1→3)]-Ara 3-*O*-{[Rha(1→2)][Xyl(1→3)]-6-*O*-acetyl Glc	THP-1 SGC-7901, BEL-7402	[66] [67]
	Momordica dioica	Bisdesmoside Tubeimoside V	K-562, BEL-7402 U87MG	[68]
	Bolbostemma paniculatum	Tubeimoside-1	HeLa CNE-2Z	[69] [70]
	Cucurbita foetidissima	Foetidissimoside B	Human colon cancer	[71]
	Momordica dioica	α-spinasterol-3-*O*-Glc	L1210	[72]
Hippocastanaceae	*Aesculus pavia L.*	Aesculiosides Ia-Ie, IIa-IId,	leukemia, NSCL, colon, CNS, melanoma, breast ovarian, renal, prostate	[73]
	Aesculus hippocastanum	β-escin	HT-29	[74]
Lardizabalaceae	*Craniotome furcata*	Craniosaponin A	Many	[75]
Leguminosea	*Acacia tenuifolia*	Saponins	Many	[76]
	Trigonella foenum graecum	Diosgenin	HT-29	[77]
	Trigonella foenumgraecum L.	Protodioscin	HL-60	[78]
	Gleditsia sinensis	Gleditsioside E	Bel-7402, BGC-823, HeLa, HL-60, MCF-7	[79]
	Gleditsia sinensis Lam.	Saponin	K562, HL-60	[79]
	Archidendron ellipticum	Elliptoside A	LOX	[80]
Molluginaceae	*Glinus lotoides L.*	lotoidoside D and lotoidoside E lotoidosides A, C, lotoidosides G	HeLa J774.A1, HEK-293, WEHI-164	[81] [82]
Myrsinaceae	*Ardisia pusilla A. DC.*	ardisiacrispin A, B 13,28-epoxyoleanane type	U251MG	[83]
	Ardisia crenata	olean-12-ene ardisiacrispin (A+B)	Bel-7402	[84]
	Ardisia gigantifolia Stapf.	Cyclamiretin A 3β-*O*-Rha-(1→3)-[Xyl-(1→2)]-Glc-(1→4)-[Glc-(1→2)]-Ara Cyclamiretin A 3β-*O*-Rha-(1→3)-[Glc-(1→3)-Xyl-(1→2)]-Glc-(1→4)-Glc-(1→2)]-Ara ardisiacrispin A	Many	[85]
Pittosporaceae	*R. parvifolius*	Total saponins	A375, B16	[86]
	Quillaja saponaria	QS-21	Melanoma, breast, prostate cancer, SCLC	[87]

(continued on next page)

Table 2 (*continued*)

Family	Species	Saponin[a]	Kinds of cancer[b]	Ref.
Polygalaceae	*Muraltia heisteria*	acylated triterpene glycosides cis-3,4,5-trimethoxycinnamoyl derivatives	Human colon cancer	[88]
	Securidaca inappendiculata	Securioside A, B	J-774.1	[89]
	Lysimachia thyrsiflora L.	LTS-4	HTB-140, HSFs	[90]
Primulaceae	*Lysimachia davurica*	3-*O*-Glc oxyuronic acid-(1→2)-Xyl-cyclamiretin A 3-*O*-Glc-(1→2)-Ara-cyclamiretin A	A-2780 cells	[91]
	Androsace umbellata	3-*O*-[Xyl-(1→2)-Glc-(1→4)-[Glc-(1→2)]-Ara] -3β-hydroxy- 13β,28-epoxy-16-oxo-oleanan-30-al 3-*O*-Xyl-(1→2)-Glc-(1→4)-Ara- 3β-hydroxy-13β,28-epoxy-16-oxo-oleanan-30-al	Human hepatoma cells	[92]
Ranunculaceae	*Anemone flaccida Fr.*	Flaccidoside II > anhuienoside E > hederasaponin B > glycoside St-I4a > glycoside St-J	HeLa cells	[93]
	Schmidt			
	Pulsatilla koreana Nakai	*Pulsatilla* saponin D	LLC in BDF1 mice	[94]
	Clematis chinensis	Monodesmosidic saponins	Many	[95]
	Clematis parviloba	Clematoside S, alpha-hederin	HCT-8, Bel-7402, BGC-823, and A-2780	[96]
	Nigella glandulifera Freyn et Sint.	Kalopanaxsaponins A and I	HepG2, R-HepG2	[97]
	Nigella sativa	α-hederin	LL/2 in BDF1 mice, P388 A549, HEp-2, HT-29, MIA PaCa-2	[98] [99]
	Pulsatilla koreana	oleanolic acid 3-*O*-Rha-(1→2)-[Glc-(1→4)]-Ara A549,SKOV-3,SK-MEL-2,HCT15 hederagenin 3-*O*-Rha-(1→2)-[Glc-(1→4)]-Ara hedragenin 3-*O*-Glc-(1→4)-*O*-Glc- (1→3)-*O*-Rha-(1→2)-Ara	BDF1 mice bearing LLC	[100]
	Cimicifuga species	Triterpene glycosides Actein	MDA-MB-453r	2007 2009
	Actaea asiatica	Asiaticoside A, 25-anhydrocimigenol-β-*O*-Xyl , asiaticoside B, HepG2, 25-*O*-ethylcimigenol-3-*O*-Xyl, 25-*O*-acetylcimigenol-3-β-*O*-Xyl	MCF-7	2006
	Xanthoceras sorbifolia Bunge x	Trisaccharide chain attached at C3 of the aglycone and two angeloyl groups acylated at C21 and C22	OVCAR3	[101]
		3-*O*-[(3-*O*-Ara-2-*O*-Gal)-Glc]-21, 22-di-*O*-angeloyl-R1-barrigenol	Six human tumour cell lines	[102]
		xanifolia-Y0, -Y2, -Y3, and -Y7	OVCAR3	[103]
Sapindaceae		16-*O*-α-21-*O*-(4-angeloyl)-Rha barringtogenol C, 28-*O*-Glc 16-deoxybarringtogenol C	A375-S2, HeLa	[101]
	Thevetia peruviana	Thevefolin, cardenolide glycosides	Human gastric adenocarcinoma cells	[104]
	Sapindus emarginatus	Four triterpenoid saponins		
	Sapindus mukorossi	Sapinmusaponins A, C, D, E	Hepa59T/VGH, NCI, HeLa, Med many	[105]
		Sapinmusaponin K, L, M, N		[106]
	Dodonaea viscosa	Dodoneasides A and B	A2780	[107]
Scrophulariaceae	*Buddleja officinalis*	Mimengosides C-G	HL-60	[108]
Zygophyllaceae	*Tribulus terrestris*	Methylprototribestin, the mixture of the 3 acetylated isomers	MDR-cancer xenograft transplanted mice	[109]
		Saponins	786-0	[110]
			BEL-7402	[111]
			Bcap37	[112]

Saponins derived from *Platycodon grandiflorum* may suppress tumor invasion and migration by inhibiting MMP-2 and MMP-9 activation [57]. Platycodon D (Fig. 6) as one of the platycodigenins, is a potentially interesting candidate for use in cancer chemotherapy. Its exposure induced apoptosis through caspase-3 dependent PARP, lamin A cleavage and ROS induced through Egr-1 activation [128]. The primary antileukemia activity is induction of endoreduplication and mitotic arrest, as a consequence of suppressing spindle MT dynamics and promoting apoptosis in human leukemia cells [59]. Furthermore, it has direct cytotoxic effect on human leukemia cells and suppresses telomerase activity through transcriptional and post-translational suppression of hTERT [58].

Soybean saponin (Fig. 7) inhibits tumor cell metastasis by suppressing MMP-2 and MMP-9 productions, and stimulating TIMP-2 secretion [129]. At physiologically relevant doses, it can suppress HCT-15 colon cancer cell proliferation through S-phase cell cycle delay, and induce macroautophagy, the hallmark of Type II PCD. B-group soyasaponins may be another colon cancer suppressive component of soy that warrants further examination as a potential chemopreventive phytochemical [130,131]. It significantly increased activity of raf-1 by a maximal 200%, suggesting that this enzyme in part modulates the enhanced ERK1/2 activity [132].

Pulsatilla koreana saponins (Fig. 8) were examined for their *in vitro* cytotoxic activity against the human solid cancer cell lines, A-549, SK-OV-3, SK-MEL-2, and HCT15, using the SRB assay method, and their *in vivo* antitumor activity using BDF1 mice bearing Lewis lung carcinoma (LLC) [100]. Pulsatilla saponin D as an antitumor component showed potent inhibition rate of tumor growth (IR, 82%) at the dose of 6.4 mg/kg on the BDF1 mice bearing LLC cells [133].

3.4. Spirostanes

Polyphyllin D (PD), formosanin C and dioscin belonging to the diosgenyl saponins, showed strong anti-cancer and immunostimulative activity.

With the ascertained chemical structure and the improved synthesis of polyphyllin D, both *in vitro* and *in vivo* studies were performed on its effect. Recent research showed that PD

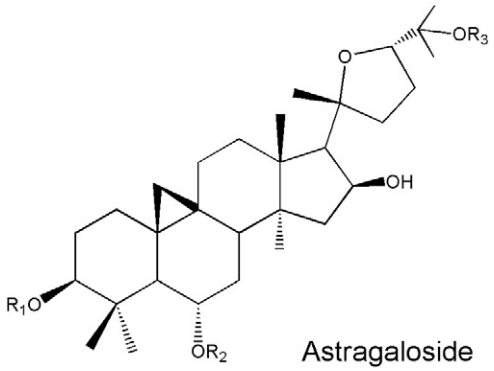

Fig. 1. The structure of astragalosides.

Table 3
Astragalosides.

	R1	R2	R3
Astragaloside I	Xyl (2,3-diAc)	Glc	H
Astragaloside IV	Xyl	H	H
Astragaloside VII	Xyl	Glc	Glc

is a potent apoptosis inducer through mitochondrial dysfunction and ER stress [134–136].

Meanwhile, dioscin [137–141] is a preclinical drug showing potent antiproliferative activities against most cell lines from leukemia and solid tumors. Proteomic analysis revealed that it induced apoptosis via the mitochondrial and some other pathway (Fig. 9 and Table 4) [142].

Formosanin C, mainly a constituent in *Rhizoma Paris* saponins either, had some effect on the immune responses. Intraperitoneal treatment with 1–2.5 mg/kg of formosanin C would retard the growth of subcutaneously transplanted MH134 mouse hepatoma. The mechanism of its antitumor effect might be associated with its modification of the immune system [143]. It can also enhance the antitumor effect of 5-fluorouracil. Activation of caspase-2 and the

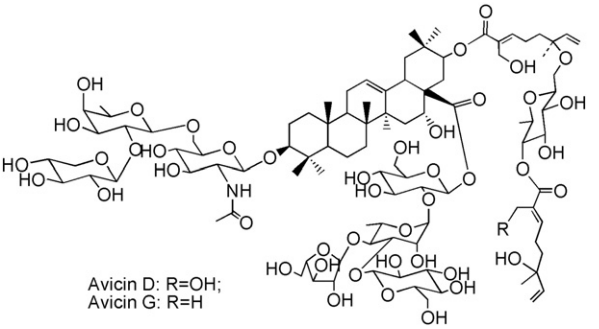

Fig. 3. Structure of avicins.

dysfunction of mitochondria maybe also contributed to its antitumor effect in human colorectal cancer HT-29 cells [144].

3.5. Furostanes

Most of furostanes only showed some anti-cancer activity. Protoneodioscin, protodioscin, protoneogracillin, and protogracillin, along with their corresponding artifacts: methyl protoneodioscin, methyl protodioscin, methyl protoneogracillin, and methyl protogracillin showed cytotoxic activities against K562 cancer cell as antineoplastic agents [18] (Fig. 10).

Methyl protogracillin was cytotoxic against all the tested cell lines from leukemia and solid tumors in the NCI's human cancer panel; it showed particular selectivity against one colon cancer line (KM12), one central nervous system (CNS) cancer line (U251), two melanoma lines (MALME-3M and M14), two renal cancer lines (786-0 and UO-31) and one breast cancer line (MDA-MB-231) [17].

4. Structure–function relationship of saponins with the antitumor properties

Differences in saponin structure which include the type, position, and number of sugar moieties attached by a

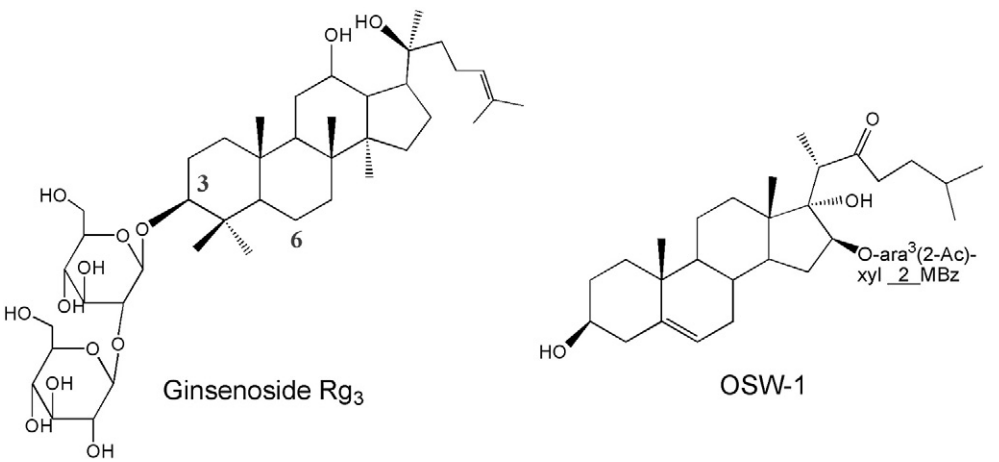

Fig. 2. Structures of ginsenosides and OSW-1.

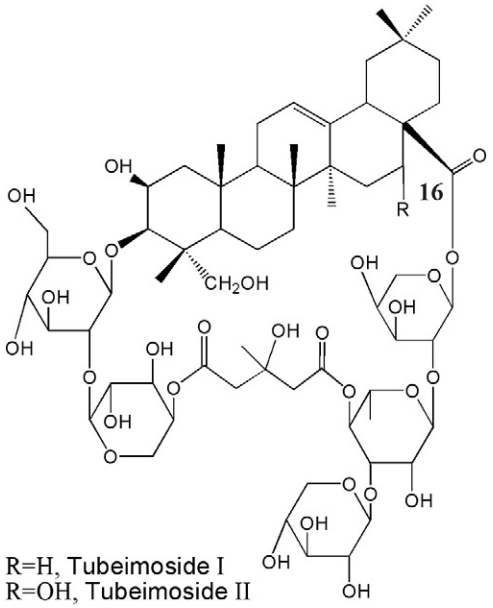

Fig. 4. Structure of tubeimosides.

glycosidic bond at different positions of the rings can characteristically influence biological responses, especially for the antitumor activity. We could draw the following structure–activity relationships in the succeeding sections.

4.1. Influence of the aglycone on the antitumor activities of saponins

Comparing different kinds of saponins, it shows that small changes such as different positions or the number of the hydroxyl groups, R/S configuration on the aglycone led to slight changes in activity, and more sizable changes diminished the activity.

4.1.1. The site of the hydroxyl group

Changes on the agycone could change the antitumor activity of saponins. C-16 hydroxyl group of tubeimoside II plays an important role in enhancing the biological activity of tubeimoside II and in decreasing its toxicity [145] (Fig. 4). C-17α-hydroxyl group to the aglycone of the active saponins slightly reduced their cytotoxicities, such as pennogenyl saponins and diosgenyl saponins [146] (Fig. 9). C-27 of the aglycone of the furostanol saponins, which also bore an additional monosaccharide at C-27 (compared to the spirostan saponins mentioned above), showed less antitumor effect (Fig. 9).

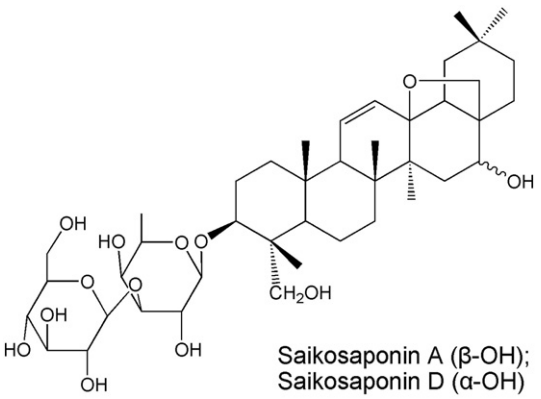

Fig. 5. Structure of saikosaponins.

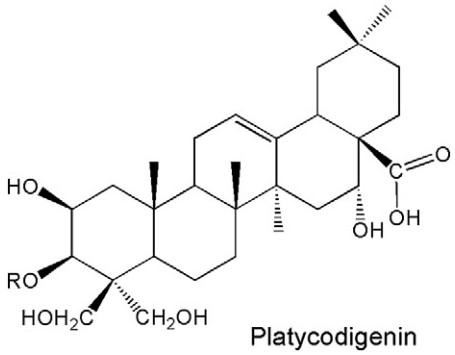

Fig. 6. Structure of platycodigenin.

4.1.2. The number of the hydroxyl group in aglycone

Ginsenosides with a dammarane structure have two main classes: panaxadiols (PPD) and panaxatriols (PPT). The activities of PPD compounds are greater than those of the PPT compounds. And the aglycones are more effective than the ginsenosides Rh1 (PPT type) and Rh2 (PPD type), which possess sugar moieties at C-6 and C-3, respectively. All the ginsenosides have similar chemical structures, but their effects on B16 melanoma cells were remarkably different (Fig. 2) [147].

4.1.3. Else

Based on structure–activity relationship, C-25 R/S configuration was critical for leukemia selectivity between methyl protoneogracillin and methyl protogracillin. Meanwhile, F-ring was critical to selectivity between furostanol (methyl

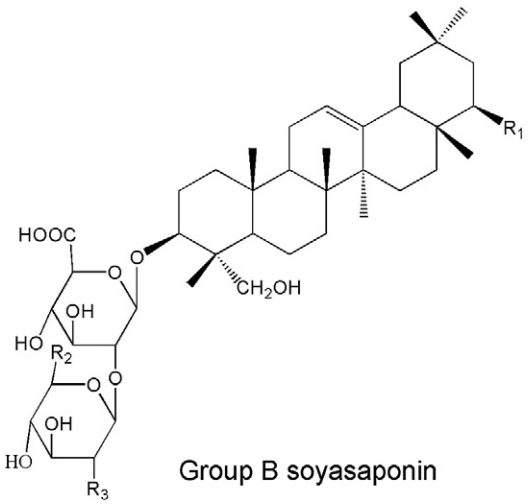

Fig. 7. Structure of soyasaponin.

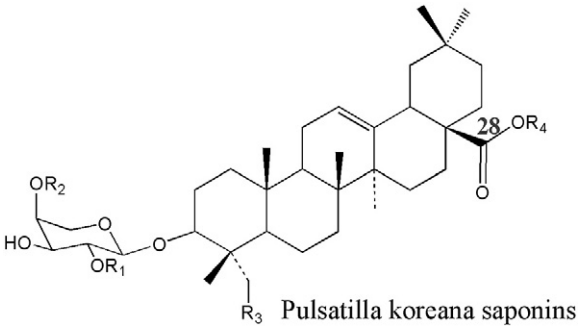

Fig. 8. Structure of *Pulsatilla koreana* saponin.

protoneogracillin and methyl protogracillin) and spirostanol (gracillin) saponins. Methyl protoneogracillin has been selected as a potential anti-cancer candidate for hollow fiber assay to nude mice, which is slightly better than methyl protogracillin, but gracillin would not be pursued due to the lack of selectivity against human cancer diseases (Fig. 9) [148].

4.2. Influence of the sugar side chain on the antitumor activities of saponins

In the comparison with the saponins bearing saccharide groups, different characteristics (sugar linkage, the number, lipophilicity, or different kinds) of sugar side chain play important roles in their antitumor effect.

4.2.1. The sugar linkage

With the same aglycone and length of sugar chain, the sugar linkage determines the antitumor potency. This point is clearly demonstrated by the four disaccharide congeners. 1→3 linkage had much lower activity than 1→2 and 1→4 linkages, respectively [149].

4.2.2. The lipophilicity of the sugar

Some saponins showed no activity with the exceptions of those possessing some acyl groups at the glycosyl moiety. Meanwhile, two deoxypyranoses, including D-fucose and L-rhamnose, were also cytotoxic. These data led us to assume that the presence of a certain degree of lipophilicity in the sugar moiety is essential for exhibiting the cytotoxic activity [146].

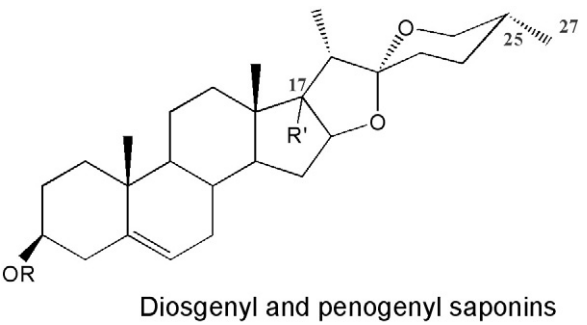

Fig. 9. Structures of diosgenyl and pennogenyl saponins.

Table 4
Diosgenyl saponins (R′ H).

R	Name(R′=H)
-H	Diosgenin
-3-*O*-Glc	Trillin
-3-*O*-Rha (1→2)-Glc	ParisV
-3-*O*-Ara (1→4)-[Rha(1→2)]-Glc	Polyphyllin D
-3-*O*-Rha(1→4)-[Rha(1→2)]-Glc	Dioscin
-3-*O*-Rha(1→2)-[Glc (1→3)]-Glc	Gracillin
-3-*O*-Rha(1→4)-Rha(1→4)-[Rha(1→2)]-Glc	Formosanin C

4.2.3. The number of the sugar

The number of the sugar also influences the antitumor effect of saponins. The activity of the various ginsenosides has been demonstrated to be in the order: monosaccharide glycoside>disaccharide glycoside>trisaccharide glycoside>tetrasaccharide glycoside, indicating that increasing the number of sugar moieties reduces the potency of the compound [147]. In the contrast, diosgenyl saponins showed the contrary rule. Diosgenin β-D-glucoside showed no cytotoxic activity against HL-60 cells (IC50 20 mg/ml), and the attachment of an α-L-rhamnosyl group at C-2 of the glucosyl moiety led to the appearance of considerable activity. Further addition of an α-L-rhamnosyl, an α-L-arabinofuranosyl or a β-D-glucosyl, with the exception of a β-D-galactosyl, to C-3 or C-4 of the inner glucosyl moiety either gave no influence on the activity or slightly increased the activity; the attachment of a β-D-galactosyl at C-3 of the glucosyl residue led to a decrease in the activity [150].

4.2.4. The kinds of sugar sequence

C-3 of oleanolic acid and hederagenin linked with a sugar sequence O-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside showed a good effect, suggesting that the two elements are essential factors for the antitumor activity [100]. Meanwhile, in some disaccharide derivatives, it was used as a nontoxic carrier moiety to enhance the activity of anti-cancer drugs [151].

5. Conclusion and perspective

The identification and development of saponins have greatly contributed to medical treatment of cancer and many of these compounds are now being used in clinical practice. Almost all saponins induce apoptosis in tumor cells; they are

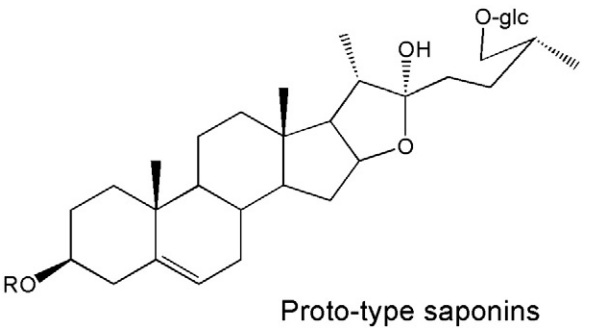

Fig. 10. Structure of proto-type saponins.

preferable drugs for the treatment of cancer, because eliminating tumor cells by apoptosis is helpful to lower side effects in patients by avoiding necrosis. A good understanding of the antitumor mechanisms of saponins is necessary for a directed improvement of saponin-based tumor therapies in the future. Meanwhile, special attention should be given to combinations of saponins and other anticarcinogenic drugs, since these offer very efficient treatment regimens against cancer. The most important is the saponin-mediated potentiation of tumor growth inhibition and the possibility to circumvent drug resistance. Furthermore, the elucidation of structure–activity relationships between different saponins in combination with conventional drugs is much more complicated than for saponins alone. Thus, it is not surprising that no mechanistic processes for these effects are known, however, detailed information on this basis is necessary for a directed improvement of saponin-based tumor therapies in the future.

It is hoped that the information collated here will provide the reader with information regarding the potential applications of saponins and stimulate further research into these compounds.

Acknowledgement

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