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Saponins as cytotoxic agents: an update (2010–2018). Part I—steroidal saponins

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Abstract Steroidal saponins are a group of glycosides widely distributed among monocotyledonous families. They exert a wide spectrum of biological effects including cytotoxic and antitumor properties which are the most studied. This review is an update of our previous paper—*Saponins as cytotoxic agents* (Podolak et al. in Phytochem Rev 9:425–474, 2010) and covers studies that were since published (2010–2018). In this paper we refer to steroidal saponins presenting results of cytotoxicity studies, mechanisms of action and structure–activity relationships.

Keywords Cytotoxicity · Steroidal glycosides · Mechanisms of action

Introduction

Steroidal saponins are an important group of glycosidic plant metabolites. They are mainly distributed among monocotyledonous families: Amarillidaceae (*Agapanthus*, *Allium*), Asparagaceae (*Agave*, *Anemarrhena*, *Asparagus*, *Convallaria*, *Hosta*, *Nolina*, *Ophiopogon*, *Ornithogalum*, *Polygonatum*, *Ruscus*, *Sansevieria*, *Tupistra*, *Yucca*), Costaceae (*Costus*), Dioscoreaceae (*Dioscorea*), Liliaceae (*Fritillaria*, *Lilium*), Melanthiaceae (*Paris*), Smilacaceae (*Smilax*). Although it is uncommon, steroidal saponins can also be found in some dicotyledonous angiosperms, such as: Fabaceae (*Trigonella*), Zygophyllaceae (*Tribulus*, *Zygophyllum*), Solanaceae (*Solanum*, *Lycopersicon*, *Capsicum*), Asteraceae (*Vernonia*), and Plantaginaceae (*Digitalis*) (Faizal and Geelen 2013; Rahman et al. 2017; Lanzotti 2005; Sobolewska et al. 2016; Tang et al. 2013; Wang et al. 2018). Moreover, these compounds have been identified in starfish and marine sponges (Ivanchina et al. 2011; Barnett et al. 1988; Regaldo et al. 2010).

Structurally, steroidal saponins are distinguished by the nature of the aglycone part. Sapogenins are polycyclic 27-C-compounds which can be divided into three distinct groups: spirostane, furostane, and open-chain (cholestane) compounds (Challinor and De Voss 2013). Some authors distinguish iso-spirostane-type saponins—possessing an equatorial oriented (hydroxy)methyl on F ring *versus* spirostane-type with an axial oriented C-27 group (Tian et al. 2017).

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Furthermore, spirosolane-type glycoalkaloids in which a nitrogen atom is incorporated in the steroid aglycone at the heterocyclic oxygen site (e.g. in solasodine) are sometimes included in the group of steroidal saponins. The sugar residue of steroidal saponins consists of one to three straight or branched sugar chains, which are composed usually of β-D-glucopyranosyl (Glc), α-L-rhamnopyranosyl (Rha), β-D-galactopyranosyl (Gal), β-L-arabinofuranosyl (Ara), β-D-xylopyranosyl (Xyl), β-D-fucopyranosyl (Fuc), β-D-mannopyranosyl (Man), or β-D-quinovopyranosyl (Qui) residues.

Since many years spirostanol sapogenins, such as e.g. disogenin or hecogenin, have been valued by pharmaceutical industry and used as substrates in the production of steroid hormones and drugs. Also, medicinal properties of saponin containing plants are well known. Some of most prominent examples include *Ruscus aculeatus*, which is used as vasoprotective agent, or *Tribulus terrestris*, found in many products dedicated to fertility stimulation in men (Masullo et al. 2016; Salgado et al. 2017). Steroidal saponins are a research target of many scientist groups. Numerous published reports have confirmed that these compounds exert a wide spectrum of pharmacological activities, including antimicrobial, anti-inflammatory, cardioprotective, cAMP phosphodiesterase inhibitory, or anti-adipogenic (Sohn et al. 2006; Huang et al. 2013; Tang et al. 2015; Ning et al. 2010; Nakamura et al. 1993; Poudel et al. 2014).

One of the activities that is especially widely explored is cytotoxic effect (Podolak et al. 2010; Böttger et al. 2012). The search for potential new chemotherapeutics within natural sources is obviously triggered by a growing need to provide effective treatment to counteract cancer. Results of studies on in vitro and in vivo cytotoxicity of steroidal saponins indicate that these compounds provide an interesting research target. In our previous review the results of experimental studies on cytotoxicity of saponins, both triterpene and steroidal, covering the period from 2005 to 2009 have been summarized (Podolak et al. 2010). Since then, a vast number of new experimental data have appeared in literature. This issue is however scarcely reviewed. Several papers that discussed biological activities of compounds found in a particular genus, like e.g. *Allium* or *Smilax*, (Sobolewska et al. 2016; Tian et al. 2017), referred also to their cytotoxic effects, but there are virtually none reviews focused entirely on this activity despite a growing number of reports with experimental data. Some more general aspects were tackled by Xu et al. (2016) who discussed anticancer saponins from Chinese plants. In a recent paper by Zhao et al. (2018), advances in antitumor potential of steroidal saponins have been focused on the mechanisms of action, and included examples of sapogenins and saponins, as well as some other compounds such as a cardiac glycoside—bufalin or cucurbitacins.

Taking into account a large number of experimental data referring to cytotoxicity of saponins, that have been published since our previous review, we decided to divide this update into two parts, each dedicated to the one of the distinct structural groups, that is triterpene and steroidal compounds.

Thus, in the current review, we present an update on the cytotoxic activity of steroidal saponins and sapogenins covering recent studies from the period of 2010 to 2018. Discussion of structure–activity data and mechanisms of action is also provided, together with a selection of most promising compounds with a potential for future development as anticancer chemotherapeutics.

The literature search was conducted in the following electronic databases: SCOPUS, EMBASE and MEDLINE/PubMed. The keywords used were: steroidal saponins, steroidal sapogenins, cancer, cytotoxicity.

Since 2010 year in vitro cytotoxicity studies have been performed on different human and animal cell cancer and normal lines, including:

- *Human cancer cell lines* Breast: BT-549, MCF-7, MDA-MB-231, MDA-MB-435, MDA-MB-468, SK-BR-3; bone: 143-B, HOS; cervix: HeLa, Caski, KB, SiHa; colon: COLO, DLD-1, HT-29, HCT 116, HCT-15, CaCo-2, SW480, SW620, W480, LOVO; esophagus: KYSE 510; gingival: Ca9-22; glioblastoma: SF-268, SF-295, U251, U87MG; larynx: Hep2; leukemia: CCRF-CEM, HL-60, Jurkat, K562; liver: HLE, Hep3B, HepG2, HuH-7, C3A, BEL-7402, BEL-7403, BEL-7404, MHCC97-L, SMMC-7721, SMMC-7221, SNU-387, WRL; lung: 95D, A549, LAC, NCI-H1299, NCI-H446, NCI-H460, SK-MES-1; melanoma: A375, A375.S2, MM96L, SK-MEL, SK-MEL-2, WM-115; neuroblastoma: IMR-32, LA-N-2, NB-69; ovary: HO-8910PM, OVCAR-8, SK-OV-3;

pancreas: BxPC-3, PANC-1; pharynx: 5-8F, CNE; prostate: DU145, PC-3; sarcoma: MG-63, Rh1; stomach: BGC-823, SGC-7901, SGC-7901/DDP [cisplatin (DDP)-resistant], HIF1α-knockdown BGC-823 (hypoxia-mimic sensitive), MGC-803; urinary bladder: ECV-304;

- *Animal cancer cell lines* Breast: EMT6; glioblastoma: C6; leukemia: Baf3-WT; lung: LL2; colon: C26; melanoma: B16; sarcoma: WEHI-164, J-774;
- *Human normal cell lines* Fibroblasts: HFF, NFF, Hs68; keratinocytes: HaCaT; kidney embryonic: HEK293; lung epithelial: MRS-5; vein endothelial: EA.hy926, HUVEC;
- *Animal normal cell lines* Cardiomyoblasts: H9c2; epidermal: JB6 $P^{+}Cl$-41; fibroblasts: 3T3; kidney epithelial: LLC-PK1; kidney fibroblasts: VERO.

The results of these studies have been summarized in Table 1.

Based on data published in years 2010–2018 it may be concluded that out of 284 substances that are included in the current review, a vast majority, that is 96.8%, were pure single compounds, both saponins and sapogenins, either structurally novel or known previously. A graph representing a number of tested substances and a number of reports published in the time scope covered by this review (2010–2018) is shown in Fig. 1.

Cytotoxicity studies were performed on animal and human cell line models, with significant predominance of the latter, which accounted to 92.7% of all assays. The effects of steroidal saponins/sapogenins against human colon, breast and liver cancers have been most widely studied, accounting to 17.9%, 16.5% and 16% of all assays on human cell lines, respectively. A graph showing the share of experiments on specific types of tumors and normal cell lines in the total number of tests performed on human cell lines is shown in Fig. 2.

The largest number of substances was analysed against following cell lines: HepG2—human hepatocellular carcinoma, MCF-7—human breast adenocarcinoma, and A549—human lung adenocarcinoma cells, which constituted 27.8%, 27.4% and 23.5% of the pool of substances under study, respectively. Tests in which normal cell lines were included in the study accounted for only 4.4% of all assays conducted on human cell lines.

The most preferred method used was the MTT assay. In most cases (80.4% of all assays) IC_{50} values for analysed saponins were compared with a positive control. Well-known anticancer drugs such as doxorubicin, cisplatin and paclitaxel were most frequently used as reference substances. Other compounds with anticancer activity were chosen definitely less often and these include: actinomycin D, adriamycin, beta-L-(−)-dioxalane-cytidine (−)-OddC, camptothecin, elipticin, etoposide, 5-FU, mitamycin C, mitoxantrone, nimustine (ACNU), podophyllotoxin, staurosporine, tamoxifen, and troxacitabine. In one study resveratrol, which is not an approved anticancer drug, served as the control (Shen et al. 2012).

In the majority of cases steroidal saponins were less active than the control substances. However, there were some noticeable examples of compounds which displayed cytotoxic effect higher than the reference drug. Three saponins isolated from *Dracaena cambodiana* dragon's blood that are glycosides of diosgenin, pennogenin and spirost-5,25(27)-dien-1β,3β-diol, exerted stronger cytotoxic activity (IC_{50}: 1.27 μM, 5.09 μM, 4.77 μM, respectively) against K-562 cells than paclitaxel (IC_{50}: 5.98 μM), while a pennogenin glycoside showed higher cytotoxic effect on BEL-7402 than paclitaxel (IC_{50}: 1.13 μM and 3.75 μM respectively) (Shen et al. 2014). Results obtained by Teponno et al. showed that a well known steroidal glycoside–dioscin–diosgenin 3-*O*-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc (for the purpose of the study isolated from *Dracaena viridiflora*) had cytotoxic activity against Jurkat, Caco-2, SK-OV-3, and A549 cells (IC_{50}: 1.70 ± 0.38 μg ml^{-1}, 2.58 ± 0.21 μg ml^{-1}, 1.90 ± 0.86 μg ml^{-1}, and 0.42 ± 0.15 μg ml^{-1}, respectively) comparable to doxorubicin used as positive control (IC_{50}: 0.61 ± 0.04 μg ml^{-1}, 2.32 ± 1.04 μg ml^{-1}, 0.84 ± 0.08 μg ml^{-1}, and 1.15 ± 0.84 μg ml^{-1}, respectively) (Teponno et al. 2017). Another diosgenin derivative named SAP-1016 (diosgenin 3-*O*-β-D-Xyl-(1 → 3)-β-D-Glc-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc) which was found in the fruits and roots of *Balanites aegyptiaca* showed potent antiproliferative activity against MCF-7 and HT-29 cancer cells (IC_{50}: 2.4 ± 0.35 and 3.3 ± 0.19 μM, respectively) higher than dioscin (IC_{50}: 3.1 ± 0.39 μM and 4.9 ± 0.32 μM, respectively) and cisplatin (IC_{50}: 30.3 ± 0.33 μM and 40.2 ± 0.44 μM, respectively) (Beit-Yannai et al. 2011).

Table 1 Cytotoxic steroidal saponins/sapogenins (2010–2018)

Source	Compound	Cell line	Concentration	Assay	References
Agave sisalana leaves			IC_{50} (μM)	Methylene blue dye assay	Chen et al. (2011b)
	Hecogenin 3-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal	NCI-H460	5.3 ± 1.8		
		MCF-7	11.9 ± 2.6		
		SF-268	4.0 ± 2.2		
	Hecogenin 3-*O*-α-L-Rha-(1 → 3)-β-D-Xyl-(1 → 2)-[β-D-Xyl-(1 → 3)-β-D-Glc-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal	NCI-H460	6.5 ± 1.1		
		MCF-7	9.5 ± 4.8		
		SF-268	8.2 ± 1.2		
	Polianthoside E	NCI-H460	> 20		
		MCF-7	> 20		
		SF-268	7.5 ± 1.4		
	Neotigogenin 3-*O*-α-L-Rha-(1 → 4)-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)-β-D-Glc-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal	NCI-H460	3.8 ± 2.7		
		MCF-7	1.2 ± 0.1		
		SF-268	1.5 ± 0.8		
	Actinomycin D (control)	NCI-H460	2.6 ± 1.6		
		MCF-7	31.1 ± 2.9		
		SF-268	7.5 ± 5.2		
Allium flavum whole plant			IC_{50} (μM)	XTT assay	Rezgui et al. (2014)
	Yuccagenin 3-*O*-β-D-Xyl-(1 → 3)-[β-D-Gal-(1 → 2)]-*O*-β-D-Gal-(1 → 4)-*O*-β-D-Gal	SW480	14.3		
	Yuccagenin 3-*O*-β-D-Xyl-(1 → 3)-[β-D-Glc-(1 → 2)]-*O*-β-D-Gal-(1 → 4)-*O*-β-D-Gal	SW480	14		
	Diosgenin 3-*O*-α-L-Rha-(1 → 4)-[β-D-Glc-(1 → 2)]-*O*-β-D-Glc	SW480	18.1		
	Doxorubicin (control)	SW480	1.47		
Allium nigrum bulbs			IC_{50} (μM)	MTT assay	Jabrane et al. (2011)
	Nigrosides A1/A2	HCT 116	47.8		
		HT-29	70.8		
	Aginoside/turoside A	HCT 116	1.59		
		HT-29	1.09		
	25(R,S)-5α-spirostan-2α,3β,6β-trio1 3-*O*-β-D-Glc-(1 → 2)-*O*-[4-*O*-(3S)-3-hydroxy-3-methylglutaryl-β-D-Xyl-(1 → 3)]-*O*-β-D-Glc-(1 → 4)-β-D-Gal	HCT 116	3.45		
		HT-29	2.82		
	Paclitaxel (control)	HCT 116	0.00321		
		HT-29	0.0014		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Allium schoenoprasum whole plant			IC_{50} (μM)	MTT assay	Timité et al. (2013)
	(25*R*)-5α-spirostane-3β,11α-diol 3-*O*-β-D-Glc-(1 → 3)-[β-D-Glc-(1 → 4)]-*O*-β-D-Gal	HCT 116	8.45		
		HT-29	8.64		
	Laxogenin 3-*O*-α-L-Rha-(1 → 2)-*O*-β-D-Glc	HCT 116	> 100		
		HT-29	> 100		
	Deltonin	HCT 116	0.4		
		HT-29	0.75		
	Deltoside	HCT 116	1.58		
		HT-29	1.56		
	Paclitaxel (control)	HCT 116	0.00275		
		HT-29	0.00206		
Allium vavilovii bulbs			IC_{50} (μg ml^{-1})	MTT assay	Zolfaghari et al. (2013)
	Vavilosides A1/A2	J-774	5.1		
		WEHI-164	4.7		
	Vavilosides B1/B2	J-774	3.5		
		WEHI-164	3.1		
	Ascalonicosides A1/A2	J-774	4		
		WEHI-164	3.7		
Anemarrhena asphodeloides rhizomes			IC_{50} (μM)	SRB assay	Kang et al. (2011)
	Timosaponin AIII	HCT-15	6.1		
		HCT 116	5.5		
		HT-29	10.3		
		SW480	13.1		
		SW620	11.1		
		normal lung epithelial (MRS-5) cells	> 50		
		fibroblast (Hs68) cells	> 50		
Anemarrhena asphodeloides rhizomes			IC_{50} (μM)	SRB assay	Guo et al. (2015)
	Timosaponin BI	HT-29	14.3		
		HeLa	12.29		
		MDA-MB-468	4.5		
	Timosaponin BII	BEL-7402	2.01		
		HT-29	1.65		
		MDA-MB-468	5.5		
	Timosaponin AIII	BEL-7402	1.65		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HT-29	2.2		
		HeLa	9.63		
		MDA-MB-468	1.6		
	Anemarsaponin F	HT-29	4.04		
	Schidigerasaponin F2	HT-29	9.42		
	Doxorubicin (control)	BEL-7402	0.3		
		HT-29	0.46		
		HeLa	6.91		
		MDA-MB-468	0.28		
Anemarrhena asphodeloides rhizomes			IC_{50} (μM)	MTT assay	Yang et al. (2017)
	Anemarsaponin R	HepG2	43.90 ± 3.36		
	Timosaponin E1	SGC7901	57.90 ± 2.88		
	Doxorubicin (control)	HepG2	8.20 ± 1.25		
		SGC7901	6.25 ± 2.18		
Anemarrhena asphodeloides rhizomes			IC_{50} (μM)	MTT assay	Zhang et al. (2017)
	Schidigerasaponin F2	MCF-7	98 ± 8.98		
		SW480	97.02 ± 14.99		
		HepG2	> 100		
		SGC7901	> 100		
	Anemarsaponin F	MCF-7	2.76 ± 0.59		
		SW480	5.56 ± 1.50		
		HepG2	11.73 ± 1.24		
		SGC7901	8.18 ± 0.26		
	Timosaponin AI	MCF-7	6.83 ± 1.99		
		SW480	4.17 ± 0.72		
		HepG2	7.83 ± 1.72		
		SGC7901	4.38 ± 0.50		
	Timosaponin AIII (control)	MCF-7	3.34 ± 1.10		
		SW480	2.94 ± 1.05		
		HepG2	4.96 ± 0.93		
		SGC7901	12.15 ± 1.36		
Anemarrhena asphodeloides rhizomes			IC_{50} (μM)	MTT assay	Yang et al. (2018)
	Aneglycoside A	HepG2	38.4 ± 2.4		
		HeLa	29.7 ± 01.9		
		SGC7901	> 100		
	Aneglycoside B	HepG2	41.8 ± 3.5		
		HeLa	34.2 ± 3.6		
		SGC7901	> 100		
	Timosaponin U	HepG2	61.8 ± 4.1		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HeLa	39.7 ± 3.7		
		SGC7901	44.5 ± 2.0		
	Doxorubicin (control)	HepG2	8.4 ± 2.2		
		HeLa	9.0 ± 1.4		
		SGC7901	6.7 ± 1.8		
Archaster typicus starfish			IC_{50} (μM)	MTS assay	Kicha et al. (2010)
	Archasteroside A	HeLa	24		
		JB6 P+ Cl41	37		
	Archasteroside B	HeLa	14		
		JB6 P+ Cl41	18		
	Regularoside A	HeLa	110		
		JB6P+Cl41	> 50		
Asparagus filicinus roots			IC_{50} (μM)	MTT assay	Wu et al. (2010)
	Filiasparoside A	MDA-MB-231	19.8 ± 1.3		
	Filiasparoside B	MDA-MB-231	> 50		
	Filiasparoside C	MDA-MB-231	3.4 ± 0.2		
	Filiasparoside E	MDA-MB-231	> 50		
	Filiasparoside F	MDA-MB-231	> 50		
	Filiasparoside G	MDA-MB-231	> 50		
	Asparagusin A	MDA-MB-231	> 50		
	Aspafilioside A	MDA-MB-231	6.6 ± 0.3		
	Aspafilioside B	MDA-MB-231	5.3 ± 0.4		
	Staurosporine (control)	MDA-MB-231	0.0145 ± 0.0004		
Aspidistra elatior rhizomes			IC_{50} (μM)	MTT assay	Zuo et al. (2018)
	(25R)-26-*O*-β-D-Glc-furost-5,20-dien-3β,26-diol-3-*O*-β-D-Glc (1 → 2)-[β-D-Glc-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal	A549	3.8		
		Caski	7.2		
		HepG2	8.2		
		MCF-7	10.7		
	Aspidsaponin A	A549	5.1		
		Caski	8.6		
		HepG2	11.1		
		MCF-7	13.8		
	Adriamycin (control)	A549	1.4		
		Caski	1.5		
		HepG2	0.7		
		MCF-7	1.7		
Avena sativa bran			IC_{50} (μM)	MTT assay	Yang et al. (2016b)
	Avenacoside B	HCT 116	175.3		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Balanites aegyptiaca fruits and roots			IC_{50} (μM)	MTT assay	Beit-Yannai et al. (2011)
	SAP-1016	MCF-7	2.4 ± 0.35		
		HT-29	3.3 ± 0.19		
		HFF	2.1 ± 0.16		
	SAP-884	MCF-7	4.3 ± 0.18		
		HT-29	7.6 ± 0.17		
		HFF	5.2 ± 0.32		
	KE-1046	MCF-7	5.3 ± 0.26		
		HT-29	10.4 ± 0.11		
		HFF	10.3 ± 0.18		
	KE-1064	MCF-7	5.1 ± 0.28		
		HT-29	7.8 ± 0.32		
		HFF	7.4 ± 0.20		
	Diosgenin	MCF-7	28.1 ± 052		
		HT-29	30.6 ± 0.33		
		HFF	20.7 ± 0.45		
	Dioscin (control)	MCF-7	3.1 ± 0.39		
		HT-29	4.9 ± 0.32		
		HFF	2.8 ± 0.19		
	Cisplatin (control)	MCF-7	30.3 ± 0.33		
		HT-29	40.2 ± 0.44		
		HFF	20.6 ± 0.30		
Bletilla striata roots			IC_{50} (μM)	SRB assay	Park et al. (2014)
	Bletilnoside A	A549	4.56 ± 0.29		
		SK-OV-3	4.00 ± 0.06		
		SK-MEL-2	3.98 ± 0.16		
		HCT-15	5.08 ± 0.51		
	Bletilnoside B	A549	8.79 ± 1.01		
		SK-OV-3	8.08 ± 0.83		
		SK-MEL-2	5.29 ± 0.34		
		HCT-15	9.29 ± 1.23		
	3-*O*-β-D-Glc-3-Epiruscogenin	A549	12.10 ± 0.40		
		SK-OV-3	11.80 ± 0.28		
		SK-MEL-2	11.55 ± 0.27		
		HCT-15	11.00 ± 0.23		
	Doxorubicin (control)	A549	0.0035 ± 0.0025		
		SK-OV-3	0.0037 ± 0.0022		
		SK-MEL-2	0.0009 ± 0.0001		
		HCT-15	0.1574 ± 0.0569		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Bletilla striata roots			IC_{50} (μM)	MTT assay	Wang and Meng (2015)
	(1α,3α)-1-*O*-[(β-D-Xyl-(1 → 2)-α-L-Rha)]-3-*O*-D-Glc-5α-spirostan	A549	12.3		
		BGC-823	15.9		
		HepG2	14.3		
		HL-60	17		
		MCF-7	15.1		
		SMMC-7721	14.7		
		W480	17.1		
	(1α,3α)-1-*O*-[(β-D-Xyl-(1 → 2)-α-L-Rha)oxy]-3-*O*-D-Glc-25(27)-ene-5α-spirostan	A549	12.7		
		BGC-823	12.2		
		HepG2	12.8		
		HL-60	13.8		
		MCF-7	11.3		
		SMMC-7721	11.7		
		W480	18.3		
	(1α,3α)-1-*O*-[(β-D-Xyl-(1 → 2)-α-L-Rha)oxy]-epiruscogenin	A549	24.3		
		BGC-823	29.4		
		HepG2	30.1		
		HL-60	31.1		
		MCF-7	30.4		
		SMMC-7721	29.7		
		W480	29.1		
	(1α,3α)-1-*O*-[(β-D-Xyl-(1 → 2)-α-L-Rha)oxy]-epineoruscogenin	A549	29.7		
		BGC-823	29.6		
		HepG2	29.4		
		HL-60	29.4		
		MCF-7	27.1		
		SMMC-7721	30.1		
		W480	24.9		
	Bletilnoside A	A549	76.3		
		BGC-823	68.7		
		HepG2	66.9		
		HL-60	72.3		
		MCF-7	76.2		
		SMMC-7721	70.8		
		W480	69.4		
	3-*O*-β-D-Glc-3-epi-neoruscogenin	A549	31.9		
		BGC-823	31.2		
		HepG2	30.7		
		HL-60	32.2		
		MCF-7	28.1		
		SMMC-7721	29.9		
		W480	27.6		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Cestrum laevigatum leaves			IC_{50} (μM)	MTT assay	Ribeiro et al. (2016a)
	(25R)-Spirost-5-ene-3β,26β-diol 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[(1 → 2)-α-L-Rha]-β-D-Glc	HL-60	6.5 (5.2–8.1)		
		OVCAR-8	10.3 (5.4–19.9)		
		HCT 116	10.1 (4.5–23.0)		
		SF-295	7.7 (4.2–14.1)		
	(25R)-Spirost-6-ene-3β,5β-diol 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[(1 → 2)-α-L-Rha]-β-D-Glc	HL-60	7.3 (6.7–7.9)		
		OVCAR-8	15.3 (11.9–19.6)		
		HCT 116	11.4 (9.6–13.5)		
		SF-295	12.9 (10.8–15.4)		
	Diosgenin 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-β-D-Glc	HL-60	> 25		
		OVCAR-8	> 25		
		HCT 116	> 25		
		SF-295	> 25		
	Chonglouoside SL-5	HL-60	8.2 (7.4–9.1)		
		OVCAR-8	10.8 (9.4–12.4)		
		HCT 116	8.6 (7.6–9.9)		
		SF-295	6.9 (5.6–8.4)		
	Paris saponin Pb	HL-60	0.6 (0.4–0.7)		
		OVCAR-8	2.4 (1.9–2.9)		
		HCT 116	1.01 (0.74–1.37)		
		SF-295	1.3 (1.0–1.6)		
	Doxorubicin (control)	HL-60	0.02 (0.01–0.02)		
		OVCAR-8	0.3 (0.2–0.3)		
		HCT 116	0.1 (0.1–0.2)		
		SF-295	0.2 (0.2–0.3)		
Cestrum laevigatum stems and roots			IC_{50} (μg ml^{-1})	MTT assay	Ribeiro et al. (2016b)
	(25R,S)-5α-spirostan-2α,3β-diol 3-*O*-β-D-Glc-(1 → 4)-β-D-Gal-(1 → 4)-β-D-Gal	HL-60	2.22 (1.55–3.17)		
		OVCAR-8	10.80 (9.51–2.27)		
		HCT 116	7.27 (5.93–8.90)		
		SF-295	6.88 (4.49–10.56)		
	(25R,S)-5α-spirostan-2α,3β-diol 3-*O*-β-D-Glc-(1 → 2)-α-L-Rha-(1 → 4)-β-D-Gal	HL-60	7.28 (6.68–7.95)		
		OVCAR-8	15.30 (11.91–19.64)		
		HCT 116	11.41 (9.63–13.51)		
		SF-295	12.90 (10.78–15.43)		
	(25R,S)-5α-spirostan-2α,3β-diol 3-*O*-β-D-Gal	HL-60	16.68 (11.85–23.49)		
		OVCAR-8	11.30 (9.21–13.87)		
		HCT 116	16.50 (14.3–19.1)		
		SF-295	> 25		
	Doxorubicin (control)	HL-60	0.02 (0.01–0.02)		
		OVCAR-8	0.26 (0.17–0.3)		
		HCT 116	0.12 (0.09–0.17)		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		SF-295	0.24 (0.02–0.27)		
Cestrum parqui leaves			IC_{50} (μM)	CCK-8 assay	Mosad et al. (2017)
	Parquispiroside	HeLa	7.7 ± 1.5		
		HepG2	7.2 ± 1.4		
		MCF-7	14.1 ± 4.5		
		U87	3.3 ± 0.63		
	Cisplatin (control)	HeLa	39.2 ± 8.2		
		HepG2	14.6 ± 5.9		
		MCF-7	7.3 ± 1.3		
		U87	23.0 ± 5.6		
Chlorophytum deistelianum aerial parts			IC_{50} (μM)	XTT assay	Tabopda et al. (2016)
	Chlorodeistelianoside A	SW480	> 22.12		
		H9c2	> 22.12		
	Chlorodeistelianoside C	SW480	> 24.12		
		H9c2	> 24.12		
	(25R)-3β-[(β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal)oxy]-5α-spirostan-12-one	SW480	9.13 ± 0.41		
		H9c2	8.25 ± 1.16		
	Solanigroside G	SW480	10.07 ± 0.61		
		H9c2	9.57 ± 0.21		
	F-gitonin	SW480	9.45 ± 0.58		
		H9c2	9.82 ± 0.30		
	Polianthoside D	SW480	> 24.43		
		H9c2	> 24.43		
	(25R)-26-[β-D-Glc)oxy]-22α-methoxy-5α-furostan-3β-yl β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal	SW480	> 24.43		
		H9c2	> 24.43		
Chlorophytum laxum roots			IC_{50} (μM l^{-1})	CKK-8 assay	Chu et al. (2018)
	25-R-Spirosta-3,5-dien-12β-ol	5-8F	24.8		
	Diosgenin	5-8F	41.9		
Chlorophytum orchidastrum roots			IC_{50} (μM)	MTT assay	Acharya et al. (2010)
	Orchidastroside A	HCT 116	1.6		
		HT-29	1.5		
	Orchidastroside C	HCT 116	1.35		
		HT-29	3.6		
	Orchidastroside D	HCT 116	2.19		
		HT-29	9.15		
	Orchidastroside F	HCT 116	2.12		
		HT-29	8.87		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	Paclitaxel (control)	HCT 116	2.4 (nM)		
		HT-29	2.1		
Cordyline fruticosa leaves			IC_{50} (μM)	MTT assay	Fouedjou et al. (2014)
	Fruticoside H	MDA-MB231	69.68		
		A375	37.83		
		HCT 116	39.8		
	Fruticoside I	MDA-MB231	50.45		
		A375	46.59		
		HCT 116	59.97		
	Fruticoside J	MDA-MB231	> 200		
		A375	> 200		
		HCT 116	> 200		
	Cisplatin (control)	MDA-MB231	7.28		
		A375	0.62		
		HCT 116	4.97		
Costus speciosus tuber			IC_{50} (μg ml^{-1})	MTT assay	Selim and Al Jaouni (2015)
	Diosgenin	HepG2	32.62		
		HL-60	22.98		
		MCF-7	11.03		
	Paclitaxel (control)	HepG2	0.48		
		HL-60	0.78		
		MCF-7	0.61		
Cynanchum paniculatum roots			IC_{50} (μM)	SRB assay	Kim et al. (2013)
	Cynanside A	A549	> 30		
		SK-OV-3	> 30		
		SK-MEL-2	26.55		
		HCT-15	> 30		
	Cynanside B	A549	> 30		
		SK-OV-3	> 30		
		SK-MEL-2	17.36		
		HCT-15	> 30		
	Doxorubicin (control)	A549	0.029		
		SK-OV-3	0.036		
		SK-MEL-2	0.001		
		HCT-15	2.041		
Datura metel whole plant			Cell death (%)	SRB assay	Mai et al. (2017)

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
	3-*O*-β-D-Xyl-(1 → 2)-α-L-Rha-(1 → 4)[α-L-Rha-(1 → 2)]-β-D-Glc (25R,26R)-spirost-5-en-3β-ol-26-acetamide	HepG2	4 (μg ml^{-1})	9.4 (%)		
		MCF-7	20	16.0		
		SK-MEL-2	100	34.9		
	Dioscoroside D	HepG2	4	12.7		
		MCF-7	20	14.1		
		SK-MEL-2	100	28.3		
	Meteloside D	HepG2	4	10.4		
		MCF-7	20	15.5		
		SK-MEL-2	100	30.0		
	Meteloside E	HepG2	4	14.1		
		MCF-7	20	16.1		
		SK-MEL-2	100	25.8		
	Camptothecin (control)	HepG2	4	6.9		
		MCF-7	20	15.5		
		SK-MEL-2	100	35.5		
			4	16.4		
			20	19.9		
			100	31.9		
			4	18.5		
			20	28.6		
			100	38.8		
			4	11.4		
			20	27.1		
			100	44.4		
			4	5.7		
			20	22.5		
			100	44.2		
			4	13.3		
			20	28.6		
			100	41.2		
			4	11.1		
			20	28.4		
			100	48.3		
			4	14.3		
			20	18.7		
			100	41.6		
			4	72.5		
			20	97.0		
			4	76.8		
			20	96.9		
			4	68.1		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
			20 84.9		
Digitalis trojana aerial parts			IC_{50} (μM)	MTT assay	Kirmizibezkmez et al. (2014)
	22-*O*-methylparvispinoside A	HT29	50.0 ± 0.90		
		MCF-7	50.0 ± 0.15		
	Parvispinoside	HT29	50.0 ± 0.20		
		MCF-7	36.5 ± 0.08		
		PC3	> 50		
	22-*O*-methylparvispinoside B	HT29	10.0 ± 0.25		
		MCF-7	46.0 ± 0.15		
		PC3	> 50		
	Staurosporine (control)	HT29	1.2 ± 0.05		
		MCF-7	1.0 ± 0.01		
		PC3	1.5 ± 0.05		
Dioscorea bulbifera var. sativa flowers			IC_{50} (μg ml^{-1})	MTT assay	Tapondjou et al. (2013)
	Spiroconazol A	ECV-304	5.8		
	Pennogenin 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	ECV-304	8.5		
	26-*O*-β-D-Glc-(25R)-5-en-furost-3ß,17α,22α, 26-tetraol-3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	ECV-304	14.3		
Dioscorea preussii rhizomes			IC_{50} (μM)	MTT assay	Tabopda et al. (2014)
	Diospreussinoside B	HCT 116	48.7		
		HT-29	31		
	(25R)-17α-hydroxyspirost-5-en-3β-yl *O*-α-L-Rha-(1 → 4)-*O*-α-L-Rha-(1 → 4)-β-D-Glc	HCT 116	37.41		
		HT-29	42.43		
	(25R)-17α-hydroxyspirost-5-en-3β-yl *O*-α-L-Rha-(1 → 2)-*O*-[*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)]-β-D-Glc	HCT 116	2.17		
		HT-29	1.64		
	Paclitaxel (control)	HCT 116	$2.65\ 10^{-3}$		
		HT-29	$2.29\ 10^{-3}$		
Dioscorea zingiberensis rhizomes			IC_{50} (μM)	MTT assay	Tong et al. (2012)
	Diosgenin	SK-OV-3	> 20		
		B16	> 20		
		LL2	> 20		
		C26	> 20		
		A549	> 20		
		HEK293	> 20		
	Trillin	SK-OV-3	> 20		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		B16	> 20		
		LL2	> 20		
		C26	18.74 ± 1.60		
		A549	> 20		
		HEK293	> 20		
	Diosgenin diglucoside	SK-OV-3	16.71 ± 0.84		
		B16	16.53 ± 0.28		
		LL2	18.02 ± 0.66		
		C26	14.51 ± 0.90		
		A549	18.86 ± 1.24		
		HEK293	> 20		
	Deltonin	SK-OV-3	3.15 ± 0.29		
		B16	4.88 ± 0.43		
		LL2	4.42 ± 0.77		
		C26	1.41 ± 0.51		
		A549	5.65 ± 0.82		
		HEK293	9.73 ± 0.85		
	Zingiberensis saponin	SK-OV-3	1.51 ± 0.53		
		B16	2.64 ± 0.49		
		LL2	2.37 ± 0.54		
		C26	0.81 ± 0.35		
		A549	2.13 ± 0.48		
		HEK293	4.15 ± 0.22		
	Protodeltonin	SK-OV-3	15.86 ± 0.55		
		B16	14.23 ± 1.60		
		LL2	15.58 ± 0.75		
		C26	12.54 ± 0.81		
		A549	14.82 ± 1.28		
		HEK293	> 20		
	Parvifloside	SK-OV-3	16.59 ± 0.72		
		B16	16.12 ± 0.90		
		LL2	14.82 ± 1.60		
		C26	13.83 ± 2.52		
		A549	14.36 ± 1.14		
		HEK293	> 20		
	Dioscin (control)	SK-OV-3	4.14 ± 0.80		
		B16	4.57 ± 0.61		
		LL2	5.03 ± 0.76		
		C26	2.81 ± 1.21		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		A549	6.82 ± 1.55		
		HEK293	6.62 ± 0.28		
	Doxorubicin (control)	SK-OV-3	0.73 ± 0.35		
		B16	0.77 ± 0.28		
		LL2	0.67 ± 0.12		
		C26	0.50 ± 0.18		
		A549	1.05 ± 0.25		
		HEK293	1.32 ± 0.52		
Dracaena cambodiana resin			IC_{50} (μM)	MTT assay	Shen et al. (2014)
	Diosgenin 3-*O*-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 3)]-β-D-Glc	K562	1.27		
		BEL-7402	4.72		
		SGC-7901	2.88		
	Pennogenin 3-*O*-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 3)]-β-D-Glc	K562	5.09		
		BEL-7402	1.13		
		SGC-7901	3.39		
	Spirost-5,25(27)-dien-1β,3β-diol 1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara	K562	4.77		
		BEL-7402	6.44		
		SGC-7901	5.61		
	Paclitaxel (control)	K562	5.98		
		BEL-7402	3.75		
		SGC-7901	1.88		
Dracaena deisteliana stem *Dracaena arborea* bark	Neoruscogenin 1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara	HT-29	IC_{50} (μM)	MTT assay	Kougan et al. (2010)
		HCT 116	values in the range 7.60–70.73		
	Manioside A	HT-29	1.67		
		HCT 116	2.04		
	Spiroconazol A	HT-29	3.21		
		HCT 116	1.4		
	Paclitaxel (control)	HT-29			
		HCT 116			
Dracaena marginata roots			IC_{50} (μg ml^{-1})	Acid phosphatase assay	Ghaly et al. (2014)
	Saponin fraction	HepG2	13.4		
		MCF7	35		
	Methylprotogracillin	HepG2	29.8		
		MCF7	> 50		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	Methylprotodioscin	HepG2	29.8		
		MCF7	> 50		
	Adriamycin (control)	HepG2	6.9		
		MCF7	2.5		
Dracaena viridiflora leaves			IC_{50} (μg ml^{-1})	MTT assay	Teponno et al. (2017)
	Trillin	Jurkat	22.36 ± 1.40		
		Caco-2	36.49 ± 2.14		
		SK-OV-3	64.78 ± 1.91		
		A549	14.14 ± 0.10		
	Prosapogenin A of dioscin	Jurkat	2.06 ± 0.12		
		Caco-2	2.51 ± 0.32		
		SK-OV-3	5.69 ± 0.88		
		A549	2.11 ± 0.54		
	Prosapogenin B of dioscin	Jurkat	21.74 ± 1.80		
		Caco-2	13.72 ± 0.84		
		SK-OV-3	62.33 ± 1.42		
		A549	42.44 ± 1.60		
	Dioscin	Jurkat	1.70 ± 0.38		
		Caco-2	2.58 ± 0.21		
		SK-OV-3	1.90 ± 0.86		
		A549	0.42 ± 0.15		
	Methylprotodioscin	Jurkat	4.82 ± 0.33		
		Caco-2	16.13 ± 0.34		
		SK-OV-3	7.07 ± 0.39		
		A549	5.26 ± 0.29		
	Doxorubicin (control)	Jurkat	0.61 ± 0.04		
		Caco-2	2.32 ± 1.04		
		SK-OV-3	0.84 ± 0.08		
		A549	1.15 ± 0.84		
Fritillaria pallidiflora bulbs			IC_{50} (μM)	MTT assay	Shen et al. (2012)
	Pallidifloside D	C6	53.2 ± 3.2		
		HeLa	75.8 ± 4.5		
	Polygonatoside B3	C6	24.1 ± 1.7		
		HeLa	28.1 ± 3.9		
	Polyphyllin V	C6	10.3 ± 2.2		
		HeLa	9.4 ± 1.1		
	Deltonin	C6	5.1 ± 0.2		
		HeLa	5.2 ± 0.9		
	Resveratrol	C6	24.8 ± 1.8		
	(control)	HeLa	28.3 ± 1.4		
Lilium longiflorum bulbs			IC_{50} (μM)	MTT assay	Esposito et al. (2013)
	(22R,25R)-spirosol-5-en-3β-yl 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc-(1 → 4)-β-D-Glc	3T3	8.2		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	(22R,25R)-spirosol-5-en-3β-yl 3-*O*-α-L-Rha-(1 → 2)-[6-*O*-acetyl-β-D-Glc-(1 → 4)]-β-D-Glc	3T3	25.8		
	(25R)-26-*O*-(β-D-Glc)-furost-5-en-3β,22α,26-triol 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc-(1 → 4)-β-D-Glc	3T3	8.7		
	(25R)-26-*O*-(β-D-Glc)-furost-5-en-3β,22α,26-triol 3-*O*-α-L-Rha-(1 → 2)-α-L-Ara-(1 → 3)-β-D-Glc	3T3	<1.0		
	(25R)-26-*O*-(β-D-Glc)-furost-5-en-3β,22α,26-triol 3-*O*-α-L-Rha-(1 → 2)-α-L-Xyl-(1 → 3)-β-D-Glc	3T3	<1.0		
Liriope graminifolia tubers			IC_{50} (μg ml^{-1})	MTT assay	Wang et al. (2011)
	Lirigramoside A	SMMC-7721	76.4 ± 6.6		
		HeLa	26.1 ± 4.4		
	Lirigramoside B	SMMC-7721	> 100		
		HeLa	18.6 ± 3.6		
	1-*O*-β-D-Xyl-3-*O*-α-L-Rha-(25S)-ruscogenin	SMMC-7721	45.8 ± 5.4		
		HeLa	13.3 ± 3.0		
	3-*O*-α-L-Rha-1-*O*-sulfo-(25S)-ruscogenin	SMMC-7721	> 100		
		HeLa	40.6 ± 6.4		
	Cisplatin (control)	SMMC-7721	12.8 ± 4.8		
		HeLa	5.4 ± 1.8		
Liriope muscari roots			IC_{50} (μM)	MTT assay	Wu et al. (2017b)
	(25S)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc	MDA-MB-435	15.99 ± 1.03		
		95D	20.13 ± 1.18		
		HepG2	49.68 ± 1.57		
		HeLa	39.98 ± 1.20		
		MCF-7	47.30 ± 1.56		
		A549	36.35 ± 1.39		
	(25R)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc	MDA-MB-435	26.01 ± 0.85		
		95D	30.00 ± 0.51		
		HepG2	40.52 ± 0.96		
		HeLa	33.42 ± 1.39		
		MCF-7	39.12 ± 1.02		
		A549	36.01 ± 1.31		
	(25S)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Xyl	MDA-MB-435	18.07 ± 1.34		
		95D	25.67 ± 0.41		
		HepG2	37.17 ± 1.71		
		HeLa	21.58 ± 1.42		
		MCF-7	45.82 ± 1.44		
		A549	43.53 ± 1.16		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	(25R)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Xyl	MDA-MB-435	17.68 ± 2.50		
		95D	17.83 ± 0.37		
		HepG2	29.48 ± 1.64		
		HeLa	22.23 ± 1.43		
		MCF-7	42.16 ± 1.26		
		A549	43.20 ± 1.53		
	(25R)-Ruscogenin 1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc	MDA-MB-435	19.63 ± 0.76		
		95D	10.82 ± 0.18		
		HepG2	15.26 ± 1.29		
		A549	35.56 ± 1.46		
	(25S)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[α-L-Ara-(1 → 3)]-β-D-Fuc	MDA-MB-435	16.34 ± 0.60		
		95D	14.34 ± 0.33		
		HepG2	27.10 ± 0.84		
		HeLa	14.76 ± 0.52		
		MCF-7	35.21 ± 2.02		
		A549	24.69 ± 0.76		
	(25R)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[α-L-Ara-(1 → 3)]-β-D-Fuc	95D	22.15 ± 1.41		
		HeLa	42.56 ± 3.75		
	Neoruscogenin-1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Xyl	MDA-MB-435	24.52 ± 0.91		
		95D	36.12 ± 1.08		
		HeLa	24.30 ± 1.55		
	Neoruscogenin 1-*O*-α-L-Rha-l-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc	MDA-MB-435	17.54 ± 1.39		
		95D	11.09 ± 0.15		
	Neoruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Fuc	MDA-MB-435	9.74 ± 0.62		
		95D	10.64 ± 0.21		
		HepG2	15.48 ± 0.52		
		HeLa	11.02 ± 0.42		
		MCF-7	10.02 ± 0.73		
		A549	21.25 ± 1.42		
	(25R)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Fuc	MDA-MB-435	4.71 ± 0.75		
		95D	11.62 ± 2.00		
		HepG2	Not active		
		HeLa	26.36 ± 2.01		
		MCF-7	NA		
		A549	23.56 ± 2.64		
	(25S)-Ruscogenin 1-*O*-β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Fuc	MDA-MB-435	5.91 ± 0.27		
		95D	11.20 ± 0.17		
		HepG2	12.76 ± 0.74		
		HeLa	8.00 ± 0.45		
		MCF-7	17.88 ± 0.97		
		A549	8.226 ± 0.78		

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
	(25S)-Ruscogenin 1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc	MDA-MB-435	9.75 ± 0.34			
		95D	19.58 ± 0.67			
		HepG2	15.24 ± 1.53			
		HeLa	14.03 ± 0.61			
		MCF-7	16.30 ± 0.73			
		A549	13.99 ± 0.64			
	5-Fluorouracil (control)	MDA-MB-435	116.8 ± 13.93			
		95D	83.55 ± 10.66			
		HepG2	91.9 ± 16.20			
		HeLa	251.3 ± 19.93			
		MCF-7	568.3 ± 54.37			
		A549	244.8 ± 21.23			
Ophiopogon japonicus roots			IC_{50} (μM)		MTT assay	Wu et al. (2018)
	Pennogenin-3-*O*-α-L-Rha-(1 → 2)-[β-D-Api-(1 → 4)]-β-D-Glc	MDA-MB-435	1.90 ± 0.17			
		HepG2	1.69 ± 0.18			
		A549	4.39 ± 0.37			
	Pennogenin-3-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-[β-D-Glc-(1 → 4)]-β-D-Glc	MDA-MB-435	9.13 ± 1.43			
		HepG2	21.18 ± 1.87			
		A549	21.27 ± 2.53			
	(25R)-Ruscogenin-1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara	MDA-MB-435	10.32 ± 2.37			
		HepG2	NA (IC50 > 50 μM)			
		A549	29.12 ± 4.66			
	5-FU (control)	MDA-MB-435	120 ± 15.53			
		HepG2	87.3 ± 12.10			
		A549	256.8 ± 19.03			
Ophiopogon japonicus tuberous roots			IC_{50} (μM)	MTT assay	Li et al. (2013)	
	Ophiopogonin Q	HepG2	24 h	2.88		
		HepG2	72 h	1.06		
		HLE	24 h	2.61		
		BEL-7402	24 h	3.59		
		BEL-7403	24 h	6.25		
		HeLa	24 h	2.74		
	Pennogenin 3-*O*-[2-*O*-acetyl-α-L-Rha-(1 → 2)] [β-D-Xyl-(1 → 4)]-β-D-Glc	HepG2	24 h	3.54		
		HepG2	72 h	1.60		
		HLE	24 h	3.63		
		BEL-7402	24 h	3.72		
		BEL-7403	24 h	12.28		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HeLa	24 h 4.26		
	Diosgenin 3-*O*-[2-*O*-acetyl-α-L-Rha-(1 → 2)][β-D-Xyl-(1 → 4)]-β-D-Glc	HepG2	24 h 3.30		
		HepG2	72 h 1.49		
		HLE	24 h 1.49		
		BEL-7402	24 h 8.06		
		BEL-7403	24 h 5.13		
		HeLa	24 h 1.47		
	Sprengerinin C	HepG2	24 h 3.07		
		HepG2	72 h 1.83		
		HLE	24 h 3.68		
		BEL-7402	24 h 8.13		
		BEL-7403	24 h 1.97		
		HeLa	24 h 1.74		
	Pennogenin 3-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc	HepG2	24 h 3.04		
		HepG2	72 h 1.71		
		HLE	24 h 3.30		
		BEL-7402	24 h 6.08		
		BEL-7403	24 h 5.14		
		HeLa	24 h 3.34		
	Taxol (control)	HepG2	24 h 33.3		
		HepG2	72 h 0.251		
		HLE a	24 h 1.95		
		BEL-7402	24 h 5.92		
		BEL-7403	24 h 11.84		
		HeLa	24 h 3.10		
Ophiopogon japonicus tubers			IC_{50} (μM)	MTT assay	Wang et al. (2017a)
	Ophiopogonin D'	MG-63	3.09		
		SNU-387	3.63		
	Diosgenin 3-*O*-[2-*O*-acetyl-]-L-Rha-(1 → 2)]-β-D-Xyl-(1 → 3)-β-D-Glc	MG-63	1.9		
		SNU-387	0.76		
	Cisplatin (control)	MG-63	11.31		
		SNU-387	5.59		
Ophiopogon japonicus fibrous roots			IC_{50} (μg ml^{-1})	MTT assay	Duan et al. (2010)
	(25R)-Ruscogenin-3-yl α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc	HeLa	9.14		
		HEp2	11.27		
	Diosgenin-3-yl 2-*O*-acetyl-α-l-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc	HeLa	10.77		
		HEp2	10.08		
	Pennogenin-3-yl 2-*O*-acetyl-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc	HeLa	13.46		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HEp2	13.32		
Ophiopogon japonicus fibrous roots			IC_{50} (μg ml^{-1})	MTT assay	Duan et al. (2018)
	Fibrophiopogonin A	A375	201.1		
	Fibrophiopogonin B	A375	42.06		
		MCF-7	45.32		
	(25R)-26-[(*O*-β-D-Glc-(1 → 2)-β-D-Glc)]-22α-hydroxyfurost-5-ene-3-*O*-[α-L-Rha-(1 → 2)]-β-D-Glc	A375	63.43		
Panicum turgidum aerial parts			IC_{50} (μM)	Neutral red uptake assay	Zaki et al. (2017)
	Pennogenin 3β-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)-*O*-α-L-Rha-1 → 4)]-*O*-β-D-Glc	SK-MEL	0.47 ± 0.15		
		KB	1.6 ± 0.4		
		BT-549	0.59 ± 0.09		
		SK-OV-3	0.81 ± 0.11		
		VERO	1.5 ± 0.2		
		LLC-PK1	1.005 ± 0.105		
	Yamogenin 3β-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)]-*O*-β-D-Glc	SK-MEL	0.76 ± 0.04		
		KB	3.5 ± 1.5		
		BT-549	3.3 ± 1.2		
		SK-OV-3	1.24 ± 0.26		
		VERO	2.8 ± 1.7		
		LLC-PK1	3.15 ± 1.15		
	Yamogenin 3β-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)-*O*-α-L-Rha-(1 → 4)]-*O*-β-D-Glc	SK-MEL	4.2 ± 1.3		
		KB	8.25 ± 3.25		
		BT-549	4.1 ± 1.9		
		SK-OV-3	3.35 ± 1.15		
		VERO	7.0 ± 3.8		
		LLC-PK1	3.7 ± 1.6		
	Pennogenin 3β-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)]-*O*-β-D-Glc	SK-MEL	0.295 ± 0.07		
		KB	1.0 ± 0.1		
		BT-549	1.55 ± 0.15		
		SK-OV-3	0.765 ± 0.015		
		VERO	0.5 ± 0.05		
		LLC-PK1	0.65 ± 0.05		
	Doxorubicin (control)	SK-MEL	3.0 ± 0.78		
		KB	1.7 ± 0.0		
		BT-549	2.9 ± 1.4		
		SK-OV-3	3.3 ± 0.17		
		VERO	> 9		
		LLC-PK1	2.5 ± 0.9		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Paris polyphylla rhizomes			IC_{50} (μM)	XTT assay	Kang et al. (2012)
	Parisyunnanoside G	CCRF-CEM	NA		
	Parisyunnanoside H	CCRF-CEM	NA		
	Parisyunnanoside I	CCRF-CEM	NA		
	Dichotomin	CCRF-CEM	0.59 ± 0.11		
	Pseudoproto-Pb	CCRF-CEM	6.52 ± 0.29		
	Parisyunnanoside A	CCRF-CEM	6.68 ± 0.22		
	Th	CCRF-CEM	5.15 ± 0.16		
	Paris saponin I	CCRF-CEM	1.23 ± 0.08		
	Protogracillin	CCRF-CEM	1.77 ± 0.14		
	Doxorubicin (control)	CCRF-CEM	2.14 ± 0.005		
Paris polyphylla var. *yunnanensis* rhizomes (Rs), leaves and stems (LSs)			IC_{50} (μg ml^{-1})	MTT assay	Qin et al. (2018)
	Total saponins Rs	HL-60	1.77		
		A-549	1.75		
		SM MC772	5.23		
		MCF-7	6.62		
		SW480	3.49		
	Total saponins LSs	HL-60	9.54		
		A-549	9.3		
		SM MC772	12.61		
		MCF-7	8.12		
		SW480	11.25		
	Cisplatin (control)	HL-60	0.87		
		A-549	6.48		
		SM MC772	3.77		
		MCF-7	6.4		
		SW480	4.18		
Paris polyphylla var. *yunnanensis* rhizomes			IC_{50} (μM)	MTT assay	Wu et al. (2012b)
	(3β,25R)-spirost-5-en-3-ol-3-*O*-β-D-Api-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	5.06 ± 1.42		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-3-*O*-β-D-Api-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	3.57 ± 1.05		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-	CNE	9.50 ± 0.80		
	3-*O*-β-D-Glc-(1 → 5)-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	188.55 ± 7.62		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-3-*O*-β-D-Xyl-(1 → 5)-α-L-Ara-(1 α 4)-β-D-Glc	CNE	134.38 ± 2.95		
	(3β,25S)-spirost-5-ene-3,27-diol-3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	35.58 ± 2.80		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	(3β,7β,25R)-spirost-5-ene-3,7-diol-3-*O*-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	164.43 ± 15.0		
	(3β,7α,25R)-spirost-5-ene-3,7-diol-3-*O*-α-L-Ara-(1 → 4)-β-D-Glc	CNE	1.50 ± 0.14		
	(3β,25R)-spirost-5-en-3-ol-3-*O*-β-D-Glc-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	63.98 ± 4.90		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-β-D-Glc	CNE	2.51 ± 0.42		
	(3β,25R)-spirost-5-ene-3-ol-3-*O*-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	7.28 ± 1.10		
	(3β,25R)-spirost-5-ene-3-ol-3-*O*-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	95.98 ± 0.65		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-3-*O*-α-L-Ara-(1 → 4)-β-D-Glc	CNE	5.92 ± 0.83		
	(3β,17α,25R)-spirost-5-ene-3,17-diol-3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	50.46 ± 2.90		
	(3β,25R)-3-hydroxyspirost-5-ene-7-one-3-*O*-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	23.73 ± 1.53		
	Cisplatin (control)				
Paris polyphylla var. *yunnanensis* rhizomes			IC_{50} (μM)	MTT assay	Wu et al. (2017a)
	(23S,24S)-spirost-5,25(27)-diene-1β,3β,21,23α,24α-pentol-1-*O*-{α-L-Rha-(1 → 2)-[β D-Xyl-(1 → 3)]-β-D-Glc}-21-*O*-β-D-Gal-24-*O*-β-D-Gal	CNE	32.56		
	Parisyunnanoside I	CNE	33.1		
	Cisplatin (control)	CNE	9.35		
Paris polyphylla var. *yunnanensis* roots			IC_{50} (μM)	MTT assay	Wu et al. (2012a)
	(3β,25R)-spirost-5-en-3-ol 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc	CNE	9.2 ± 0.7		
	(3β,25R)-spirost-5-en-3-ol 3-*O*-β-D-Glc-(1 → 6)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	52.9 ± 3.7		
	(3β,25R)-spirost-5-en-3-ol 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	4.7 ± 1.1		
	(3β,17α,25R)-spirost-5-ene-3,17-diol 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc	CNE	11.1 ± 4.7		
	(3β,17α,25R)-spirost-5-ene-3,17-diol 3-*O*-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	CNE	2.7 ± 1.1		
	Cisplatin (control)	CNE	23.7 ± 1.5		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Paris polyphylla var. *yunnanensis* rhizomes			IC_{50} (μM)	MTT assay	Wen et al. (2015)
	Parisyunnanoside H	HEK293	0.9		
		HepG2	5.6		
	Paris saponin I	HEK293	1.8		
		HepG2	1.8		
	Trigofoenoside A	HEK293	3.4		
		HepG2	5.6		
	Dichotomin	HEK293	0.58		
		HepG2	0.9		
	Parisyunnanoside B	HEK293	2.5		
		HepG2	1.2		
	Pseudoproto-Pb	HEK293	1.8		
		HepG2	1.8		
	(−)-OddC (control)	HEK293	0.3		
		HepG2	0.17		
Paris polyphylla var. *yunnanensis* leaves			IC_{50} (μM)	MTT assay	Qin et al. (2016)
	Nuatigenin 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc	HepG2	2.9 ± 0.5		
		HEK293	5.0 ± 0.6		
	Abutiloside L	HepG2	7.0 ± 0.8		
		HEK293	12.9 ± 2.7		
	Troxacitabine (control)	HepG2	0.17 ± 0.02		
		HEK293	0.30 ± 0.03		
Paris quadrifolia rhizomes			IC_{50} (μg ml^{-1})	MTT assay	Stefanowicz-Hajduk et al. (2011)
	Saponin-rich fractions:	HL-60	13 ± 1.3		
	Solid residue	HeLa	10 ± 0.5		
		MDA-MB-468	27 ± 1.3		
		fibroblasts	28 ± 1.4		
	Butanolic fraction	HL-60	15 ± 2		
		HeLa	24 ± 1.2		
		MDA-MB-468	60 ± 5		
		fibroblasts	60 ± 6		
Paris quadrifolia rhizomes			IC_{50} (μg ml^{-1})	MTT assay	Gajdus et al. (2014)
	Pennogenin 3-*O*-α-L-Rha-(1 → 4)-β-D-Glc	HL-60	47 ± 2.8		
	Pennogenin 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc	HL-60	16 ± 0.8		
		HeLa	18 ± 0.9		
		MCF-7	25 ± 1.5		
	Pennogenin 3-*O*-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	HL-60	1.0 ± 0.04		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HeLa	1.8 ± 0.072		
		MCF-7	2.4 ± 0.096		
	Pennogenin 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	HL-60	2.0 ± 0.08		
		HeLa	2.5 ± 0.125		
		MCF-7	3.2 ± 0.128		
	Etoposide (control)	HL-60	0.45 ± 0.022		
		HeLa	> 50		
		MCF-7	> 50		
	Mitoxantrone (control)	HL-60	0.06 ± 0.004		
		HeLa	0.4 ± 0.012		
		MCF-7	0.2 ± 0.008		
Paris quadrifolia rhizomes			IC_{50} (μg ml^{-1})	MTT assay	Stefanowicz-Hajduk et al. (2015)
	PS-1	HeLa	0.93 ± 0.15		
		HaCaT	0.82 ± 0.13		
	PS-2	HeLa	0.55 ± 0.01		
		HaCaT	0.58 ± 0.04		
Paris thibetica rhizomes			IC_{50} (μmol l^{-1})	MTT assay	Jing et al. (2017)
	PARIS saponin II	BEL-7402	0.48		
Paris vietnamensis rhizomes			IC_{50} (μM)	CCK-8 assay	Liu et al. (2018b)
	25(R)-Diosgenin-3-*O*-α-L-Rha-(1 → 2)-α-L-Rha-(1 → 3)-β-D-Glc	U251	2.16 ± 0.65		
		U87MG	2.33 ± 1.03		
	25(R)-Spirost-5-en-3β,17α-diol-3-*O*-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc	U251	3.14 ± 1.26		
		U87MG	2.97 ± 0.94		
	ACNU (control)	U251	0.96 ± 0.05		
		U87MG	0.88 ± 0.04		
Sansevieria trifasciata aerial parts			IC_{50} (μM)	MTS assay	Teponno et al. (2016)
	Trifasciatoside B	HeLa	47.1		
	Trifasciatoside D	HeLa	40.7		
	Trifasciatoside I	HeLa	26.5		
	Trifasciatoside J	HeLa	26.5		
Sansevieria cylindrica aerial parts			IC_{50} (μg ml^{-1})	MTT assay	Raslan et al. (2017)
	(25S)-Ruscogenin-1-*O*-α-L-Rha-(1 → 2)-β-D-Glc	MCF-7	24 ± 1		
		HCT 116	23 ± 1		
		HepG2	21 ± 1		

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
	(25S)-Ruscogenin-3-*O*-α-L-Rha-(1 → 4)-β-D-Glc	MCF-7	12 ± 1			
		HCT 116	11 ± 2			
		HepG2	13 ± 1			
	(25S)-Ruscogenin-3-*O*-β-D-Glc	MCF-7	> 50			
		HCT 116	> 50			
		HepG2	> 50			
	(25S)-Ruscogenin-1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara	MCF-7	7 ± 2			
		HCT 116	4 ± 2			
		HepG2	9 ± 2			
	(25R)-26-*O*-β-D-Glc-furost-5-ene-1β,3β,22α,26-tetrol-1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara	MCF-7	25 ± 1			
		HCT 116	19 ± 1			
		HepG2	21 ± 1			
	Doxorubicin hydrochloride (control)	MCF-7	13 ± 1			
		HCT 116	2 ± 3			
		HepG2	1 ± 1			
Sansevieria cylindrica aerial parts			IC_{50} (μM)		SRB assay	Said et al. (2015)
		HCT 116	38			
	1β-Hydroxy-kryptogenin-1-*O*-α-L-Rha-(1 → 2)-α-L-Ara	MCF-7	153			
		PC-3	175			
		HCT 116	90			
	Alliospiroside A	MCF-7	69			
		PC-3	99			
		HCT 116	10			
	Doxorubicin (control)	MCF-7	6			
		PC-3	4			
Schizocapsa plantaginea tubers			IC_{50} (μM)		MTT assay	Sun et al. (2016)
	Taccaoside	SMMC-7721	24 h	2.55		
			48 h	1.72		
		BEL-7404	24 h	8.10		
			48 h	5.94		
Smilacina japonica rhizomes and roots			IC_{50} (μM)		MTT assay	Liu et al. (2012c)
	Japonicoside A	SMMC-7221	1.19 ± 0.03			
		DLD-1	1.66 ± 0.08			
	Japonicoside B	SMMC-7221	5.40 ± 0.11			
		DLD-1	1.21 ± 0.05			
	Japonicoside C	SMMC-7221	3.14 ± 0.11			
		DLD-1	2.16 ± 0.09			
	Taxol (control)	SMMC-7221	3.14 ± 0.11			

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		DLD-1	2.16 ± 0.09		
Smilax glauco-china tubers			IC_{50} (μM)	MTT assay	Liu et al. (2017b)
	Glauco-chinaoside A	SGC-7901	2.7		
	Glauco-chinaoside B	SGC-7901	11.5		
	Glauco-chinaoside E	SGC-7901	6.8		
	Cisplatin (control)	SGC-7901	Not specified		
Smilax korthalsii leaves			IC_{50} (μM)	MTT assay	Hamid et al. (2016)
	Diosgenin	K562	6.25		
		WRL	14.34		
		MCF-7	38		
		COLO	12.4		
	Tamoxifen (control)	K562	7.26		
		WRL	12.25		
		MCF-7	8.54		
		COLO	10.08		
Smilax ornata roots and rhizomes			Inhibition of cell proliferation (μg ml^{-1})	SRB assay	Challinor et al. (2012)
	Sarsaparilloside B	NFF	> 50		
		HeLa	> 50		
		HT29	> 50		
		MCF-7	> 50		
		MM96L	> 50		
		K562	> 50		
	Sarsaparilloside C	NFF	27		
		HeLa	42		
		HT29	4.8		
		MCF-7	24		
		MM96L	23		
		K562	28		
	Sarsaparilloside	NFF	13		
		HeLa	12		
		HT29	5		
		MCF-7	9.5		
		MM96L	14		
		K562	22		
	Δ20(22)-sarsaparilloside	NFF	4.5		
		HeLa	40		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		HT29	14		
		MCF-7	3.4		
		MM96L	3.8		
		K562	4.3		
	Parillin	NFF	> 50		
		HeLa	> 50		
		HT29	> 50		
		MCF-7	> 50		
		MM96L	> 50		
		K562	> 50		
Smilax scobinicaulis rhizomes and roots			IC_{50} (μM)	MTT assay	Zhang et al. (2013)
	(25 R)-5α-spirostan-3β, 6β-diol 3-*O*-β-D-Glc-(1 → 4)-[α-L-Ara-(1 → 6)]-β-D-Glc	A549	3.7		
		LAC	5.7		
		HeLa	3.64		
	Doxorubicin (control)	A549	1.08		
		LAC	0.95		
		HeLa	1.16		
Smilax scobinicaulis rhizomes			IC_{50} (μM)	MTT assay	Shu et al. (2017)
	Smilscobinoside D	HCT 116	10.5		
		SGC-7901	21.4		
	Smilscobinoside D	HCT 116	7.8		
		SGC-7901	15.8		
Smilax trinervula rhizomes and roots			IC_{50} (μM)	MTT assay	Liang et al. (2016)
	Trinervuloside B	SGC-7901	8.1		
		HCT-116	5.5		
Solanum glabratum var. *sepicula* aerial parts			IC_{50} (μM)	MTT assay	Abdel-Sattar et al. (2015)
	23-β-D-Glc-(23S, 25R)-spirost-5-en-3, 23 diol 3-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)]-β-D-Glc	PC3	> 32		
		HT29	> 2		
	(25R)-spirost-5-en-3-ol 3-*O*-α-L-Rha-(1 → 2)-*O*-[β-D-Glc-(1 → 3)]-β-D-Gal	PC3	14		
		HT29	16.7		
	(23S,25R)-spirost-5-en-3, 23 diol 3-*O*-α-L-Rha-(1 → 2)-*O*-[α-L-Rha-(1 → 4)]-β-D-Glc	PC3	> 32		
		HT29	> 32		
	Digitonin (positive control)	PC3	1.8		
		HT29	3		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
Solanum incanum roots/ *S. heteracanthum* roots			IC_{50} (μM)	MTT assay (with HCT 116 and HT-29)	Manase et al. (2012)
	(23S,25R)-spirost-5-en-3β,23-diol 3-*O*-{β-D-Xyl-(1 → 2)-*O*-α-L-Rha-(1 → 4)-[*O*-α-L-Rha-(1 → 2)]-β-D-Glc}	HCT 116	62.42 ± 0.66	XTT assay (with SW480, DU145 and EMT6)	
	Protodioscin	HT-29	72.24 ± 20.62		
		SW480	> 29.53		
		DU145	> 29.53		
		EMT6	> 29.53		
	Methyl-protodioscin	HCT 116	2.26 ± 2.29		
		HT-29	3.48 ± 3.01		
		SW480	6.68		
		DU145	> 28.63		
		EMT6	6.68		
	Indioside D	HCT 116	2.76 ± 1.93		
		HT-29	3.30 ± 3.00		
		SW480	> 28.25		
		DU145	> 28.25		
		EMT6	> 28.25		
	Paclitaxel (control)	HCT 116	3.87 ± 2.51		
		HT-29	5.28 ± 0.51		
		SW480	20.68		
		DU145	> 28.20		
		EMT6	24.44		
	Etoposide (control)	HCT 116	2.65 10^{-3}		
		HT-29	2.29 10^{-3}		
		SW480	13.22 ± 3.79		
		DU145	41.26 ± 17.57		
		EMT6	> 200		
Solanum procumbens whole plant			IC_{50} (μM)	MTT assay	Hien et al. (2018)
	Solaprocumoside A	HepG2	55.7 ± 1.5		
	Solaprocumoside B	HepG2	48.1 ± 2.2		
	Paniculonin B	HepG2	78.3 ± 2.4		
	Elipticine (control)	HepG2	1.43 ± 0.17		
Solanum surattense aerial parts			IC_{50} (μM)	MTT assay	Lu et al. (2011)
	(22R,25R)-16β-H-22α-N-spirosol-3β-ol-5-ene 3-*O*-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 4)]-β-D-Glc	A549	20.3 ± 1.1		
		MGC-803	45.6 ± 1.5		
		HepG2	26.1 ± 0.6		
	(22R,23S,25R)-3β,6α,23-trihydroxy-5α-spirostane 6-*O*-β-D-Xyl-(1 → 3)-β-D-Qui	A549	71.2 ± 2.0		

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
		MGC-803	NA		
		HepG2	NA		
	(22R,23S,25S)-3β,6α,23-trihydroxy-5α-spirostane 6-*O*-β-D-Xyl-(1 → 3)-*O*-β-D-Qui	A549	NA		
		MGC-803	63.2 ± 0.8		
		HepG2	NA		
	(22R,23R,25S)-3β,6α,23-trihydroxy-5α-spirostane 6-*O*-β-D-Xyl-(1 → 3)-*O*-β-D-Qui	A549	62.5 ± 1.6		
		MGC-803	NA		
		HepG2	88.8 ± 1.2		
	Khasianine	A549	26.7 ± 1.5		
		MGC-803	35.4 ± 0.7		
		HepG2	45.3 ± 2.1		
	Solamargine	A549	15.7 ± 0.6		
		MGC-803	NA		
		HepG2	23.2 ± 0.8		
	Cisplatin (control)	A549	7.6 ± 1.6		
		MGC-803	3.5 ± 0.3		
		HepG2	8.7 ± 0.4		
Solanum violaceum whole plant			IC_{50} (μg ml^{-1})	MTT assay	Yen et al. (2012)
	Indioside H	HepG2	2.22 ± 0.01		
		Hep3B	2.95 ± 0.02		
		MCF-7	4.78 ± 0.02		
		A549	3.09 ± 0.02		
		Ca9-22	2.95 ± 0.07		
		MDA-MB-231	6.12 ± 0.15		
	Indioside I	HepG2	5.33 ± 0.16		
		Hep3B	3.32 ± 0.42		
		MCF-7	11.57 ± 0.70		
		A549	7.27 ± 0.07		
		Ca9-22	6.76 ± 0.15		
		MDA-MB-231	8.04 ± 0.12		
	Borassoside D	HepG2	> 20		
		Hep3B	> 20		
		MCF-7	> 20		
		A549	> 20		
		Ca9-22	> 20		
		MDA-MB-231	> 20		
	Yamogenin 3-*O*-α-L-Rha-(1 → 2)-β-D-Glc	HepG2	6.48 ± 0.01		
		Hep3B	6.98 ± 0.05		
		MCF-7	5.84 ± 0.04		
		A549	4.26 ± 0.02		

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
		Ca9-22	4.51 ± 0.24			
		MDA-MB-231	7.25 ± 0.15			
	Borassoside E	HepG2	1.83 ± 0.12			
		Hep3B	2.03 ± 0.03			
		MCF-7	2.61 ± 0.10			
		A549	2.34 ± 0.02			
		Ca9-22	2.33 ± 0.02			
		MDA-MB-231	2.75 ± 0.10			
	3-*O*-chacotriosyl-(25S)-spirost-5-en-3β-ol	HepG2	6.44 ± 0.45			
		Hep3B	2.87 ± 0.04			
		MCF-7	8.84 ± 0.12			
		A549	4.09 ± 0.08			
		Ca9-22	3.77 ± 0.02			
		MDA-MB-231	5.84 ± 0.06			
	Doxorubicin (control)	HepG2	0.18 ± 0.00			
		Hep3B	1.31 ± 0.12			
		MCF-7	0.80 ± 0.03			
		A549	1.40 ± 0.02			
		Ca9-22	0.31 ± 0.01			
		MDA-MB-231	1.39 ± 0.00			
Tacca integrifolia rhizomes			IC_{50} (μM)		MTT assay	Shwe et al. (2010)
	(3β,25R)-spirost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[β-D-Glc-(1 → 4)-6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc	HeLa	72 h	3.0 ± 0.5		
	(3β,25R)-spirost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc	HeLa	72 h	1.2 ± 0.4		
	(3β,22R,25R)-26-(β-D-Glc)-22-hydroxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc	HeLa	72 h	1.5 ± 0.3		
	(3β,22R,25R)-26-(β-D-Glc)-22-methoxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc	HeLa	72 h	3.5 ± 0.5		
	(3β,22R,25R)-26-(β-D-Glc)-22-hydroxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[β-D-Glc-(1 → 4)-6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc	HeLa	72 h	4.0 ± 0.6		
	Podophyllotoxin (control)	HeLa	72 h	0.1 ± 0.02		
Trillium kamtschaticum whole plant			IC_{50} (μM)		MTT assay	Qin et al. (2017)
	Trillikamtoside L	HCT 116	17.28 ± 2.69			

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
	Trillikamtoside P	HCT 116	4.92 ± 1.00			
	Trillikamtoside Q	HCT 116	22.48 ± 8.68			
	Trillikamtoside R	HCT 116	5.84 ± 1.05			
	Camptothecin (control)	HCT 116	0.0115 ± 0.0009			
Trillium tschonoskii rhizomes			IC_{50} (μM)		Trypan blue dye exclusion assay	Huang and Zou (2015)
	Pennogenin 3-*O*-α-L-Rha-(1 → 2)[α-L-Rha-(1 → 4)]-β-D-Glc (TTB2)	Rh1	48 h	7.5		
Tupistra chinensis rhizomes			IC_{50} (μM)		MTT assay	Pan et al. (2012)
	Tupichinin A	HL-60	18.58			
		SMMC-7721	> 40			
		A549	19.99			
		MCF-7	11.01			
		SW480	10.78			
	3-Epi-neoruscogenin 3-β-D-Glc	HL-60	10.02			
		SMMC-7721	12.76			
		A549	11.4			
		MCF-7	5.02			
		SW480	28.26			
	Cisplatin (control)	HL-60	2.03			
		SMMC-7721	13.54			
		A549	12.56			
		MCF-7	18.65			
		SW480	19.7			
Tupistra chinensis rhizomes			IC_{50} (μM)		MTT assay	Liu et al. (2012b)
	Tupisteroide C	A549	25.9			
	Mitomycin C	A549	not specified			
Tupistra chinensis rhizomes			IC_{50} (μM)		MTT assay	Liu et al. (2012a)
	(25R)-26-*O*-β-D-Glc-furost-1β,3β,22α,26-tetraol 3-*O*-β-D-Glc	A549	6.6			
	(25R)-26-*O*-β-D-Glc-furost-5-en-1β,3α,22α,26-tetraol 3-*O*-β-D-Glc	A549	6.7			
	(25R)-26-*O*-β-D-Glc-furost-1β,3β,5β,22α,26-pentaol-3-*O*-β-D-Glc	A549	29.1			
Tupistra chinensis roots and rhizomes			IC_{50} (μM l^{-1})		MTT assay	Li et al. (2015)
	(20S,22R)-Spirost-25 (27)-en-1β,3β,5β-trihydroxy-1-*O*-β-D-Xyl	A549	86.63 ± 2.33			
		NCI-H1299	88.21 ± 1.34			

Table 1 continued

Source	Compound	Cell line	Concentration	Assay	References
	5-FU (control)	A549	38.65 ± 1.59		
		NCI-H1299	42.78 ± 1.63		
Vernonia amygdalina leaves			Concentration not specified	MTT assay	Wang et al. (2018)
			(%) Inhibition		
	Vernoniamyoside A	BT-549	63.61		
		MDA-MB-231	28.97		
		MCF-7	46.54		
	Vernoniamyoside B	HeLa	42.05		
		BT-549	62.17		
		MDA-MB-231	27.78		
		MCF-7	37.07		
	Vernoniamyoside C	HeLa	31.64		
		BT-549	34.18		
		MDA-MB-231	32.74		
		MCF-7	39.38		
	Vernoniamyoside D	HeLa	26.73		
		BT-549	44.00		
		MDA-MB-231	31.53		
		MCF-7	31.36		
	Vernonioside B_2	HeLa	32.93		
		BT-549	36.41		
		MDA-MB-231	33.61		
		MCF-7	49.72		
	Vernoamyoside D	HeLa	21.48		
		BT-549	51.14		
		MDA-MB-231	30.75		
		MCF-7	39.08		
	Doxorubicin (control)	HeLa	35.63		
		BT-549	83.79		
		MDA-MB-231	83.39		
		MCF-7	95.32		
		HeLa	92.70		
Ypsilandra thibetica whole plant			IC_{50} (μM)	MTT assay	Lu et al. (2010)
	Ypsilandroside H	A549	> 40		
	Ypsilandroside I	HL-60	Not specified		
	Ypsilandroside J	PANC-1			
	Ypsilandroside K	SMMC-7721			
	Ypsilandroside L	SK-BR-3			
	Polyphylloside III				
	Cisplatin (control)				

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
Yucca de-smetiana leaves			IC_{50} (μM)		MTT assay	Eskander et al. (2013)
	Smilagenin 3-*O*-[β-D-Glc-(1 → 2)-*O*-β-D-Gal]	HCT 116	4.4 ± 0.47			
		MCF-7	4.0 ± 0.85			
		A549	16.5 ± 1.45			
		HepG2	3.5 ± 0.41			
	Desmettianoside C	HCT 116	2.4 ± 0.57			
		MCF-7	2.6 ± 0.49			
		A549	10.2 ± 0.97			
		HepG2	1.1 ± 0.56			
	Doxorubicin (control)	HCT 116	6.86			
		MCF-7	5.46			
		A549	0.84			
		HepG2	7.36			
			IC_{50} (μM)		MTT assay	Tong et al. (2011)
	Deltonin	C26	48 h	1.22 ± 0.22		
		SW620	48 h	1.29 ± 0.69		
		SW480	48 h	1.30 ± 0.05		
		LOVO	48 h	2.11 ± 0.68		
			IC_{50} (μM)		MTT assay	Tao et al. (2017)
	Dioscin	PC3	5.6			
			IC_{50} (μM)		CCK-8 assay	Tong et al. (2014)
	Dioscin	C26	7.36			
		EA.hy926	3.87			
		HUVEC	1.6			
			IC_{50} (μM)		MTT assay	Zhiyu et al. (2012)
	Dioscin	KYSE 510	5.4			
			IC_{50} (μM)		MTT assay	Rahmati-Yamchi et al. (2013)
	Diosgenin	A549	24 h	47		
			48 h	44		
			72 h	43		
			IC_{50} (mg ml^{-1})		MTT assay	Mirunalini et al. (2011)
	Diosgenin	HEp2	0.125			
			IC_{50} (μM)		MTS assay	Watanabe et al. (2017)
	Polyphyllin D	IMR-32	25			
		LA-N-2	20			
		NB-69	5			

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
			Inhibitory rate (%)		MTT assay	Kong et al. (2010)
	Polyphyllin I	A549	0.625 (μg ml^{-1})			
		NCI-H460	24 h	10.0 ± 8.7 (%)		
		SK-MES-1	48 h	27.2 ± 5.6		
			72 h	27.9 ± 11.9		
			1.25 (μg ml^{-1})			
			24 h	16.9 ± 3.2 (%)		
			48 h	60.4 ± 5.9		
			72 h	66.6 ± 6.6		
			2.5 (μg ml^{-1})			
			24 h			
			48 h	76.9 ± 2.8		
			72 h	84.7 ± 4.8		
			5 (μg ml^{-1})			
			24 h	68.7 ± 3.2 (%)		
			48 h	87 ± 1.5		
			72 h	93.9 ± 0.5		
			10 (μg ml^{-1})			
			24 h	79.3 ± 1.4 (%)		
			48 h	87.8 ± 1.2		
			72 h	93.7 ± 0.7		
			0.625 (μg ml^{-1})			
			24 h	27.9 ± 10.1 (%)		
			48 h	16.1 ± 7.3		
			72 h	12.9 ± 8.4		
			1.25 (μg ml^{-1})			
			24 h	39.6 ± 3.6 (%)		
			48 h	22.8 ± 9.0		
			72 h	24.5 ± 7.0		
			2.5 (μg ml^{-1})			
			24 h	60.3 ± 10.6 (%)		
			48 h	49.1 ± 7.5		
			72 h	52.1 ± 2.2		
			5 (μg ml^{-1})			
			24 h	81.2 ± 11.8 (%)		
			48 h	79.3 ± 3.4		
			72 h	87.5 ± 1.5		
			10 (μg ml^{-1})			

Table 1 continued

Source	Compound	Cell line	Concentration		Assay	References
			24 h	93.4 ± 0.6 (%)		
			48 h	88.8 ± 2.8		
			72 h	94.8 ± 0.4		
			0.625 (μg ml^{-1})			
			24 h	14.5 ± 8.9 (%)		
			48 h	8.6 ± 4.3		
			72 h	19.3 ± 5.0		
			1.25 (μg ml^{-1})			
			24 h	31.9 ± 8.9 (%)		
			48 h	25.3 ± 5.9		
			72 h	39.7 ± 8.4		
			2.5 (μg ml^{-1})			
			24 h	67.8 ± 8.9 (%)		
			48 h	60.2 ± 2.7		
			72 h	71.9 ± 2.9		
			5 (μg ml^{-1})			
			24 h	83.1 ± 3.3 (%)		
			48 h	81.2 ± 2.4		
			72 h	82.8 ± 2.2		
			10 (μg ml^{-1})			
			24 h	80.3 ± 4.5 (%)		
			48 h	85.7 ± 0.8		
			72 h	90.8 ± 0.8		
			IC_{50} (μg ml^{-1})		CCK-8 assay	Yu et al. (2018b)
	Polyphyllin I	HCT-116	72 h	0.7107 ± 0.103		

Human cancer cell lines: breast: BT-549, MCF-7, MDA-MB-231, MDA-MB-435, MDA-MB-468, SK-BR-3; cervix: Caski, HeLa, KB; colon: CaCo-2, COLO, DLD-1, HCT 116, HCT-15, HT-29, LOVO SW480, SW620, W480; esophagus: KYSE 510; gingival: Ca9-22; glioblastoma: SF-268, SF-295, U251, U87MG; leukemia: CCRF-CEM, HL-60, Jurkat, K562; larynx: Hep2; liver: BEL-7402, BEL-7403, BEL-7404, HLE, Hep3B, HepG2, SMMC-7721, SMMC-7221, SNU-387, WRL; lung: 95D, A549, LAC, NCI-H1299, NCI-H460, SK-MES-1; melanoma: A375, MM96L, SK-MEL, SK-MEL-2; neuroblastoma: IMR-32, LA-N-2, NB-69; ovary: OVCAR-8, SK-OV-3; pancreas: PANC-1; pharynx: 5-8F, CNE; prostate: DU145, PC-3; sarcoma: MG-63, Rh1; stomach: BGC-823, MGC-803, SGC-7901; urinary bladder: ECV-304

Animal cancer cell lines: breast: EMT6; glioblastoma: C6; lung: LL2; colon: C26; melanoma: B16; sarcoma: WEHI-164, J-774

Human normal cell lines: fibroblasts: HFF, NFF, Hs68; keratinocytes: HaCaT; kidney embryonic: HEK293; lung epithelial: MRS-5; vein endothelial: EA.hy926, HUVEC

Animal normal cell lines: cardiomyoblasts: H9c2; epidermal: JB6 P^{+}Cl-41; fibroblasts: 3T3; kidney epithelial: LLC-PK1; kidney fibroblasts: VERO

NA not active

Structure–activity correlation

Despite a vast number of papers that cite the results of cytotoxic activity of steroidal saponins only a relatively small number include some reference to potential structure–activity elationships. These are usually not fully conclusive statements resulting from the observations made on a very limited number of compounds. In the time-span covered by this review, only a few studies have been specially designed to

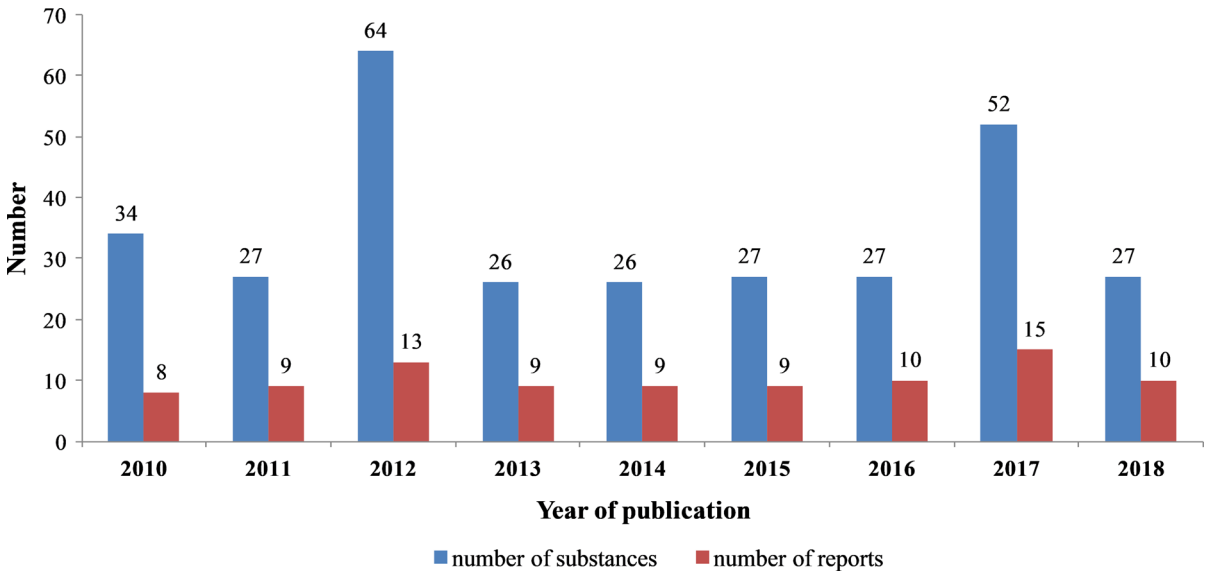

Fig. 1 The number of tested substances and number of reports published in the time scope covered by this review (2010–2018)

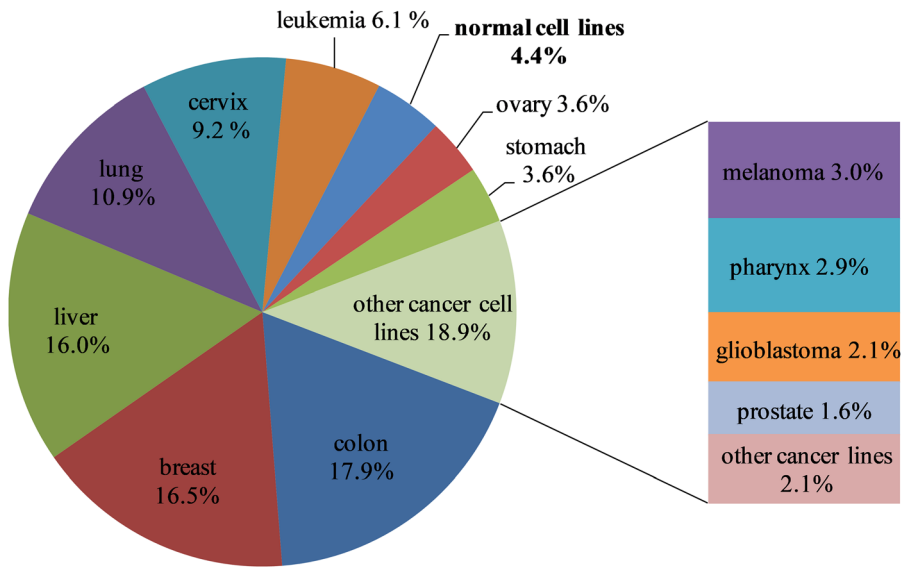

Fig. 2 The share of experiments on specific types of tumors and normal cell lines in the total number of tests performed on human cell lines

explore structure–activity correlations. These include the one by Pérez-Labrada et al. (2012a, b) who, for the purpose of their study, had synthesized twelve spirostanol glycosides differing mainly in C-ring functional groups, which influenced the lipophilicity and conformational flexibility of compounds (Pérez-Labrada et al. 2012a). These included methylene-, methoxyl-, α,β-unsaturated ketone and lactone. Two glycosylation pathways led to a series of 3,6-dipivaloylated β-D-glucosides (pivaloyl = 2,2-dimethylpropanoyl) and a series of β-chacotriosides (α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 4)]-β-D-Glc). The obtained compounds were analysed with respect to their cytotoxicity against the human myeloid leukemia cell line (HL-60) and benign blood cells. The results indicate that among the two glycosidic series, the one

based on a β-chacotrioside moiety was more potent. This activity was however greatly correlated with the rigidity of the aglycone and its hydrophobic character. From among all tested saponins, chacotriosides either with a methylene group at C-12 or no substitution in C-ring showed the highest cytotoxic potential against malignant cell line. However, their selectivity as compared to 3,6-dipivaloylated spirostanyl glucosides was much lower.

In a subsequent study by the same research group on a larger variety of synthetic spirostanol glycosides, the partially pivaloylated β-D-glucosides of 5α-hydroxy-laxogenin were the most potent (Pérez-Labrada et al. 2012b). Comparison of the results obtained for different β-chacotriosides, has again confirmed that vast differences can be seen with a change in the aglycone part. Hecogenin derivative was highly cytotoxic against the tested HL-60 cell line (IC_{50} 4.3 ± 1.0 μM) whereas 5α-hydroxy-laxogenin β-chacotrioside showed a complete loss of activity ($IC_{50} > 100$ μM).

Other studies in which any references to possible structure–activity relationships were made, generally indicate that both structural features of steroidal saponins, that is the nature of the aglycone and the sugar moiety, together determine their cytotoxicity.

Thirteen saponins isolated from the roots of *Liriope muscari* were analysed in this respect against a fairly wide panel of cancer cell lines (MDA-MB-435, 95D, HepG2, HeLa, MCF-7 and A549) (Wu et al. 2017b). The authors were able to distinguish three groups based on the structural features of the aglycone, namely the (25S)-ruscogenin, (25R)-ruscogenin, and neoruscogenin groups. This allowed to compare the potential contribution to the cytotoxic activity of the specific configuration at C-25, either 25R, 25S or 25,27-double bond. The obtained cytotoxicity results have shown that the impact of this structural feature is related to the nature of the sugar chain. In all saponins bearing β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Xyl or β-D-Glc-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc sugar chains at C-1, the configuration at C-25 was of no consequence in all tested cell lines. Interestingly, a different sugar chain composed of β-D-Glc-(1 → 2)-[β-D-Ara-(1 → 3)]-β-D-Fuc, together with 25R configuration seemed to have a detrimental effect on the cytotoxicity, which was observed against all the tested cell lines. Similar regularity was seen when comparing compounds with yet another sugar chains, however not in case of the whole spectrum of tested cell lines.

In another study on ten saponins from *Asparagus filicinus* similar results with respect to C-25 configuration were obtained, suggesting that 25S spirostanol aglycone may be a more important structural feature (Wu et al. 2010). Another conclusion drawn from these studies refers to the sugar moiety, clearly indicating that its presence at C-23 significantly reduces the cytotoxic potential of these compounds.

Beit-Yannai et al. (2011) in their study on saponins from *Balanites aegyptiaca* have seen a pronounced difference in cytotoxicity against MCF-7 human breast cancer and HT-29 human colon cancer cells between two compounds differing in only one terminal sugar (dioscin vs SAP-884—diosgenin 3-*O*-β-D-Glc-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc) led the authors to postulate that terminal L-rhamnose seems to be more beneficial than D-glucose (Beit-Yannai et al. 2011). Results of their study also confirmed previous observations with regard to the general aglycone type, that furostane derivatives have lesser cytotoxic effect as compared to spirostanes.

Also Wu et al., who analysed the activity of three new saponins from *Paris polyphylla* var. *yunanensis* against CNE cells, concluded that the presence of F ring in steroidal saponins may be the structural feature essential for their cytotoxicity (Wu et al. 2017a).

However, a study of Kang et al. showed contradictory results against human CCRF-CEM leukemia cells. From among twenty compounds (including saponins, sapogenins and sterols) isolated from *P. polyphylla*, only furostanols were active and their activity was highly potent. Both spirostanol saponins and sterols lacked any effect on this cell line (Kang et al. 2012).

In some papers included in this review the authors tried to draw conclusions referring solely to the composition and structure of the sugar moieties. This was possible when the isolated saponins differed only with respect to the sugar chain. However, the number of compounds was usually so small that it is hardly possible to consider these observations as contributing to more general statements which would be conclusive. For example, two pennogenyl saponins from *Paris quadrifolia* differing in the length and number of monosaccharides were compared on a single cell line, namely HeLa. Compound bearing a sugar chain at C-3 composed of two rhamnose unit was slightly more

active than the one with single rhamnose unit (Stefanowicz-Hajduk et al. 2015).

Zolfaghari et al. (2013) in their study of four furostane glycosides from *Allium vavilovii* have suggested that xylose instead of galactose and glucose instead of rhamnose seem to enhance cytotoxicity against J-744 (murine macrophage) and WEHI-164 (murine fibrosarcoma) cell lines.

Mechanisms of action

Similarly to what have been published in our previous work (Podolak et al. 2010), most of the steroidal saponins, which are discussed in the present review, triggered cell death by apoptosis stimulation, mainly on its intrinsic pathway. Other effects observed while testing steroidal saponins impact on cancer cells included the stimulation of autophagy, phagocytosis or oncosis, the inhibition of metastatic properties of the tested cells or angiogenesis.

Results of in vitro studies

Apoptosis stimulation

Lin et al. (2018) described the effect of protodioscin on human cervical cancer cells, trying to determine the molecular mechanism of the compound. The authors observed that protodioscin inhibited the viability of cervical cancer cells by stimulating apoptotic process in the cells, expressed by the up-regulation of caspases 8, 3 and 9, but also down-regulation of Bcl-2 expression. Moreover, protodioscin stimulated ROS and ER stress pathway in the examined cells and increased p38 and JNK levels. The authors suggest that protodioscin stimulated ER-stress dependent apoptosis in the human cervical cancer cells and the observed effect could be additionally mediated by the activation of JNK and p38 pathways (Lin et al. 2018). Terrestrosin D (hecogenin 3-*O*-β-D-Gal-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal), isolated from *T. terrestris*, significantly decreased the viability of androgen-independent (DU-145, PC-3, PC-3M) and androgen-dependent (LNCaP, 22RV1) human prostate cancer cells, in dose-dependent manner (Wei et al. 2014). Moreover, the compound induced PC-3 cell cycle arrest in G1 phase and stimulated caspase-independent apoptosis in the cells. Wang et al. indicated that macrostemonoside A (tigogenin 3-*O*-β-D-Glc-(1 → 2)-[β-D-Glc-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal) stimulated apoptosis in colorectal cancer SW480 cells, manifesting as caspase activation, increase in proapoptotic and decrease of antiapoptotic Bcl-2 family proteins expression. Moreover, the compound induced reactive oxygen species (ROS) production in the examined cells (Wang et al. 2013c). Two studies concern the activity of saponins isolated from *P. polyphylla*. In the first one, four pennogenyl saponins PS1–PS4 were examined on a panel of human cancer and normal cell lines. The results indicated that only saponins PS1 (pennogenin 3-*O*-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc) and PS2 (pennogenin 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc) markedly inhibited cell viability in HepG2, MCF-7 and PC-3 cells. The two compounds also induced apoptosis and caused cell cycle arrest in HepG2 cells affecting multiple targets, including mitochondrial caspase-dependent and independent pathway, cyclin-dependent kinase 1 activation or PI3K/Akt signalling (Long et al. 2015). In another study *P. polyphylla* steroidal saponins decreased the viability of human lung cancer A549 cells through both apoptosis and autophagy, with the activation of caspase-8 and 3 and PARP cleavage for the former, and up-regulation of Beclin1 and conversion from LC3 I to LC3 II for the latter process, respectively (He et al. 2014). For the same cell line, A549, an apoptosis inducement was described as the effect of a treatment with novel steroidal saponin cholestanol glucoside CG. The compound had cytotoxic effect also in PC-3 and HepG2 cells, but A549 cell line was most susceptible, with the observed ROS generation inducement and the loss of mitochondrial membrane permeability (Valayil et al. 2016). Similar effect of ROS accumulation was also described for aspafilioside B (sarsasapogenin 3-*O*-β-D-Xyl-(1 → 4)-[α-L-Ara-(1 → 6)]-β-D-Glc), isolated from *Asparagus filicinus*. The compound additionaly inhibited both viability and proliferation of HepG2 cells, by arresting the cells in G2 phase and stimulating apoptosis. The underlying mechanism included up-regulation of H-Ras and N-Ras proteins, c-Raf phosphorylation and the activation of ERK and p38. Interesting proapoptotic mechanism was recently proposed for a sapogenin–diosgenin by Chen et al. (2018). The compound was found to inhibit TAZ, one

of the transcription co-activators in Hippo signalling pathway, which may play a role as an oncogenic factor in the cells. Diosgenin also inhibited the growth and migration of human liver cancer cells (Chen et al. 2018). Its widely known glycoside–dioscin exerted rare mechanism of proapoptotic activity by triggering both intrinsic (loss of mitochondrial membrane potential, activation of tBid and Bak proteins) and extrinsic (up-regulation of death ligands and receptors) apoptosis pathways in human leukemia cells. Additionally, the compound induced the differentiation of promyelocytes to granulocytes and monocytes (Chan et al. 2018).

Oncosis stimulation

Oncosis is a non-apoptotic cell death mode, manifested as marked cell swelling, coagulation of the cytoplasm and alterations in cell cytoskeleton elements, noted within a short time after the application of the tested substance. The only report describing oncosis stimulation for steroidal saponins was published by Sun et al. (2011) for solamargine (solasodine 3-*O*-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 4)]-β-D-Glc)—a steroidal alkaloid glycoside in human K562 leukemia and KB squamous carcinoma cells. The authors suggested that compound initiated cell membrane blebbing, the increase in cytoplasm volume and also disrupted microtubules and actin filaments within the tested cells (Sun et al. 2011).

Angiogenesis inhibition

Terrestrosin D isolated from *T. terrestris* effectively inhibited viability of HUVEC cells and also induced cell cycle arrest and apoptosis in the cells, which suggests its antiangiogenic potential in vitro (Wei et al. 2014). Similar observations were made for ASC (diosgenin 3-*O*-[2-*O*-acetyl-α-L-Rha-(1 → 2)]-[β-D-Xyl-(1 → 4)]-β-D-Glc), a steroidal saponin from *Ophiopogon japonicus*, which markedly inhibited the proliferation of HUVEC cells and induced G2/M phase arrest in the cells by decreasing the expression of cdc2 and cyclin B1. The compound also significantly inhibited the invasive potential of the examined cells in transwell migration and tube formation assays. Moreover, ASC was found to be a strong inhibitor of Src/Akt/mTOR-dependent metalloproteinases pathway, which may explain its antiangiogenic properties (Zeng et al. 2015). Antiangiogenic properties were also described for another compound from the *O. japonicus*, ophiopogonin T (26-*O*-β-D-Glc (25R)-furost-5-ene-1β,3β,22β,26-tetraol 1-*O*-β-D-Xyl-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Fuc), which inhibited tube formation of HUVEC cells (Lee et al. 2016).

Metastasis inhibition

Ophiopogonin D (25(R)-ruscogenin 1-*O*-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-β-D-Fuc) isolated from *O. japonicus* significantly decreased not only the proliferation of MDA-MB-435 melanoma cells, but also decreased the cell invasion properties, probably through the inhibition of the MMP-9 matrix metalloproteinase expression and suppression of the p38/MAPK pathway. The compound inhibited also the adhesion of melanoma cells to human umbilical vascular endothelial cells and fibronectin (Zhang et al. 2015). An interesting explanation for the antiinvasive potential was proposed for dioscin in the experiment on murine B16 melanoma cells. The compound significantly affected the transcription and translation of connexin 43 via retinoid acid signalling pathway and at the same time enhanced the transporting function of connexin 43. Additionally, dioscin increased the secretion of pro-inflammatory interleukines 6 and 1β and TNFα, but also the increase in phagocytic activity of tumor-associated magrophages was observed (Kou et al. 2017).

Multidrug resistance decreasing

Interesting study was described by Wang et al. on the potential of steroidal saponin from *Trillium tschonoskii* in reversing multidrug resistance (MDR) in hepatocellular carcinoma cells (Wang et al. 2013a). The compound not only reversed MDR in the cells but also enhanced the chemosensitization of the cells to doxorubicin, demonstrated as the significant decrease in IC_{50} value for the anticancer drug. Moreover, the compound suppressed the P-glucoprotein expression in the drug resistant cells, which led to the accumulation of doxorubicin inside the cells, and also blocked the expression of some genes coding multidrug resistance (Wang et al. 2013a).

Results of in vivo studies

Only a small number of papers describe the in vivo effects of steroidal saponins. In one of them, after 35 days of intraperitoneal administration of 10, 50 or 100 mg kg^{-1} daily of macrostemonoside A to BALB/c nude mice (with SW480 cells injected s.c.), a significant decrease in tumor volume and weight was noted (Wang et al. 2013c). Similar effect was described by Wei et al. (2014) for terrestrosin D, a steroidal saponin isolated from *T. terrestris*. The compound at the doses of 25 or 50 mg kg^{-1} was administered 3 times a week for 4 weeks to BALB/c nude mice bearing PC-3 prostate cancer cells and reduced the tumor growth when compared to the control animals. Moreover, no toxic effect was noted during the treatment. Another steroidal saponin, aspafilioside B, significantly inhibited tumor growth in nude mice bearing HepG2 human hepatocellular carcinoma cells, when administered in 5 and 10 mg kg^{-1} doses. Further analysis indicated the increase in the expression of H-Ras and N-Ras signalling proteins in the tumor cells obtained from aspafilioside B treated animals. Moreover, no side effects were observed during treatment in terms of haematological or histopathological parameters. In a similar study, dioscin revealed significant anti-metastatic effects, activating the expression of a gap junction protein connexin 43 both in metastatic lung nodes and in situ tumor animal models (Kou et al. 2017). An interesting experiment was described by Chen et al. (2016) on the effect of dioscin aglycone–diosgenin on benign prostate hyperplasia in rats (Chen et al. 2016). After 3 weeks of administration the compound at the doses of 50 and 100 mg kg^{-1} significantly decreased prostate index and PSA level but also improved the pathological changes of the prostate in the treated animals. Moreover, diosgenin down-regulated the expression of Bcl-2 and up-regulated that of Bax and p53 in the treated animals, which suggests the efficacy of the compound in the treatment of prostate enlargement. Interesting antiangiogenic properties of ASC, isolated from *O. japonicus*, were described in matrigel plug in vivo assay. The compound significantly inhibited the formation of new blood vessels and decreased the number of the cells with the expression of PECAM-1, cell adhesion molecule, but also the number of MMP-2, MMP-9 and VEGF positive cells (Zeng et al. 2015).

Compounds with a potential as future anti-cancer therapeutic agents

Several reports indicate that some saponins/sapogenins can be considered as potential candidates for cancer treatment. In many studies on human cancer cell lines of different origin they displayed significant in vitro and in vivo activities through different signaling pathways associated with cell cycle. What is most important, apart from direct cytotoxic effect these compounds revealed also other activities, for example anti-inflammatory, that may be of importance in order to obtain the multidirectional therapeutic effect in cancer treatment. The authors of the present review have chosen five compounds: diosgenin, dioscin, polyphyllin I, paris saponin II, and timosaponin III, which, in our opinion have some interesting features, that make them especially promising for future development as anticancer agents. All selected saponins, except timosaponin AIII, share a common structural feature that is the same sapogenin–diosgenin as well as the presence of one branched sugar chain. It is noteworthy that this sapogenin itself can be considered as a potential lead compound for future development. Below, a short summary of the most interesting data referring to complex mechanisms of action is provided. Moreover, the results of the studies referring to their mechanisms of action at the molecular level, that were published in years 2010–2018 are summarized in details in Table S2 (Tab. S2)—see supplementary material. The structures of selected compounds are presented on Fig. 3.

Diosgenin (3β,25R)-spirost-5-en-3-ol, was discovered for the first time in *Dioscorea tokoro* in 1935 (Chen et al. 2015). Since then it has been found in numerous plants of several genera: *Dioscorea*, *Costus*, *Smilax*, *Paris*, *Alteris*, *Allium*, *Helicteres*, *Trillium*, and *Trigonella* (Sethi et al. 2018; Sobolewska et al. 2016; Deshpande and Bhalsing 2014–2015). Diosgenin exerts different pharmacological activities: hypolipemic, neuroprotective, gastro- and hepatoprotective (Jesus et al. 2016; Sethi et al. 2018). Of current interest are its anti-proliferative properties as well as anti-inflammatory effects.

Multiple molecular targets of this sapogenin are noteworthy. It is able to modulate various oncogenic processes (cancer cells proliferation, migration, apoptosis), inhibit angiogenesis, reverse multi-drug resistance in cancer cells and sensitize cancer cells to

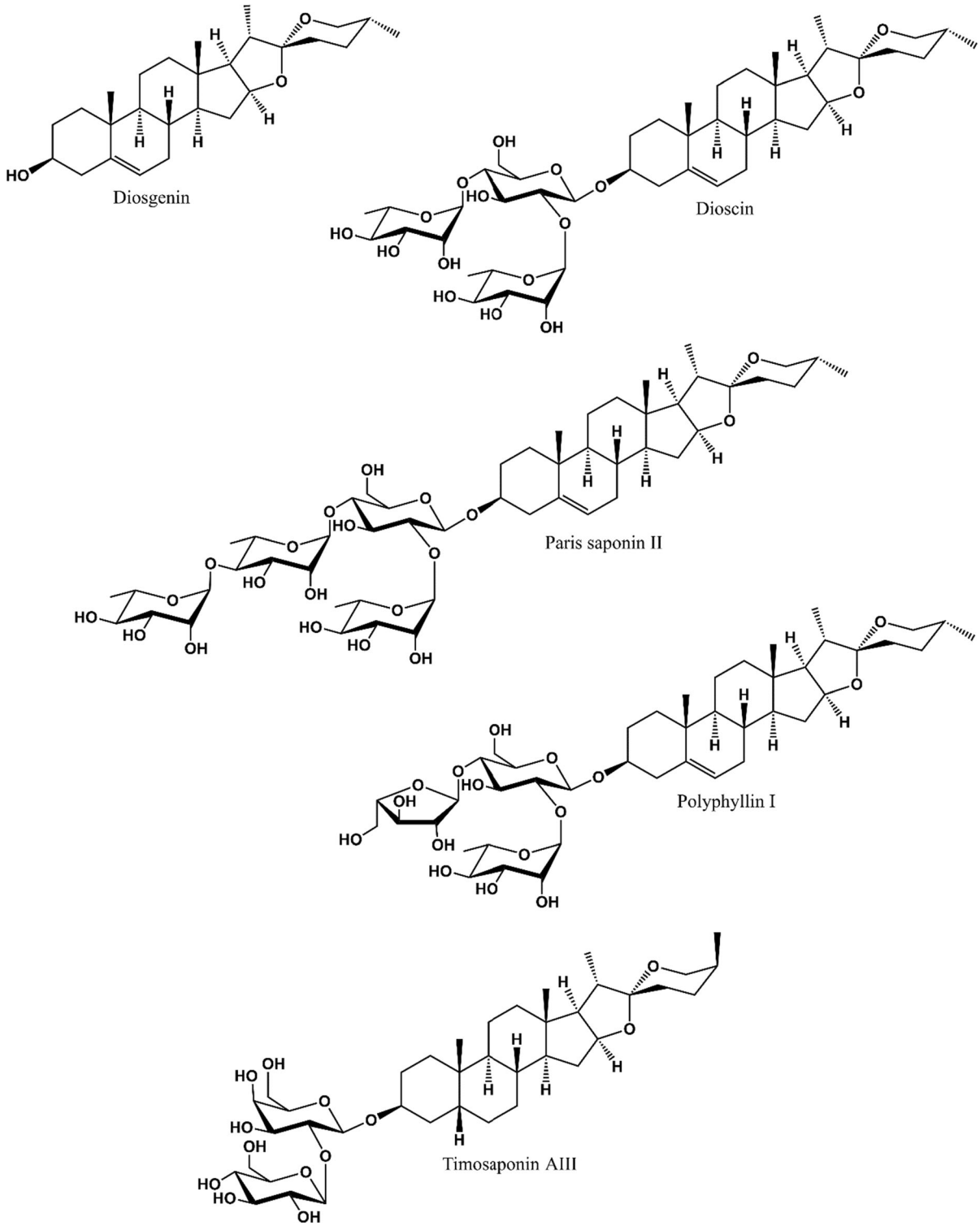

Fig. 3 Chemical structures of some of the promising anticancer steroidal saponins/sapogenins

chemotherapy (Stehi et al. 2018; Chen et al. 2015). Diosgenin was suggested to be a good candidate for lung cancer therapy as an inhibitor of hTERT gene expression (Rahmati-Yamchi et al. 2013). Its activity against lung cancer cell line A549 was time- and dose-dependent, with the best effect after 72 h. The compound revealed also antimetastatic potential, which was observed for example on breast cancer cell line MDA-MB-231 (He et al. 2014). A significant suppression of cell migration was seen at the concentration as low as 5 μM, after only 24 h of incubation, without affecting cell proliferation. Moreover, except from downregulation of STAT3 signaling pathway and the inhibition of human hepatocellular carcinoma cells proliferation, diosgenin also potentiated paclitaxel and doxorubicin apoptotic effects (Li et al. 2010). This synergistic effect may be of special importance for further studies of this compound. Diosgenin also downregulated the peroxidation reaction and enhanced the indigenous antioxidant defense system in female rats with NMU-induced mammary cancer (Jagadeesan et al. 2012). As cancer is often related to the hyperactivity of free radicals, this activity profile completes and expands the direct impact of diosgenin on cancer cells.

Dioscin Diosgenin 3-*O*-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc, is a spirostanol saponin found mostly in *Dioscorea* species; and also in other genera such as *Allium*, *Polygonatum,* and *Smilax* (Sobolewska et al. 2016; Rani et al. 2012; Xu et al. 2016; Wang et al. 2001; Tian et al. 2017). *Dioscorea nipponica* and *Dioscorea zingiberensis* are especially good sources of dioscin and provide raw material for the synthesis of steroid hormone drugs. Many pharmacological studies described antimicrobial, lipid-lowering, hepatoprotective, and anti-allergic activities of dioscin (Cho et al. 2013; Kwon et al. 2003; Tao et al. 2018). A large number of experimental data have confirmed not only its direct cytotoxicity towards cancer cells but also anti-inflammatory and immunoregulatory activities that may contribute to the widely reported anti-tumor effect (Tao et al. 2018; Wu et al. 2015).

Numerous studies were focused on the possible mechanism of antitumor activity of dioscin (Tab. S2). The compound was found to inhibit cancer cell viability via different pathways: G2/M cell arrest, induction of apoptosis and autophagy, downregulation of anti-apoptotic proteins, induction DNA damage mediated by ROS (Xu et al. 2016). Dioscin treatment increased cellular apoptosis in ovarian cancer SK-OV-3 cells in a dose-dependent manner. At the concentrations of 2.5 or 5 μM it significantly decreased PI3K and phosphorylated (*p*)-AKT, VEGFR2 protein expression compared with the non-treated control group, and induced expression of p-p38 protein (Guo and Ding 2018). Dioscin induced apoptosis in SGC-7901 cells in a dose-dependent manner (Hu et al. 2011). It was more active than hCPT (IC_{50} of 1.2 μg ml^{-1} and IC_{50} of 25.2 μg ml^{-1}, respectively).

Paris saponin II (PSII, formosanin C) Diosgenin 3-*O*-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc is one of the main active components of *Paridis rhizoma* obtained from *P. polyphylla* var. *yunnanensis* and *P. polyphylla* var. *chinensis*. This saponin was reported also in other *Paris* sp., as well as in *Cestrum*, *Allium*, *Ypsilandra*, and *Dioscorea* species (Xia et al. 2016; Ribeiro et al. 2016a, b; Sobolewska et al. 2006). With respect to the mechanisms underlying its cytotoxic activity it was found that paris saponin II induced apoptosis via activation of caspase 2, S-phase arrest, and suppressed expression of metalloproteinases MMP-1, -2, and -9 (Li et al. 2014; Man et al. 2011). Intraperitoneal administration of formosanin C at 15 and 25 mg kg^{-1} in a xenograft mouse model of ovarian cancer led to a 46% and 70% tumor growth inhibition, respectively (Xiao et al. 2012). It is noteworthy that a combination of PSII and curcumin exerted synergic anti-cancer activity on different lung cancer cells, revealed as the increase in the cellular uptake and the bioavailability of both compounds (Man et al. 2018). Additionally, formosanin C showed immunomodulatory activity when given intraperitoneally to mice. The compound activated natural killer cells and induced interferon production (Wu et al. 1990), what can be considered as another aspect of multitargeted anticancer treatment.

Polyphyllin I (PPI) Diosgenin 3-*O*-α-L-Rha-(1 → 2)-[β-L-Ara-(1 → 4)]-β-D-Glc, is a spirostanol saponin isolated from the rhizomes of *P. polyphylla*. Polyphyllin I significantly suppressed in vitro proliferation of A549, NCI-H460 and SK-MES-1 cell lines with significantly low values of IC_{50} 1.24, 2.40, and 2.33 μg ml^{-1}, respectively and the tumor growth of A549 cells in the nude mice (Kong et al. 2010). PPI inhibited also the vasculogenic mimicry formation in both hepatocellular carcinoma cell lines (HCC) and

xenografts of HCC (Xiao et al. 2018). The activity of PPI against osteosarcoma was examined both in vitro and in vivo, with interesting results. The compound was found to suppress in vitro growth of osteosarcoma 143-B and HOS cells, as well as the primary cells from a osteosarcoma patient and, what is more important, inhibited in vivo intratibial primary tumor growth in xenograft orthotopic mouse model. Moreover, it induced cell apoptosis, cell cycle arrest and inhibited the invasion and migration of osteosarcoma cells (Chang et al. 2017). Other interesting effects were obtained in the studies on concomitant administration of PPI with other compounds, including currently used chemotherapeutics. The combination of polyphyllin I and paris saponin II showed synergistic anti-tumor activity on HepG2 cells. Both compounds inhibited liver cancer growth through the induction of apoptosis, G1 phase arrest and inhibition of the cellular migration (Liu et al. 2016a). It was shown that the combined treatment of PPI and erlotinib resulted in the strengthened drug response and prolonged survival of lung cancer patients (Lou et al. 2017).

Timosaponin AIII (TAIII) Sarsasapogenin 3-*O*-β-D-Glc-(1 → 2)-β-D-Gal, was isolated by Kawasaki et al. in 1963 (Kawasaki and Yamauchi 1963; Kawasaki et al. 1963). It is the main active ingredient of the rhizomes of *Anemarrhena asphodeloides*. The compound exerts a wide range of pharmacological effects including anti-inflammatory, antiplatelet, antithrombotic, anti-diabetic, anti-depressant, improving learning and memory deficits activities (Han et al. 2018; Cong et al. 2016). In recent years, it was found that timosaponin AIII is a promising compound that inhibits the growth of a variety of tumor cells. In different studies it was reported that TAIII may induce autophagy in cancer cells followed by apoptotic cell death, cell cycle arrest in the G0/G1 and G2/M phases, and suppresses HGF-induced invasiveness of cancer cells (Sy et al. 2008; Huang et al. 2015).

Summary

A large number of experimental data that are published each year on antitumor potential of steroidal saponins and their interesting results indicate that these natural compounds are considered to be valuable research targets in the process of development of novel chemotherapeutics for human cancers. Similarly to previous years, the majority of experiments were performed in in vitro conditions with a relatively small number of compounds to enter in vivo studies. Assays performed on human cancer-derived cell lines were definitely predominant over animal cell models. Interestingly several cell lines were used most widely and the pool of experimental data is therefore more conclusive. These include: HepG2—human hepatocellular carcinoma, MCF-7—human breast adenocarcinoma, and A549—human lung adenocarcinoma. Based on the studies summarized in this review (see Tab. 1), it can be seen that the analyzed steroidal saponins/sapogenins revealed a differentiated cytotoxic effect. It is worth noting, however, that tests in which normal cell lines were included in the study accounted for only about 4% of all assays conducted on human cell lines. In addition, simultaneous studies on the cytotoxic activity of a given compound on cancer cells and normal cells derived from the same organ or tissue were extremely rare. Thus, it is difficult to draw more general conclusions with regard to selectivity of steroidal saponins towards cancer cells. Similarly, studies relevant to structure–activity relationships are lacking. It is noteworthy that some species containing steroidal saponins have been more frequently evaluated as sources of cytotoxic compounds in comparison to other, three of them were especially extensively analysed: *A. asphodeloides*, *P. polyphylla* var. *yunanensis*, and *O. japonicus*.

Several compounds, such as diosgenin, dioscin, paris saponin II, polyphyllin I, and timosaponin AIII seem to be specially promising as candidates for future antitumor agents. Not only their activity has been confirmed by numerous studies, but also these compounds are easily accessible for isolation being present in substantial amounts in several plant species. All of them have revealed multidirectional mechanisms of cytotoxicity as well as other effects, e.g. anti-inflammatory, that may contribute to the overall antitumor activity. Moreover, they were effective not only in in vitro assays, but also in animal models and in most cases a significant reduction in tumor size and angiogenesis was seen, especially with respect to prostate, breast, and lung cancers, of which non-small lung cancer seems to be most susceptible. Further studies on steroidal saponins with respect to their anticancer potential are certainly needed and worth continuing with more attention paid to compound

selectivity and synergistic effects of combinations with currently applied chemotherapeutics.

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