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: Amaranthaceae (Amaranthus, 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).
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 sapogenins, 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 sapogenins from Chinese plants. In a recent paper by Zhao et al. (2018), advances in antitumor potential of steroidal sapogenins 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-F, 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 normal 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) IC50 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, 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 cambodiensis’ dragon’s blood which are glycosides of diosgenin, penogenin and spirost-5,25(27)-dien-1β,3β-diol, exerted stronger cytotoxic activity (IC50: 1.72 μM, 5.09 μM, 4.77 μM, respectively) against K-562 cells than paclitaxel (IC50: 5.98 μM), while a penogenin glycoside showed higher cytotoxic effect on BEL-7402 than paclitaxel (IC50: 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 (IC50: 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 (IC50: 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 (IC50: 2.4 ± 0.35 and 3.3 ± 0.19 μM, respectively) higher than dioscin (IC50: 3.1 ± 0.39 μM and 4.9 ± 0.32 μM, respectively) and cisplatin (IC50: 30.3 ± 0.33 μM and 40.2 ± 0.44 μM, respectively) (Beit-Yannai et al. 2011).
| Source                  | Compound                                                                 | Cell line | Concentration | Assay                      | References                  |
|-------------------------|---------------------------------------------------------------------------|-----------|---------------|----------------------------|----------------------------|
| *Agave sisalana* leaves | 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     | Methylene blue dye assay   | Chen et al. (2011b)         |
|                         |                                                                           | 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 | 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          | XTT assay                  | Rezgui et al. (2014)        |
|                         | 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   | Nigrosides A1/A2                                                          | HCT 116   | 47.8          | MTT assay                  | Jabrane et al. (2011)       |
|                         |                                                                           | 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        |                            |                            |
| Source                  | Compound                                                                 | Cell line | Concentration | Assay  | References                  |
|------------------------|--------------------------------------------------------------------------|-----------|---------------|--------|-----------------------------|
| *Allium schoenoprasum* | whole plant                                                             |           |               |        |                             |
|                        | (25R)-5α-spirostan-3β,11α-diol 3-O-β-ᴅ-Glc-(1→3)[β-ᴅ-Glc-(1→4)]-O-β-ᴅ-Gal | HCT 116   | 8.45          | MTT    | Timité et al. (2013)        |
|                        | Laxogenin 3-O-α-L-Rha-(1→2)-O-β-ᴅ-Glc                                    | HT-29     | 8.64          |        |                             |
|                        |                                                                          | HCT 116   | > 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                                                                   |           |               |        |                             |
|                        | Vavilosides A1/A2                                                        | J-774     | 5.1           | MTT    | Zolfaghari et al. (2013)    |
|                        |                                                                          | 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 |                                                                     |           |               |        |                             |
|                        | Timosaponin AIII                                                        | HCT-15    | 6.1           | SRB    | Kang et al. (2011)          |
|                        |                                                                          | 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 |                                                                     |           |               |        |                             |
|                        | Timosaponin BI                                                          | HT-29     | 14.3          |        | Guo et al. (2015)           |
|                        |                                                                          | 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          |        |                             |
| Source                          | Compound                     | Cell line   | Concentration | Assay     | References       |
|--------------------------------|------------------------------|-------------|---------------|-----------|------------------|
|                                | Anemarsaponin F              | HT-29       | 2.2           | MTT       | Yang et al. (2017) |
|                                | Schidigerasaponin F2         | HT-29       | 4.04          | MTT       |                   |
|                                | Doxorubicin (control)        | BEL-7402    | 0.3           | MTT       |                   |
|                                |                              | HT-29       | 0.46          | MTT       |                   |
|                                |                              | HeLa        | 6.91          | MTT       |                   |
|                                |                              | MDA-MB-468  | 1.6           | MTT       |                   |
|                                | Anemarrhena asphodeloides    | IC₅₀ (µM)   | 43.90 ± 3.36  | MTT assay | Yang et al. (2017) |
|                                | rhizomes                     | HepG2       |               |           |                  |
|                                | Anemarsaponin R              | HepG2       | 57.90 ± 2.88  | MTT       | Zhang et al. (2017) |
|                                |                              | SGC7901     |               |           |                  |
|                                | Timosaponin E1               | HepG2       | 8.20 ± 1.25   | MTT       |                   |
|                                |                              | SGC7901     | 6.25 ± 2.18   | MTT       |                   |
|                                | Schidigerasaponin F2         | MCF-7       | 98 ± 8.98     | MTT       | Zhang et al. (2018) |
|                                |                              | SW480       | 97.02 ± 14.99 | MTT       |                   |
|                                |                              | HepG2       | > 100         | MTT       |                   |
|                                |                              | SGC7901     | > 100         | MTT       |                   |
|                                | Anemarsaponin F              | MCF-7       | 2.76 ± 0.59   | MTT       | Zhang et al. (2018) |
|                                |                              | SW480       | 5.56 ± 1.50   | MTT       |                   |
|                                |                              | HepG2       | 11.73 ± 1.24  | MTT       |                   |
|                                |                              | SGC7901     | 8.18 ± 0.26   | MTT       |                   |
|                                | Timosaponin AI               | MCF-7       | 6.83 ± 1.99   | MTT       |                   |
|                                |                              | SW480       | 4.17 ± 0.72   | MTT       |                   |
|                                |                              | HepG2       | 7.83 ± 1.72   | MTT       |                   |
|                                |                              | SGC7901     | 4.38 ± 0.50   | MTT       |                   |
|                                | Timosaponin AIII (control)   | MCF-7       | 3.34 ± 1.10   | MTT       |                   |
|                                |                              | SW480       | 2.94 ± 1.05   | MTT       |                   |
|                                |                              | HepG2       | 4.96 ± 0.93   | MTT       |                   |
|                                |                              | SGC7901     | 12.15 ± 1.36  | MTT       |                   |
|                                | Anemarrhena asphodeloides    | IC₅₀ (µM)   | 38.4 ± 2.4    | MTT assay | Yang et al. (2018) |
|                                | rhizomes                     | HepG2       |               |           |                  |
|                                | Aneglycoside A               | HeLa        | 29.7 ± 0.19   | MTT       |                   |
|                                |                              | SGC7901     | > 100         | MTT       |                   |
|                                | Aneglycoside B               | HepG2       | 41.8 ± 3.5    | MTT       |                   |
|                                |                              | HeLa        | 34.2 ± 3.6    | MTT       |                   |
|                                |                              | SGC7901     | > 100         | MTT       |                   |
|                                | Timosaponin U                | HepG2       | 61.8 ± 4.1    | MTT       |                   |
| 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          |           |               |       |                 |
|                      | 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             |           |               |       |                 |
|                      | 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          |           |               |       |                 |
|                      | (25R)-26-O-β-D-Glc-furost-5,20-dien-3β,26-diol-3-O-β-D-Glc (1 → 2)-[β-β-D-Glc-(1 → 3)]-β-D-Glc-(1 → 4)-β-D-Gal | A549 | 3.8 | Zuo et al. (2018) |
|                      |                   | 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 | Yang et al. (2016b) |
|                      |                   | Caski     | 1.5           |       |                 |
|                      |                   | HepG2     | 0.7           |       |                 |
|                      |                   | MCF-7     | 1.7           |       |                 |
| **Avena sativa**     | bran              |           |               |       |                 |
|                      | Avenacoside B     | HCT 116   | 175.3         |       |                 |
| Source                      | Compound                  | Cell line          | Concentration | Assay | References                  |
|-----------------------------|---------------------------|--------------------|---------------|-------|-----------------------------|
| *Balanites aegyptiaca*      |                           |                    | IC₅₀ (µM)      | MTT   | Beit-Yannai et al. (2011)   |
| fruits and roots            | 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 ± 0.52   |       |                             |
|                             |                           | 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    |                           |                    | IC₅₀ (µM)      | SRB   | 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||               |
| Source        | Compound                                                                 | Cell line | Concentration | Assay       | References                  |
|---------------|---------------------------------------------------------------------------|-----------|---------------|-------------|-----------------------------|
| *Bletilla striata* roots | (1α,3α)-1-O-[(β-D-Xyl-(1 → 2)-α-L-Rha)]-3-O-β-D-Glc-5α-spirostan        | A549      | 12.3          | MTT assay   | Wang and Meng (2015)        |
|               |                                                                           | 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-β-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          |             |                             |
| Source          | Compound                                                                 | Cell line | Concentration | Assay     | References                  |
|-----------------|---------------------------------------------------------------------------|-----------|---------------|-----------|------------------------------|
| Cestrum laevigatum leaves | (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) | MTT assay | Ribeiro et al. (2016a)     |
|                 |                                                                           | 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 | (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) |           |                              |
| Source                  | Compound                                      | Cell line | Concentration | Assay     | References       |
|------------------------|-----------------------------------------------|-----------|---------------|-----------|------------------|
| **Cestrum parqui leaves** | Parquispiroside                               | HeLa      | 7.7 ± 1.5     | CCK-8     | Mosad et al. (2017) |
|                        |                                               | 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** | Chlorodeistelanoside A                      | SW480     | > 22.12       | XTT       | Tabopda et al. (2016) |
|                        |                                               | H9c2      | > 22.12       |           |                  |
|                        | Chlorodeistelanoside 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** | 25-R-Spirosta-3,5-dien-12β-ol               | 5-8F      | 24.8          | CCK-8     | Chu et al. (2018) |
|                        | Diosgenin                                     | 5-8F      | 41.9          |           |                  |
| **Chlorophytum orchidastrum roots** | Orchidastroside A                          | HCT 116   | 1.6           | MTT       | Acharya et al. (2010) |
|                        |                                               | 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)      | MTT assay     | Fouedjou et al. (2014)     |
|                               |                           | HT-29     | 2.1           |               |                            |
| Cordyline fruticosa leaves    | Fruticoside H             |           | 69.68         | MTT assay     | Selim and Al Jaouni (2015) |
|                               | Fruticoside I             |           | 50.45         | MTT assay     |                            |
|                               | Fruticoside J             |           | > 200         | MTT assay     |                            |
| Cisplatin (control)           |                           | MDA-MB231 | 7.28          | MTT assay     | Selim and Al Jaouni (2015) |
| Costus speciosus tuber        | Diosgenin                 | HepG2     | 32.62         | MTT assay     |                            |
|                               |                           | HL-60     | 22.98         | MTT assay     |                            |
|                               |                           | MCF-7     | 11.03         | MTT assay     |                            |
| Paclitaxel (control)          |                           | HepG2     | 0.48          | SRB assay     |                            |
| Cynanchum paniculatum roots   | Cynanside A               | A549      | > 30          | SRB assay     | Kim et al. (2013)          |
|                               |                           | SK-OV-3   | > 30          | SRB assay     |                            |
|                               |                           | SK-MEL-2  | 26.55         | SRB assay     |                            |
|                               |                           | HCT-15    | > 30          | SRB assay     |                            |
| Doxorubicin (control)         |                           | A549      | 0.029         | SRB assay     | Mai et al. (2017)          |
|                               |                           | SK-OV-3   | 0.036         | SRB assay     |                            |
|                               |                           | SK-MEL-2  | 0.001         | SRB assay     |                            |
|                               |                           | HCT-15    | 2.041         | SRB assay     |                            |

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| Source                  | Compound | Cell line | Concentration | Assay | References |
|------------------------|----------|-----------|---------------|-------|------------|
|                        | 3-0-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  |            |
| Source                        | Compound                                                                 | Cell line | Concentration | Assay   | References                  |
|-------------------------------|---------------------------------------------------------------------------|-----------|---------------|---------|-----------------------------|
|                               |                                                                          |           | IC₅₀ (µM)     |         |                             |
|                               |                                                                          | HT29      | 50.0 ± 0.90   | MTT     | Kirmizibezkmez et al. (2014) |
|                               |                                                                          | MCF-7     | 50.0 ± 0.15   |         |                             |
|                               |                                                                          | HT29      | 50.0 ± 0.20   |         |                             |
|                               |                                                                          | MCF-7     | 36.5 ± 0.08   |         |                             |
|                               |                                                                          | PC3       | > 50          |         |                             |
|                               |                                                                          | HT29      | 10.0 ± 0.25   |         |                             |
|                               |                                                                          | MCF-7     | 46.0 ± 0.15   |         |                             |
|                               |                                                                          | PC3       | > 50          |         |                             |
|                               |                                                                          | HT29      | 1.2 ± 0.05    |         |                             |
|                               |                                                                          | MCF-7     | 1.0 ± 0.01    |         |                             |
|                               |                                                                          | PC3       | 1.5 ± 0.05    |         |                             |
|                               |                                                                          | HT29      | 4.87          |         |                             |
|                               |                                                                          | HT-29     | 31            |         |                             |
|                               |                                                                          | HCT 116   | 48.7          |         |                             |
|                               |                                                                          | HCT 116   | 37.41         |         |                             |
|                               |                                                                          | HT-29     | 42.43         |         |                             |
|                               |                                                                          | HCT 116   | 2.17          |         |                             |
|                               |                                                                          | HT-29     | 1.64          |         |                             |
|                               |                                                                          | HCT 116   | 2.65 10⁻³     |         |                             |
|                               |                                                                          | HT-29     | 2.29 10⁻³     |         |                             |
|                               |                                                                          | SK-OV-3   | > 20          |         |                             |
|                               |                                                                          | B16       | > 20          |         |                             |
|                               |                                                                          | LL2       | > 20          |         |                             |
|                               |                                                                          | C26       | > 20          |         |                             |
|                               |                                                                          | A549      | > 20          |         |                             |
|                               |                                                                          | HEK293    | > 20          |         |                             |
|                               |                                                                          | SK-OV-3   | > 20          |         |                             |
Table 1 continued

| Source  | Compound              | Cell line | Concentration | Assay | References |
|---------|-----------------------|-----------|---------------|-------|------------|
|         | 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   |       |            |
| Source                      | Compound                                                                 | Cell line | Concentration  | Assay         | References                  |
|-----------------------------|--------------------------------------------------------------------------|-----------|----------------|---------------|-----------------------------|
| A549                        | Doxorubicin (control)                                                    | K562      | 1.27           | MTT assay     | Shen et al. (2014)          |
| HEK293                      |                                                                          | BEL-7402  | 4.72           | MTT assay     |                             |
| SK-OV-3                     |                                                                          | SGC-7901  | 2.88           | MTT assay     |                             |
| B16                         | Diosgenin 3-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 3)]-β-D-Glc                    | K562      | 5.09           | MTT assay     |                             |
| LL2                         | Pennogenin 3-α-L-Rha-(1 → 2)-[α-L-Rha-(1 → 3)]-β-D-Glc                   | K562      | 1.13           | MTT assay     |                             |
| C26                         | 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           | MTT assay     |                             |
| A549                        | Paclitaxel (control)                                                     | BEL-7402  | 6.44           | MTT assay     |                             |
| HEK293                      |                                                                          | SGC-7901  | 5.61           | MTT assay     |                             |
| SK-OV-3                     | Neoruscogenin 1-O-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 3)]-α-L-Ara              | HT-29     | 6.04           | MTT assay     | Kougan et al. (2010)        |
| HCT 116                     | values in the range 7.60–70.73                                           |           |                |               |                             |
| Manioside A                 |                                                                          | HT-29     | 1.67           | Acid           |                             |
| HCT 116                     |                                                                          | HT-116    | 2.04           | phosphatase    |                             |
| Spiroconazol A              |                                                                          | HT-29     | 3.21           | MTT assay     |                             |
| HCT 116                     |                                                                          | HT-116    | 1.4            | MTT assay     |                             |
| Paclitaxel (control)        |                                                                          | HT-29     | 1.4            | MTT assay     |                             |
| HCT 116                     |                                                                          | HT-116    | 1.4            | MTT assay     |                             |
| Saponin fraction            |                                                                          | HepG2     | 13.4           | Acid           |                             |
| MCF7                        |                                                                          |           | 35             | phosphatase    |                             |
| Methylprotogracillin        |                                                                          | HepG2     | 29.8           | MTT assay     |                             |
| MCF7                        |                                                                          |           | > 50           | MTT assay     |                             |
| Source                    | Compound                     | Cell line | Concentration | Assay   | References          |
|--------------------------|------------------------------|-----------|---------------|---------|---------------------|
|                          | Methylprotodioscin           | HepG2     | 29.8          |         |                     |
|                          |                              | MCF7      | > 50          |         |                     |
|                          | Adriamycin (control)         | HepG2     | 6.9           |         |                     |
|                          |                              | MCF7      | 2.5           |         |                     |
| Dracaena viridiflora     | IC₅₀ (µg ml⁻¹) MTT assay     | Teponno et al. (2017) |
| leaves                   | 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| IC₅₀ (µM) MTT assay           | Shen et al. (2012) |
| bulbs                    | Pallidiflside 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 (control)        | C6        | 24.8 ± 1.8    |         |                     |
|                          |                              | HeLa      | 28.3 ± 1.4    |         |                     |
| Lilium longiflorum       | IC₅₀ (µM) MTT assay           | Esposito et al. (2013) |
| bulbs                    | (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 | | |
| Source | Compound | Cell line | Concentration | Assay   | References          |
|--------|----------|-----------|---------------|---------|---------------------|
|        | (22R,25R)-spirosol-5-en-3β-yl 3-O-α-L-Rha-(1→2)-[β-O-acetyl]-β-d-Glc-(1→4)]-β-d-Glc | 3T3 | 25.8 | IC₅₀ (µg ml⁻¹) | MTT assay | Wang et al. (2011) |
|        | (25R)-26-O-([β-d-Glc]-furost-5-en-3β,22α,26-triol 3-O-α-L-Rha-(1→2)-α-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 | | | | | |
|        | Lirigramoside A | SMMC-7721 | 76.4 ± 6.6 | IC₅₀ (µg ml⁻¹) | MTT assay | | |
|        | | 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 | | | | | | |
|        | (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 | | | | |
| Source | Compound | Cell line | Concentration | Assay | References |
|-------|----------|-----------|---------------|-------|------------|
| (25R)-Ruscogenin 1-O-β-D-Glc-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Xyl | MDA-MB-435 | 17.68 ± 2.50 | HepG2 | 29.48 ± 1.64 |
| | 95D | 17.83 ± 0.37 | HeLa | 22.23 ± 1.43 |
| | HepG2 | 19.48 ± 0.37 | MCF-7 | 42.16 ± 1.26 |
| | A549 | 43.20 ± 1.53 | | |
| | (25R)-Ruscogenin 1-O-α-L-Rha-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Glc | MDA-MB-435 | 19.63 ± 0.76 | 95D | 10.82 ± 0.18 |
| | 95D | 11.09 ± 0.17 | HepG2 | 15.26 ± 1.29 |
| | A549 | 26.36 ± 2.01 | HeLa | 42.56 ± 3.75 |
| | | | MCF-7 | 35.56 ± 1.46 |
| | (25S)-Ruscogenin 1-O-β-D-Glc-(1 → 2)-[α-α-L-Ara-(1 → 3)]-β-D-Fuc | MDA-MB-435 | 16.34 ± 0.60 | 95D | 14.34 ± 0.33 |
| | 95D | 14.76 ± 0.52 | A549 | 42.56 ± 3.75 |
| | | | HeLa | 24.69 ± 0.76 |
| | Neoruscogenin 1-O-β-D-Glc-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Xyl | MDA-MB-435 | 24.52 ± 0.91 | 95D | 36.12 ± 1.08 |
| | 95D | 24.30 ± 1.55 | A549 | 42.56 ± 3.75 |
| | | | HeLa | 35.21 ± 2.02 |
| | Neoruscogenin 1-O-α-L-Rha-l-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Glc | MDA-MB-435 | 17.54 ± 1.39 | 95D | 11.09 ± 0.15 |
| | | | HeLa | 24.30 ± 1.55 |
| | Neoruscogenin 1-O-β-D-Glc-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Fuc | MDA-MB-435 | 9.74 ± 0.62 | 95D | 10.64 ± 0.21 |
| | 95D | 8.00 ± 0.45 | A549 | 24.69 ± 0.76 |
| | | | HepG2 | 15.48 ± 0.52 |
| | | | HeLa | 11.02 ± 0.42 |
| | | | MCF-7 | 10.02 ± 0.73 |
| | | | A549 | 26.36 ± 2.01 |
| | (25R)-Ruscogenin 1-O-β-D-Glc-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Fuc | MDA-MB-435 | 4.71 ± 0.75 | 95D | 11.62 ± 2.00 |
| | 95D | 11.02 ± 0.17 | HepG2 | 22.36 ± 2.01 |
| | | | HeLa | 8.00 ± 0.45 |
| | | | MCF-7 | 23.56 ± 2.64 |
| | | | A549 | 5.91 ± 0.27 |
| | (25S)-Ruscogenin 1-O-β-D-Glc-(1 → 2)-[β-α-Xyl-(1 → 3)]-β-D-Fuc | MDA-MB-435 | 5.91 ± 0.27 | 95D | 11.20 ± 0.17 |
| | 95D | 12.76 ± 0.74 | HepG2 | 11.02 ± 0.73 |
| | | | 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 | | | | |
| 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 | 29.12 ± 4.66 | | |
| | A549 | 256.8 ± 19.03 | | |
| 5-FU (control) | MDA-MB-435 | 120 ± 15.53 | | |
| | HepG2 | 87.3 ± 12.10 | | |
| | A549 | 256.8 ± 19.03 | | |
| Ophiopogon japonicus tuberous roots | | | | |
| Ophiopogonin Q | | | | |
| Pennogenin 3-O-[2-O-acetyl-α-L-Rha- (1 → 2)]-[β-D-Xyl-(1 → 4)]-β-D-Glc | | | | |

**Note:** Wu et al. (2018), Li et al. (2013)
| Source           | Compound                                 | Cell line | Concentration | Assay | References            |
|------------------|------------------------------------------|-----------|---------------|-------|-----------------------|
| Ophiopogon japonicus tubers | Diosgenin 3-O-[2-O-acetyl-α-L-Rha-(1 → 2)][β-D-Xyl-(1 → 4)]-β-D-Glc | HeLa      | 24 h          | 4.26  |                       |
|                  |                                          | HepG2     | 24 h          | 3.30  |                       |
|                  |                                          |           | 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  |                       |
|                  |                                          |           | 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 fibrous roots | Ophiopogonin D’                       | MG-63     | 3.09          |       | Wang et al. (2017a)   |
|                  | Diosgenin 3-O-[2-O-acetyl-α-L-Rha-(1 → 2)][β-D-Xyl-(1 → 3)]-β-D-Glc | SNU-387   | 3.63          |       |                       |
|                  | Cisplatin (control)                      | MG-63     | 1.9           |       |                       |
|                  |                                            | SNU-387   | 0.76          |       |                       |
|                  |                                            | MG-63     | 11.31         |       |                       |
|                  |                                            | SNU-387   | 5.59          |       |                       |
|                  | (25R)-Ruscogenin-3-yl α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc | HeLa      | 9.14          |       |                       |
|                  | Diosgenin-3-yl 2-O-acetyl-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc | HEp2      | 11.27         |       |                       |
|                  | Pennogenin-3-yl 2-O-acetyl-α-L-Rha-(1 → 2)-[β-D-Xyl-(1 → 4)]-β-D-Glc | HeLa      | 10.77         |       |                       |
|                  |                                            | HEp2      | 10.08         |       |                       |
|                  |                                            | HeLa      | 13.46         |       |                       |
Table 1 continued

| Source                  | Compound                                                                 | Cell line | Concentration | Assay               | References               |
|-------------------------|--------------------------------------------------------------------------|-----------|---------------|----------------------|--------------------------|
| *Ophiopogon japonicus*  | fibrous roots                                                            | HEp2      | 13.32         | IC$_{50}$ (µg ml$^{-1}$) | MTT assay | Duan et al. (2018)       |
|                         | Fibrophiopoginin A                                                      | A375      | 201.1         |                      |                          |                          |
|                         | Fibrophiopoginin B                                                      | A375      | 42.06         |                      |                          |                          |
|                         | (25R)-26-[(O-β-D-Glc-(1 → 2)-β-D-Glc)-22α-hydroxyfurost-5-ene-3-O-[α-1-Rha-(1 → 2)]-β-D-Glc | MCF-7     | 45.32         |                      |                          |                          |
|                         |                                                                          | 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-1-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-1-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-1-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-1-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     |                      |                          |                          |
| Source | Compound | Cell line | Concentration | Assay | References |
|--------|----------|-----------|---------------|-------|------------|
| *Paris polyphylla* rhizomes | | | IC50 (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) | | | IC50 (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 | | | IC50 (µM) | MTT assay | Wu et al. (2012b) |
| | (3β,25R)-spirost-5-en-3-ol-3-O-β-D-Apis-(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-Apis-(1→3)-[α-L-Rha-(1→2)]-β-D-Glc | CNE | 3.57 ± 1.05 | | |
| | (3β,17α,25R)-spirost-5-ene-3,17-diol-3-O-β-D-Glc-(1→5)-α-L-Ara-(1→4)-[α-L-Rha-(1→2)]-β-D-Glc | CNE | 9.50 ± 0.80 | | |
| | (3β,17α,25R)-spirost-5-ene-3,17-diol-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-Glc-(1→5)-α-L-Ara-(1→4)-[α-L-Rha-(1→2)]-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 | | |
| Source                      | Compound                                                                 | Cell line | Concentration | Assay     | References       |
|----------------------------|----------------------------------------------------------------------------|-----------|---------------|-----------|------------------|
|                            | (3β,7β,25R)-spirost-5-en-3,7-diol-3-O-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 164.43 ± 15.0 | MTT assay | Wu et al. (2017a) |
|                            | (3β,7α,25R)-spirost-5-en-3,7-diol-3-O-α-L-Ara-(1 → 4)-β-D-Glc              | CNE       | 1.50 ± 0.14   | MTT assay | Wu et al. (2017a) |
|                            | (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  | MTT assay | Wu et al. (2017a) |
|                            | (3β,17α,25R)-spirost-5-en-3,17-diol-3-O-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-β-D-Glc | CNE       | 2.51 ± 0.42   | MTT assay | Wu et al. (2017a) |
|                            | (3β,25R)-spirost-5-en-3-ol-3-O-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 7.28 ± 1.10   | MTT assay | Wu et al. (2017a) |
|                            | (3β,25R)-spirost-5-en-3-ol-3-O-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 95.98 ± 0.65  | MTT assay | Wu et al. (2017a) |
|                            | (3β,17α,25R)-spirost-5-en-3,17-diol-3-O-α-L-Ara-(1 → 4)-β-D-Glc            | CNE       | 5.92 ± 0.83   | MTT assay | Wu et al. (2017a) |
|                            | (3β,17α,25R)-spirost-5-en-3,17-diol-3-O-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 50.46 ± 2.90  | MTT assay | Wu et al. (2017a) |
|                            | (3β,25R)-3-hydroxy-3-hydroxyspirost-5-en-3-ol-3-O-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 23.73 ± 1.53  | MTT assay | Wu et al. (2017a) |
| *Paris polyphylla* var.   | *yunnanensis* rhizomes                                                    |           |               |           |                  |
|                            | (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         | MTT assay | Wu et al. (2012a) |
|                            | Parisyunnanoside I                                                         | CNE       | 33.1          | MTT assay | Wu et al. (2012a) |
|                            | Cisplatin (control)                                                        | CNE       | 9.35          | MTT assay | Wu et al. (2012a) |
| *Paris polyphylla* var.   | *yunnanensis* roots                                                        |           |               |           |                  |
|                            | (3β,25R)-spirost-5-en-3-ol-3-O-α-L-Rha-(1 → 2)-β-D-Glc                     | CNE       | 9.2 ± 0.7     | MTT assay | Wu et al. (2012a) |
|                            | (3β,25R)-spirost-5-en-3-ol-3-O-β-D-Glc-(1 → 3)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 52.9 ± 3.7    | MTT assay | Wu et al. (2012a) |
|                            | (3β,25R)-spirost-5-en-3-ol-3-O-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 4.7 ± 1.1     | MTT assay | Wu et al. (2012a) |
|                            | (3β,17α,25R)-spirost-5-en-3,17-diol-3-O-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 11.1 ± 4.7    | MTT assay | Wu et al. (2012a) |
|                            | (3β,17α,25R)-spirost-5-en-3,17-diol-3-O-α-L-Ara-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | CNE       | 2.7 ± 1.1     | MTT assay | Wu et al. (2012a) |
|                            | Cisplatin (control)                                                        | CNE       | 23.7 ± 1.5    | MTT assay | Wu et al. (2012a) |
| Source                        | Compound                                      | Cell line   | Concentration | Assay     | References                |
|------------------------------|-----------------------------------------------|-------------|---------------|-----------|---------------------------|
| *Paris polyphylla* var.      | Parisyunnanoside H                            | HEK293      | 0.9           | MTT assay | Wen et al. (2015)         |
| *yunnanensis* rhizomes       |                                               | HepG2       | 5.6           |           |                           |
|                              | Paris saponin I                               | HEK293      | 1.8           | MTT assay |                           |
|                              |                                               | HepG2       | 1.8           |           |                           |
|                              | Trigofoenoside A                              | HEK293      | 3.4           | MTT assay |                           |
|                              |                                               | HepG2       | 5.6           |           |                           |
|                              | Dichotomin                                    | HEK293      | 0.58          | MTT assay |                           |
|                              |                                               | HepG2       | 0.9           |           |                           |
|                              | Parisyunnanoside B                            | HEK293      | 2.5           | MTT assay |                           |
|                              |                                               | HepG2       | 1.2           |           |                           |
|                              | Pseudoproto-Pb                                | HEK293      | 1.8           | MTT assay |                           |
|                              |                                               | HepG2       | 1.8           |           |                           |
|                              | (−)-OddC (control)                            | HEK293      | 0.3           | MTT assay |                           |
|                              |                                               | HepG2       | 0.17          |           |                           |
| *Paris polyphylla* var.      | Nuatigenin 3-O-α-L-Rha-(1 → 2)-β-D-Glc       | HepG2       | 2.9 ± 0.5     | MTT assay | Qin et al. (2016)         |
| *yunnanensis* leaves         |                                               | HEK293      | 5.0 ± 0.6     |           |                           |
|                              | Abutiloside L                                 | HepG2       | 7.0 ± 0.8     | MTT assay |                           |
|                              |                                               | HEK293      | 12.9 ± 2.7    |           |                           |
|                              | Troxacitabine (control)                       | HepG2       | 0.17 ± 0.02   | MTT assay |                           |
|                              |                                               | HEK293      | 0.30 ± 0.03   |           |                           |
| *Paris quadrifolia*          | Saponin-rich fractions:                       | HL-60       | 13 ± 1.3      | MTT assay | Stefanowicz-Hajduk et al. (2011) |
| rhizomes                     | Solid residue                                 | HeLa        | 10 ± 0.5      | MTT assay |                           |
|                              |                                               | MDA-MB-468  | 27 ± 1.3      | MTT assay |                           |
|                              |                                               | fibroblasts | 28 ± 1.4      | MTT assay |                           |
|                              | Butanolic fraction                            | HL-60       | 15 ± 2        | MTT assay |                           |
|                              |                                               | HeLa        | 24 ± 1.2      | MTT assay |                           |
|                              |                                               | MDA-MB-468  | 60 ± 5        | MTT assay |                           |
|                              |                                               | fibroblasts | 60 ± 6        | MTT assay |                           |
| *Paris quadrifolia*          | Pennogenin 3-O-α-L-Rha-(1 → 4)-β-D-Glc       | HL-60       | 47 ± 2.8      | MTT assay | Gajdus et al. (2014)      |
| rhizomes                     | Pennogenin 3-O-α-L-Rha-(1 → 2)-β-D-Glc       | HL-60       | 16 ± 0.8      | MTT assay |                           |
|                              |                                               | HeLa        | 18 ± 0.9      | MTT assay |                           |
|                              |                                               | MCF-7       | 25 ± 1.5      | MTT assay |                           |
|                              | Pennogenin 3-O-α-L-Rha-(1 → 4)-[α-L-L-Rha-(1 → 2)]-β-D-Glc | HL-60 | 1.0 ± 0.04 | MTT assay | |
| Source | Compound                                                                 | Cell line | Concentration | Assay  | References                  |
|--------|---------------------------------------------------------------------------|-----------|---------------|--------|----------------------------|
|        | Pennogenin 3-O-α-L-Rha-(1 → 4)-α-L-Rha-(1 → 4)-[α-L-Rha-(1 → 2)]-β-D-Glc | HeLa      | 1.8 ± 0.072   | MTT    | Stefanowicz-Hajduk et al. (2015) |
|        |                                                                           | MCF-7     | 2.4 ± 0.096   |        |                            |
|        | Etoposide (control)                                                      | HL-60     | 2.0 ± 0.08    |        |                            |
|        | Mitoxantrone (control)                                                   | HeLa      | > 50          |        |                            |
|        |                                                                           | MCF-7     | > 50          |        |                            |
|        | Paris quadrifolia rhizomes                                               |           |               |        |                            |
|        | PS-1                                                                      | HeLa      | 0.93 ± 0.15   | MTT    | Jing et al. (2017)         |
|        |                                                                           | HaCaT     | 0.82 ± 0.13   |        |                            |
|        | PS-2                                                                      | HeLa      | 0.55 ± 0.01   | MTT    | Liu et al. (2018b)         |
|        |                                                                           | HaCaT     | 0.58 ± 0.04   |        |                            |
|        | Paris thibetica rhizomes                                                 |           |               |        |                            |
|        | PARIS saponin II                                                          | BEL-7402  | 0.48          |        |                            |
|        | Paris vietnamensis rhizomes                                               |           |               |        |                            |
|        | 25(R)-Diosgenin-3-O-α-L-Rha-(1 → 2)-α-L-Rha-(1 → 3)-β-D-Glc              | U251      | 2.16 ± 0.65   | CCK-8  | Teponno et al. (2016)     |
|        |                                                                           | 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   |        |                            |
|        | ACNU (control)                                                            | U87MG     | 2.97 ± 0.94   |        |                            |
|        |                                                                           | U251      | 0.96 ± 0.05   |        |                            |
|        |                                                                           | U87MG     | 0.88 ± 0.04   |        |                            |
|        | Sansevieria trifasciata aerial parts                                      |           |               |        |                            |
|        | Trifasciatoside B                                                         | HeLa      | 47.1          | MTT    | Raslan et al. (2017)      |
|        | Trifasciatoside D                                                         | HeLa      | 40.7          |        |                            |
|        | Trifasciatoside I                                                         | HeLa      | 26.5          |        |                            |
|        | Trifasciatoside J                                                         | HeLa      | 26.5          |        |                            |
|        | Sansevieria cylindrica aerial parts                                       |           |               |        |                            |
|        | (25S)-Ruscogenin-1-O-α-L-Rha-(1 → 2)-β-D-Glc                            | MCF-7     | 24 ± 1        | MTT    | Raslan et al. (2017)      |
|        |                                                                           | HCT 116   | 23 ± 1        |        |                            |
|        |                                                                           | HepG2     | 21 ± 1        |        |                            |
| Source                        | Compound                                                                 | Cell line         | Concentration | Assay   | References          |
|------------------------------|--------------------------------------------------------------------------|-------------------|---------------|---------|---------------------|
|                              | (25S)-Ruscogenin-3-\(O-\alpha-L-Rha-(1 \rightarrow 4)-\beta-D-Glc)     | MCF-7             | 12 ± 1        |         |                     |
|                              |                                                                          | HCT 116           | 11 ± 2        |         |                     |
|                              |                                                                          | HepG2             | 13 ± 1        |         |                     |
|                              | (25S)-Ruscogenin-3-\(\beta-D-Glc\)                                      | MCF-7             | > 50          |         |                     |
|                              |                                                                          | HCT 116           | > 50          |         |                     |
|                              |                                                                          | HepG2             | > 50          |         |                     |
|                              | (25S)-Ruscogenin-1-\(O-\alpha-L-Rha-(1 \rightarrow 2)-[\beta-D-Xyl-(1 \rightarrow 3)]-\alpha-L-Ara\) | MCF-7             | 7 ± 2         |         |                     |
|                              |                                                                          | HCT 116           | 4 ± 2         |         |                     |
|                              |                                                                          | HepG2             | 9 ± 2         |         |                     |
|                              | (25R)-26-\(O-\beta-D-Glc\)-furost-5-ene-1\beta,3\beta,22\alpha,26-tetrol-1-\(O-\alpha-L-Rha-(1 \rightarrow 2)-[\beta-D-Xyl-(1 \rightarrow 3)]-\alpha-L-Ara\) | 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\(_{50}\) (\(\mu\)M) | SRB assay   | Said et al. (2015) |
|                              |                                                                          | HCT 116           | 38           |         |                     |
|                              | 1\(\beta\)-Hydroxy-kryptogenin-1-\(O-\alpha-L-Rha-(1 \rightarrow 2)-\alpha-L-Ara\) | 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                                                  |                   | IC\(_{50}\) (\(\mu\)M) | MTT assay  | Sun et al. (2016) |
|                              | tubers                                                                   |                   |             |         |                     |
|                              | Taccaoside                                                               | SMMC-7721         | 24 h         | 2.55    |                     |
|                              |                                                                          |                   | 48 h         | 1.72    |                     |
|                              |                                                                          | BEL-7404          | 24 h         | 8.10    |                     |
|                              |                                                                          |                   | 48 h         | 5.94    |                     |
|                              | Smilacina japonica                                                       |                   | IC\(_{50}\) (\(\mu\)M) | MTT assay  | Liu et al. (2012c) |
|                              | rhizomes and roots                                                       |                   |             |         |                     |
|                              | 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      |
|-------------------------|---------------------------|-----------|---------------|----------|-----------------|
| **Smilax glaucochina**  |                           |           |               |          |                 |
| tubers                  |                           |           |               |          |                 |
| Glauco-chinaoside A     | SGC-7901                  |           | 2.7           | IC₅₀ (µM) | MTT assay       |
| Glauco-chinaoside B     | SGC-7901                  |           | 11.5          |          |                 |
| Glauco-chinaoside E     | SGC-7901                  |           | 6.8           |          |                 |
| Cisplatin (control)     | SGC-7901                  |           | Not specified |          |                 |
| **Smilax korthalsii**   |                           |           |               |          |                 |
| leaves                  |                           |           |               |          |                 |
| Diosgenin               | K562                      |           | 6.25          | IC₅₀ (µM) | MTT assay       |
|                         | 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      |                           |           |               |          |                 |
| Sarsaparilloside B      | NFF                       |           | > 50          | Inhibition of cell proliferation (µg ml⁻¹) | SRB assay |
|                         | 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            |          |                 |
| Source                      | Compound                                                                 | Cell line | Concentration | Assay  | References       |
|-----------------------------|--------------------------------------------------------------------------|-----------|---------------|--------|------------------|
| Parillin                    |                                                                          | HT29      | 14            |        |                  |
|                             |                                                                          | MCF-7     | 3.4           |        |                  |
|                             |                                                                          | MM96L     | 3.8           |        |                  |
|                             |                                                                          | K562      | 4.3           |        |                  |
| Smilax scobinicaulis rhizomes and roots | (25R)-5α-spirostan-3β, 6β-diol 3-O-β-D-Glc-(1 → 4)-\{α-L-Ara-(1 → 6)\}-β-D-Glc | A549      | 3.7           | MTT    | Zhang et al. (2013) |
|                             |                                                                          | LAC       | 5.7           |        |                  |
|                             |                                                                          | HeLa      | 3.64          |        |                  |
| Smilax scobinicaulis rhizomes |                                                                          | HCT 116   | 10.5          | MTT    | Shu et al. (2017) |
|                             |                                                                          | SGC-7901  | 21.4          |        |                  |
| Smilax trinervula rhizomes and roots |                                                                          | HCT 116   | 7.8           | MTT    | Liang et al. (2016) |
|                             |                                                                          | SGC-7901  | 15.8          |        |                  |
| Solanum glabratum var. sepicula aerial parts | 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          | MTT    | Abdel-Sattar et al. (2015) |
|                             |                                                                          | HT29      | > 2           |        |                  |
|                             |                                                                          | PC3       | 14            |        |                  |
|                             |                                                                          | HT29      | 16.7          |        |                  |
|                             |                                                                          | PC3       | > 32          |        |                  |
|                             |                                                                          | HT29      | > 32          |        |                  |
|                             |                                                                          | PC3       | 1.8           |        |                  |
|                             |                                                                          | HT29      | 3             |        |                  |
| Source                  | Compound                                                                 | Cell line | Concentration Assay | References                      |
|-------------------------|---------------------------------------------------------------------------|-----------|---------------------|---------------------------------|
| *Solanum incanum* roots | *(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   | IC<sub>50</sub> (μM) | MTT assay (with HCT 116 and HT-29) | Manase et al. (2012) |
|                         |                                                                          |           |                     |                                 |                    |
|                         | Protodioscin                                                             | HCT 116   | 62.42 ± 0.66        | XTT assay (with SW480, DU145 and EMT6) |                    |
|                         |                                                                          | 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<sup>-3</sup> |                                 |                    |
|                         |                                                                          | HT-29     | 2.29 × 10<sup>-3</sup> |                                 |                    |
|                         |                                                                          | SW480     | 13.22 ± 3.79        |                                 |                    |
|                         |                                                                          | DU145     | 41.26 ± 17.57       |                                 |                    |
|                         |                                                                          | EMT6      | > 200               |                                 |                    |
| *Solanum procumbens* whole plant | *(22R,25R)-16β-H-22α-N-spiroso-3β-ol-5-ene 3-O-α-L-Rha-(1→2)-[O-α-L-Rha-(1→4)]-β-D-Glc* | AS49      | IC<sub>50</sub> (μM) | MTT assay | Hien et al. (2018) |
|                         |                                                                          | MGC-803   | 45.6 ± 1.5          |                                 |                    |
|                         |                                                                          | HepG2     | 26.1 ± 0.6          |                                 |                    |
| *Solanum surattense* aerial parts | *(22R,23S,25R)-3β,6α,23-trihydroxy-5α-spirostane 6-O-β-D-Xyl-(1→3)-β-D-Qui* | AS49      | IC<sub>50</sub> (μM) | MTT assay | Lu et al. (2011) |
|                         |                                                                          | MGC-803   | 45.6 ± 1.5          |                                 |                    |
|                         |                                                                          | HepG2     | 26.1 ± 0.6          |                                 |                    |
| Source            | Compound                                                                 | Cell line | Concentration | Assay              | References               |
|-------------------|---------------------------------------------------------------------------|-----------|---------------|--------------------|--------------------------|
|                   | (22R,23S,25S)-3β,6α,23-trihydroxy-5α-spirostane 6-O-β-o-Xyl-(1 → 3)-O-β-D-Qui | MGC-803   | NA            |                   |                          |
|                   |                                                                           | HepG2     | NA            |                   |                          |
|                   |                                                                           | A549      | NA            |                   |                          |
|                   | (22R,23R,25S)-3β,6α,23-trihydroxy-5α-spirostane 6-O-β-o-Xyl-(1 → 3)-O-β-D-Qui | MGC-803   | 63.2 ± 0.8    |                   |                          |
|                   |                                                                           | HepG2     | NA            |                   |                          |
|                   |                                                                           | A549      | 62.5 ± 1.6    |                   |                          |
|                   | Khasianine                                                               | A549      | 26.7 ± 1.5    |                   |                          |
|                   | Solamargine                                                              | A549      | 15.7 ± 0.6    |                   |                          |
|                   |                                                                            | MGC-803   | 35.4 ± 0.7    |                   |                          |
|                   |                                                                            | HepG2     | 45.3 ± 2.1    |                   |                          |
|                   | Cisplatin (control)                                                      | A549      | 7.6 ± 1.6     |                   |                          |
|                   |                                                                            | MGC-803   | 3.5 ± 0.3     |                   |                          |
|                   |                                                                            | HepG2     | 8.7 ± 0.4     |                   |                          |
| Solanum violaceum | whole plant                                                               |           | IC₅₀ (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   |                   |                          |
| Source               | Compound                                                                 | Cell line       | Concentration | Assay   | References          |
|---------------------|---------------------------------------------------------------------------|-----------------|---------------|---------|---------------------|
| Ca9-22              | Borassoside E                                                             |                 |               |         |                     |
|                     |                                                                           |                 | 4.51 ± 0.24   |         |                     |
| MDA-MB-231          |                                                                           |                 | 7.25 ± 0.15   |         |                     |
| HepG2               |                                                                           |                 | 1.83 ± 0.12   |         | Shwe et al. (2010)  |
| Hep3B               |                                                                           |                 | 2.03 ± 0.03   |         |                     |
| MCF-7               |                                                                           |                 | 2.61 ± 0.10   |         |                     |
| A549                |                                                                           |                 | 2.34 ± 0.02   |         | Qin et al. (2017)   |
| Ca9-22              |                                                                           |                 | 2.33 ± 0.02   |         |                     |
| MDA-MB-231          |                                                                           |                 | 2.75 ± 0.10   |         | Qin et al. (2017)   |
| HepG2               | 3-O-chacotriosyl-(25S)-spirost-5-en-3β-ol                                |                 | 6.44 ± 0.45   |         | Shwe et al. (2010)  |
| Hep3B               |                                                                           |                 | 2.87 ± 0.04   |         |                     |
| MCF-7               |                                                                           |                 | 8.84 ± 0.12   |         |                     |
| A549                |                                                                           |                 | 4.09 ± 0.08   |         | Qin et al. (2017)   |
| Ca9-22              |                                                                           |                 | 3.77 ± 0.02   |         | Qin et al. (2017)   |
| MDA-MB-231          |                                                                           |                 | 5.84 ± 0.06   |         | Qin et al. (2017)   |
| HepG2               | Doxorubicin (control)                                                     |                 | 0.18 ± 0.00   |         | Qin et al. (2017)   |
| Hep3B               |                                                                           |                 | 1.31 ± 0.12   |         | Qin et al. (2017)   |
| MCF-7               |                                                                           |                 | 0.80 ± 0.03   |         | Qin et al. (2017)   |
| A549                |                                                                           |                 | 1.40 ± 0.02   |         | Qin et al. (2017)   |
| Ca9-22              |                                                                           |                 | 0.31 ± 0.01   |         | Qin et al. (2017)   |
| MDA-MB-231          |                                                                           |                 | 1.39 ± 0.00   |         | Qin et al. (2017)   |
| Tacca integrifolia  | rhizomes                                                                  |                 | IC₅₀ (µM)     | MTT assay|                     |
|                     | (3β,25R)-spirost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[β-D-Glc-(1 → 4)-6- | HeLa            | 72 h          | 3.0 ± 0.5| Shwe et al. (2010)  |
|                     | deoxy-α-L-Man-(1 → 3)]-β-D-Glc                                           |                 |               |         |                     |
|                     | (3β,25R)-spirost-5-en-3-yl 6-deoxy-α-L-Man-(1 → 2)-[6-deoxy-α-L-Man- | HeLa            | 72 h          | 1.2 ± 0.4| Qin et al. (2017)   |
|                     | (1 → 3)]-β-D-Glc                                                         |                 |               |         | Qin et al. (2017)   |
|                     | (3β,25R)-26-(β-D-Glc)-22-hydroxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → | HeLa            | 72 h          | 1.5 ± 0.3| Qin et al. (2017)   |
|                     | 2)-[6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc                                     |                 |               |         | Qin et al. (2017)   |
|                     | (3β,25R)-26-(β-D-Glc)-22-methoxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → | HeLa            | 72 h          | 3.5 ± 0.5| Qin et al. (2017)   |
|                     | 2)-[6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc                                     |                 |               |         | Qin et al. (2017)   |
|                     | (3β,25R)-26-(β-D-Glc)-22-hydroxyfurost-5-en-3-yl 6-deoxy-α-L-Man-(1 → | HeLa            | 72 h          | 4.0 ± 0.6| Qin et al. (2017)   |
|                     | 2)-[β-D-Glc-(1 → 4)-6-deoxy-α-L-Man-(1 → 3)]-β-D-Glc                   |                 |               |         | Qin et al. (2017)   |
| Podophyllotoxin (control) |                                                                  | HeLa            | 72 h          | 0.1 ± 0.02| Qin et al. (2017)   |
| Trillium kamtschaticum | whole plant                                                             |                 | IC₅₀ (µM)     | MTT assay|                     |
|                     | Trillicamtoside L                                                        | HCT 116         | 17.28 ± 2.69  |         | Qin et al. (2017)   |
| Source                        | Compound                                                                 | Cell line | Concentration | Assay                  | References          |
|------------------------------|---------------------------------------------------------------------------|-----------|---------------|------------------------|---------------------|
| Trillium tschonoskii rhizomes| Trillikamtside P                                                          | HCT 116   | 4.92 ± 1.00   |                        |                     |
|                              | Trillikamtside Q                                                          | HCT 116   | 22.48 ± 8.68  |                        |                     |
|                              | Trillikamtside R                                                          | HCT 116   | 5.84 ± 1.05   |                        |                     |
|                              | Camptothecin (control)                                                    | HCT 116   | 0.0115 ± 0.0009 |                      |                     |
|                              | *Trillium tschonoskii* rhizomes                                           |           |               |                        |                     |
|                              | Pennogenin 3-O-α-L-Rha-(1 → 2)[α-1-L-Rha-(1 → 4)]-β-D-Glc (TTB2)          | Rh1       | 48 h          | Trypan blue dye exclusion assay | Huang and Zou (2015) |
|                              | *Tupistra chinensis* rhizomes                                             |           |               |                        |                     |
|                              | Tupichinin A                                                              | HL-60     | 18.58         | MTT assay              | Pan et al. (2012)   |
|                              |                                                                           | 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                                             |           |               |                        |                     |
|                              | Tupisteroide C                                                            | A549      | 25.9          | MTT assay              | Liu et al. (2012b)  |
|                              | Mitomycin C                                                               | A549      | not specified | MTT assay              | Liu et al. (2012a)  |
|                              | *Tupistra chinensis* rhizomes                                             |           |               |                        |                     |
|                              | (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                                    |           |               |                        |                     |
|                              | (20S,22R)-Spirost-25 (27)-en-1β,3β,5β-trihydroxy-1-O-β-D-Xyl              | A549      | 86.63 ± 2.33  | MTT assay              | Li et al. (2015)    |
|                              |                                                                           | NCI-H1299 | 88.21 ± 1.34  |                        |                     |
| Source          | Compound                  | Cell line     | Concentration | Assay | References         |
|-----------------|---------------------------|---------------|---------------|-------|--------------------|
|                 | 5-FU (control)            | A549          | 38.65 ± 1.59  |       |                    |
|                 |                            | NCI-H1299     | 42.78 ± 1.63  |       |                    |
| Vernonia        | Vernonia amygdalina       |               |               |       |                    |
|                 | leaves                    |               |               |       |                    |
|                 |                            |               | Concentration |       | MTT assay          |
|                 |                            |               | not specified |       | Wang et al. (2018) |
|                 | Vernamioside A            | BT-549        | 63.61         |       |                    |
|                 |                            | MDA-MB-231    | 28.97         |       |                    |
|                 |                            | MCF-7         | 46.54         |       |                    |
|                 | Vernamioside B            | HeLa          | 42.05         |       |                    |
|                 |                            | BT-549        | 62.17         |       |                    |
|                 |                            | MDA-MB-231    | 27.78         |       |                    |
|                 |                            | MCF-7         | 37.07         |       |                    |
|                 | Vernamioside C            | HeLa          | 31.64         |       |                    |
|                 |                            | BT-549        | 34.18         |       |                    |
|                 |                            | MDA-MB-231    | 32.74         |       |                    |
|                 |                            | MCF-7         | 39.38         |       |                    |
|                 | Vernamioside D            | HeLa          | 26.73         |       |                    |
|                 |                            | BT-549        | 44.00         |       |                    |
|                 |                            | MDA-MB-231    | 31.53         |       |                    |
|                 |                            | MCF-7         | 31.36         |       |                    |
|                 | Vernamioside B2           | HeLa          | 32.93         |       |                    |
|                 |                            | BT-549        | 36.41         |       |                    |
|                 |                            | MDA-MB-231    | 33.61         |       |                    |
|                 |                            | MCF-7         | 49.72         |       |                    |
|                 | Vernamioside 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         |       |                    |
|                 | Ypsilandra thibetica      |               | IC50 (μM)     |       |                    |
|                 | whole plant               |               |               |       | MTT assay          |
|                 | Ypsilandroside H          | A549          | > 40          |       | Lu et al. (2010)   |
|                 | Ypsilandroside I          | HL-60         | Not specified |       |                    |
|                 | Ypsilandroside J          | PANC-1        |               |       |                    |
|                 | Ypsilandroside K          | SMMC-7721     |               |       |                    |
|                 | Ypsilandroside L          | SK-BR-3       |               |       |                    |
|                 | Polyphylloside III        |               |               |       |                    |
|                 | Cisplatin (control)       |               |               |       |                    |
| Source                  | Compound                                                 | Cell line | Concentration | Assay   | References                  |
|------------------------|----------------------------------------------------------|-----------|---------------|---------|-----------------------------|
| *Yucca dem-               | Smilagenin 3-O-[β-D-Glc-(1 → 2)-O-β-D-Gal]               | HCT 116   | 4.4 ± 0.47    | MTT assay | Eskander et al. (2013)     |
|                        |                                                          | MCF-7     | 4.0 ± 0.85    |         |                             |
|                        |                                                          | A549      | 16.5 ± 1.45   |         |                             |
|                        |                                                          | HepG2     | 3.5 ± 0.41    |         |                             |
|                        | Smilagenin 3-O-[β-D-Glc-(1 → 2)-O-β-D-Gal]               |            |               |         |                             |
|                        | Desmertianoside 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          |         | Tong et al. (2011)          |
|                        |                                                          | MCF-7     | 5.46          |         |                             |
|                        |                                                          | A549      | 0.84          |         |                             |
|                        |                                                          | HepG2     | 7.36          |         |                             |
|                        | Deltonin                                                | C26       | 48 h          | 1.22 ± 0.22 | MTT assay | Tao et al. (2011)         |
|                        |                                                          | SW620     | 48 h          | 1.29 ± 0.69 |         |                             |
|                        |                                                          | SW480     | 48 h          | 1.30 ± 0.05 |         |                             |
|                        |                                                          | LOVO      | 48 h          | 2.11 ± 0.68 |         |                             |
|                        | Deltonin                                                |            |               |         |                             |
|                        | Dioscin                                                 | PC3       | 5.6           | CCK-8 assay | Tong et al. (2014)         |
|                        |                                                          |           | IC<sub>50</sub> (μM) |         |                             |
|                        | Dioscin                                                 | C26       | 7.36          |         | Zhiyu et al. (2012)        |
|                        |                                                          | EA.hy926  | 3.87          |         |                             |
|                        |                                                          | HUVEC     | 1.6           |         |                             |
|                        |                                                          | IC<sub>50</sub> (μM) |         |         |                             |
|                        | Dioscin                                                 | KYSE 510  | 5.4           |         | Rahmati-Yamchi et al. (2013)|
|                        |                                                          |           | IC<sub>50</sub> (μM) |         |                             |
|                        | Diosgenin                                               | A549      | 24 h          | 47      | MTT assay | Mirunalini et al. (2011)   |
|                        |                                                          | 48 h      | 44            |         |                             |
|                        |                                                          | 72 h      | 43            |         |                             |
|                        |                                                          | IC<sub>50</sub> (mg ml<sup>-1</sup>) |         |         |                             |
|                        | Diosgenin                                               | HEP2      | 0.125         |         | MTS assay | Watanabe et al. (2017)     |
|                        |                                                          |           | IC<sub>50</sub> (μM) |         |                             |
|                        | Polyphyllin D                                           | IMR-32    | 25            |         |                             |
|                        |                                                          | LA-N-2    | 20            |         |                             |
|                        |                                                          | NB-69     | 5             |         |                             |
| Source      | Compound | Cell line | Concentration | Assay     | References      |
|------------|----------|-----------|---------------|-----------|-----------------|
| Polyphyllin I | A549     |           | 0.625 (μg ml⁻¹) |           |                 |
| NCI-H460    |          | 24 h      | 10.0 ± 8.7 (%)  | MTT assay | Kong et al. (2010) |
| 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      | 76.9 ± 2.8     |           |                 |
|             |          | 48 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) |           |           |                 |
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

Table 1 continued

| Source | Compound | Cell line | Concentration | Assay | References |
|--------|----------|-----------|---------------|-------|-------------|
|        |          |           | 24 h          |       |             |
|        |          |           | Concentration |       |             |
|        |          |           | 48 h          |       |             |
|        |          |           | 72 h          |       |             |
|        |          |           | 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 |           |
|        |          |           | IC₅₀ (µg ml⁻¹) |       |             |
|        |          |           | 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 |           |
|        |          |           | IC₅₀ (µg ml⁻¹) |       |             |
|        |          |           | 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 |           |

Polyphyllin I HCT-116 72 h 0.7107 ± 0.103 CCK-8 assay Yu et al. (2018b)

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
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

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
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 (IC50 4.3 ± 1.0 µM) whereas 5α-hydroxy-laxogenin β-chacotrioside showed a complete loss of activity (IC50 > 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. yunnanensis 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 oncrosis, 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-Glc-(1 → 2)-[β-D-Xyl-(1 → 2)]-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 (penngenin 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 Beclin 1 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 aspasflilioside B (sarsasapogenin 3-O-β-D-Xyl-(1 → 4)-[α-L-Ara-(1 → 6)]-β-D-Glc), isolated from *Asparagus filicinus*. The compound additionally 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 a 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 3-0-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 3-0-[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 macrophages 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 IC50 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 (Steih 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 due to 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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