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## Anticancer Agents: Saponin and Tannin

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### ABSTRACT

Herbs are ancient sources of flavoring aromatic compounds and medicines, not only for merely culinary application. The increasing interest in the powerful biological activities makes them interesting in terms of their phytochemical contents. Saponin and tannin are coined as effective phytochemical agents. Saponins have long been known to be plant- originated, but they can also be found in marine organisms. Saponins, from a structural viewpoint, are composed of one or more hydrophilic glycoside moieties along with a lipophilic and derived aglycone and finally one or more sugar chains. Therefore, it is not a surprise that they exhibit pharmacological effects. Anticancer activity is one of these important properties. Saponins interfere with the replication of cellular DNA and they prevent the proliferation of cancer cells. Tannins, on the other hand, are of polyphenolic nature. The features distinguishing tannins from plant-based polyphenols of other types are basically the properties of the binding of the former to proteins, basic compounds, pigments, large-molecular compounds and metallic ions and also the display of anti-oxidant activities. In this review we reported the anticancer activity of different plants having a rich content of saponin and tannin.

**Key words:** Anticancer activity, phytochemical agents, proliferation, pharmacological effect, aromatic compounds

### INTRODUCTION

Pharmacological and chemical investigations of medicinal plants have provided a wide variety of natural compounds to possess significant cytotoxic as well as chemo-preventive activity. Among these components, as well as primer metabolite such as fat, protein, carbohydrates, secondary metabolites such as alkaloids, phenolic components, flavonoids, steroids and saponin, tannin, glycosides, carotenoid and organic acids are located. Primary metabolites are compounds that are directly essential to growth, development and plant's survival whereas secondary metabolites need to growth and development of plants but are not required for the plant to survive. A common role of secondary metabolites in plants is defense mechanisms. They are used to fight off herbivores, pests and pathogens. Also they are utilized in anti-feeding activity. Moreover, seconder metabolites have a lot of pharmacological activity such as antioxidant (Kosanic and Rankovic, 2015), antimicrobial (Chen *et al.*, 2015) and others. However, the presently studies focuses on the anticancer potential of these constituents. Also, plant secondary metabolites also show promise for the cancer chemoprevention, which has been defined bas “the use of non-cytotoxic nutrients or pharmacological agents to enhance physiological mechanisms that protect the organism against mutant clones of malignant cells” (Morse and Stoner, 1993). In this review aimed to report the anticancer activity of different plants having a rich content saponin and tannin.

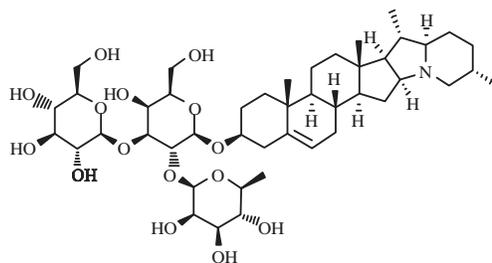


Fig. 1: Structure of the saponin

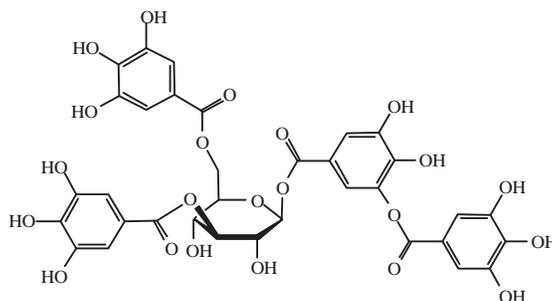


Fig. 2: Structure of the tannin

Saponin is a diverse group of compounds widely distributed in the plant kingdom, which are usually characterized by their structure containing a steroidal or triterpenoid aglycone and one or more sugar chains (Kensil, 1996) (Fig. 1). Because of their lyobipolar properties, they are able to interact with cellular membranes and are also able to decrease the surface tension of an aqueous solution. It has antioxidant and anticancer properties (Vuong *et al.*, 2014).

Tannin is widely distributed in plant flora. They are phenolic compounds of high molecular weight. Tannins are soluble in water and alcohol and are found in the root, bark, stem and outer layers of plant tissue (Fig. 2). Tannins have a characteristic feature to tannic to convert things into the color of leather. They are acidic in reaction and this is attributed to the presence of phenolic or carboxylic groups (Kar, 2007). They form complexes with proteins, carbohydrates, gelatin and alkaloids. It has antioxidant and antibacterial effect (Widsten *et al.*, 2014).

**Saponin's anticancer properties:** Saponins have been ascribed to a number of pharmacological actions, such as immunomodulatory potential via cytokine interplay (Sun *et al.*, 2009) cytostatic and cytotoxic effects on malignant tumor cells (Bachran *et al.*, 2008).

*Acacia victoriae* (Fabaceae), is an Australian desert tree. In about this, it has been shown to induce cell cycle (G1) arrest of the human MDA-MB-453 breast cancer cell line and apoptosis of the Jurkat (T cell leukemia) and MDA-MB-435 (breast cancer) cell lines (Haridas *et al.*, 2009, 2001).

*Agave scottii* (Asparagaceae) is in the sonoran, its effect component saponin and gitogenin. These components were identified to inhibited Walker carcinoma 256 (Bianchi and Cole, 1969).

It is reported for the extract from the plant *Androsace umbellata* Merr (Primulaceae), that the triterpene saponins (saxifragifolin B and saxifragifolin D) isolated from the plant resulted in inhibition of cancer cell growth and also induction of apoptosis (Park *et al.*, 2010).

In a published work, it was determined that *Astragalus* (Fabaceae) saponins possess antitumor properties in HT-29 human colon cancer cells and tumor xenografts. They inhibit cell proliferation through accumulation in S phase and G2/M arrest, with concomitant suppression of p21 expression and inhibition of cyclin-dependent kinase activity. Besides, AST promotes apoptosis in HT-29 cells through caspase 3 activation and poly (ADP-ribose) polymerase cleavage, which is indicated by DNA fragmentation and nuclear chromatin condensation (Tin *et al.*, 2007).

In another study, the investigated cytotoxic effect of triterpene saponins from the leaves of *Aralia elata* (Araliaceae) was investigated. The compounds showed significant cytotoxic activity against HL60 and A549 cancer cells (Zhang *et al.*, 2012).

Saponins isolated from *B. aegyptiaca* (Zygophyllaceae) had anti-proliferative property. This saponin exhibited potent anti-proliferative activity against MCF-7 human breast, cancer cells and HT-29 human colon cancer cell (Beit-Yannai *et al.*, 2011).

Different steroidal saponins from *Dioscorea zingiberensis* Wright (DZW) (Dioscoreaceae) isolated saponin different. Zingiberensis Saponin (ZS) had more cytotoxic effect against to murine colon carcinoma cell line C26. The proliferation inhibitory effect of ZS was associated with its apoptosis-inducing effect by activation of caspase-3 and caspase-9 and specific proteolytic cleavage of poly (ADP-ribose) polymerase. Exposure of C26 to ZS also resulted in Bax up regulation and Bcl-2 down regulation (Tong *et al.*, 2012).

The anticancer mechanism in human gastric cancer cell lines of akebia saponin PA (AS), purified from *Dipsacus asperoides* (Caprifoliaceae) was investigated. It was shown that AS-induced cellular death is caused by autophagy and apoptosis in AGS cells (Xu *et al.*, 2013).

In another a study, a new triterpenoid saponin (GC-1) was extracted from the fruit of *Gymnocladus chinensis* Baillon (Fabaceae) and its biological actions were investigated. GC-1 was demonstrated to induce apoptosis in HL-60 cells in a dose-dependent manner (Ma *et al.*, 2007).

According to a work published in 2014, the researchers identified that the major component of triterpene saponins extracted from *N. glandulifera* (Nepenthaceae), exhibited growth inhibition in the human lung carcinoma A-549 cell line (Hu *et al.*, 2014).

Reng-Ping Z and others identified in their work that MDA-MB-435 cell proliferation, migration and adhesion were performed to assess the anticancer activity of DT-13, a saponin from *Ophiopogon japonicus* (Asparagaceae) (Zhao *et al.*, 2014).

Saponin fractions from the leaves of *Panax notoginseng* (Araliaceae) were determined to have the cytotoxic effects against KP4 cells (human pancreatic cancer), NCI-H727 cells (human lung cancer), HepG2 cells (human hepatocellular cancer) and SGC-7901 cells (human gastric adenocarcinoma). This saponin could be a new alternative source of anticancer property (Qian *et al.*, 2014).

It was also determined that from *Polygonatum sibiricum* (Asparagaceae) the isolated neosibiricosides A-D saponins effective against to MCF-7 cell (Man *et al.*, 2009; Ahn *et al.*, 2006).

Reported that purified saponins from *Pulsatilla chinensis* (Ranunculaceae) significantly inhibited the growth of human hepatocellular carcinoma SMCC-7721 cells and pancreatic BXPC3 and SW1990 cancer cells (Liu *et al.*, 2014).

*Pulsatilla koreana* (Ranunculaceae) saponins were examined for in their *in vitro* cytotoxic activity against the human solid cancer cell lines, A-549, SK-OV-3, SK-MEL-2 and HCT15, using the SRB assay method and there *in vivo* antitumor activity determined using BDF1 mice bearing Lewis Lung Carcinoma (LLC) (Bang *et al.*, 2015).

The total saponin extract obtained from *P. villosa* (SPV) (Rosaceae), was investigated from the antitumor effects and the possible mechanisms; the four cancer cell lines were examined mouse melanoma cell line B16, MCF-7 human breast cancer cells, HeLa human epithelial cervical cancer cells and L1210 mouse lymphocytic leukemia cells. Consequently, it was suggested that SPV and FPV possessed cancer chemo-preventive potential on different types of cancer cells (Guo and Gao, 2013).

*Quillaja saponaria* (Quillajaceae) grows in South America. Saponin fraction induces apoptosis in U937B lymphoma cells (Akhov and Shyshova, 2002).

A study designed to examine the *in vitro* cytotoxic activities of the saponin fraction isolated from *Solanum trilobatum* (SFST) (Solanaceae) on HEp-2 cell line. Consequently, dose-dependent suppression of cell proliferation and the IC<sub>50</sub> value was found to be 1000 µg mL<sup>-1</sup>. At a dose of 1000 µg mL<sup>-1</sup>, marked morphological changes including cell shrinkage and condensation of chromosomes were observed (Kanchana and Balakrishna, 2011).

Recent studies have been indicated that dietary sources of saponins offer a preferential chemopreventive strategy in lowering the risk of human cancers. For example, soybean saponins suppressed the growth of HT-29 colon cancer T cells (Gurfinkel and Rao, 2003).

A saponin was purified from *Xanthoceras sorbifolia* Bunge (Sapindaceae) saponin purified. Its anticancer effect was determined against to HTB-9 (bladder), HeLa-S3 (cervix), DU145 (prostate), H460 (lung), MCF-7 (breast), K562 (leukocytes), HCT116 (colon), HepG2 (liver), U2OS (bone), SK-Mel-5 (skin), T98G (brain) and OVCAR3 (ovary) according to results this saponin important contributing anticancer activity (Chan, 2007).

*Yucca schidigera* (Asparagaceae) is desert a plant. Its stem and roots include steroid saponin and furostanol saponins. Steroid saponin displayed carcinostatic and mutagenesis-inhibitory effects (Man *et al.*, 2009). Its inhibits the growth of KB human oral epidermoid carcinoma cells (Kaminobe *et al.*, 2002).

According to a work in publish in the 2010 year; steroidal saponins and its aglycone diosgenin also have been extensively studied on its antitumor effect by cell cycle arrest and apoptosis were identified (Man *et al.*, 2010).

It was determined that saponins, gymnemagenol and dayscyphin C have significant anticancer-cytotoxic activity on HeLa cells under *in vitro* conditions (Khanna and Kannabiran, 2009).

**Tannin's anticancer properties:** Maplexins A-I are a series of structurally related gallotannins recently isolated from the red maple (*Acer rubrum*) species. In a study, maplexins A-I were evaluated for anticancer effects against human tumorigenic (colon, HCT-116; breast, MCF-7) and non-tumorigenic (colon, CCD-18Co) cell lines. Consequently, maplexin has anticancer property (Gonzalez-Sarria *et al.*, 2012).

Cuphiin D1 (CD1), is a new macrocyclic hydrolysable tannin, it was isolated from *Cuphea hyssopifolia* (Lythraceae) and it has been shown to exert antitumor activity against to HL-60 cells (Wang *et al.*, 2000).

Ellitannin isolated from the *C. ladanifer* (Cistaceae) showed to inhibit the proliferation of M220 pancreatic cancer cells and MCF7/HER2 and JIMT-1 breast cancer cells (Barrajon-Catalan *et al.*, 2010).

Ellagiattannin was investigated in term of the effect on human colon cancer Caco-2 and colon normal CCD-112CoN cells. These components provoked the same effects on Caco-2 cells:

down-regulation of cyclins A and B1 and upregulating of cyclin E, cell-cycle arrest in S phase, induction of apoptosis via intrinsic pathway (FAS-independent, caspase 8-independent) through bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol, activation of initiator caspase 9 and effector caspase-3 (Larrosa *et al.*, 2006).

From *Eugenia jambos* L. (Myrtaceae) the researchers isolated tannins and its anticancer activity had been determined. All significantly inhibited human promyelocytic leukemia cell line HL-60 and showed less cytotoxicity to human adenocarcinoma cell line SK-HEP-1 and normal cell lines of human lymphocytes and Chang liver cells. Thus, these compounds were inhibited the dose-dependent manner in HL-60 cells (Yang *et al.*, 2000).

In a study; it was determined that gallotannin's inhibit the proliferation and to induce apoptosis in a human colon cancer cell line (T-84) (Gali-Muhtasib *et al.*, 2001).

Fifty seven tannins and related compounds including gallotannin, ellagitannin and complex tannins were evaluated for their cytotoxicity against human tumor cells which are malignant melanoma, ilolecal adenocarcinoma, lung cancer, medulloblastoma cells and epidermoid carcinoma (Kashiwada *et al.*, 1992).

Isolated from *Geranium wilfordii maxim* (Geraniaceae) of hydrolysable tannin was shown to exhibit moderate cytotoxicity against cultured human tumor cell lines including A549, SK-OV-3, HT-1080, K562 and S180 *in vitro* (Li *et al.*, 2013).

From the *Limonium axillere* (Plumbaginaceae) isolation hydrolyzable tannin's which are derivatives of ellagitannin showed an inhibition of Ehrlich ascita carcinoma were determined (Ahmed *et al.*, 1999).

Musaceas (plantain)(Musaceae) plant of tannin's isolated inhibited the tumor cell proteasome activity. Thus, this plant exhibited anticancer activity (Kazi *et al.*, 2003).

Pomegranate (*Punica granatum* L.) (Lythraceae) fruits are widely consumed as juice (abbreviated as PJ). Total Pomegranate Tannin (TPT) extract and PJ were evaluated for anti-proliferative activity *in vitro* on human oral (KB, CAL27), colon (HT-29, HCT116, SW480, SW620) and prostate (RWPE-1, 22Rv1) tumor cells and apoptotic effects were evaluated against the HT-29 and HCT116 colon cancer cell lines. They were shown to induce apoptosis and decreased the viable cell number of human oral, prostate and colon tumor cells (Seeram *et al.*, 2005).

Corilagin is a member of the tannin family that has been discovered in many medicinal plants and has been used as an anti-inflammatory agent. In a study aimed to investigate the anticancer properties of corilagin against to ovarian cancer cells. As result; Corilagin inhibited the growth of the ovarian cancer cell lines SKOv3ip, Hey and HO-8910PM Corilagin induced cell cycle arrest at the G2/M stage and enhanced apoptosis in ovarian cancer cells. Consequently, corilagin isolated from *Phyllanthus niruri* L. was showed to be therapeutic a agent against the growth of ovarian cancer cells via targeted action against the TGF- $\beta$ /AKT/ERK/Smad signaling pathways (Jia *et al.*, 2013).

*Rubus odoratus* (Rosaceae), *Cornus canadensis* (Cornaceae), *Lespedeza capita* var. (Fabaceae), *Calycogonium squamulosum* (Melastomataceae) were shown to incorporate tannins in their water soluble fractions determined. Antitumor activity against the Walker 256 (IM) carcino sarcoma. Consequently, these plants exhibited quite mark antitumor activity (Fong *et al.*, 2006).

It was determined that tannins were exhibited anti-tumor and anticancer activity against to HeLa cell and murine leukemia cells (L1210/0), murine mammary carcinoma cells (FM3A) and human T-lymphocyte cells (Molt4/C8, CEM/0) (Pizzi, 2008).

According to a work published in the 2010 year; tannic acid were prevented the activation of PARP-1, reduced Bax and increased Bcl-2 expression in H9c2 cells, thus, preventing doxorubicin-induced cell death (Tikoo *et al.*, 2011).

Researchers showed that tannic acid TA-induced apoptotic death in acute myeloid leukemia (AML) HL-60 cells via dose- and time-dependent manner as well as increase of sub-G1 fraction, chromosome condensation and DNA fragmentation (Chen *et al.*, 2009).

Tannic acid was shown to possess anti-carcinogenic activity against to hepatic neoplasms (adenomas plus carcinomas). Consequently, this component therefor exhibited chemo protective activity (Nepka *et al.*, 1999).

Sakagami and colleagues identified in their work that hydrolyzable tannins showed higher cytotoxic activity against human oral squamous cell carcinoma and salivary gland tumor cell lines than against normal human gingival fibroblast (Sakagami *et al.*, 2000).

Xiong Y and friends explored that the protective effects of tannins in *Sanguisorba radix* (Rosaceae) (TSR) on myelo suppression mice induced by cyclophosphamide (CTX). Consequently, TSR could significantly increase the numbers of white blood cells, red blood cells and platelets of myeloid suppression in mice. Moreover, it could accelerate bone marrow hematopoietic stem/progenitor cells (HSPCs) in myeloid suppression mice and enhance cell proliferation by promoting cell cycles from G<sub>0</sub>/G<sub>1</sub> phase to access into S and G<sub>2</sub>/M phases (Xiong *et al.*, 2014).

Apoptotic activity is increased in breast cancer and prostate cancer cells in response to exposure to tannin extracts (Bawadi *et al.*, 2005).

## CONCLUSION

Saponin and tannin are important bioactive components in plants. Not only do they have anticancer activity, but also they have very important properties such as antioxidant, antimicrobial, antibacterial etc. These contents are include in a lot plants and plants use can be useful in many techniques for therapeutic situations.

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