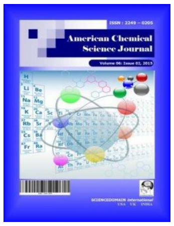

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Saponin Terpenoids; A Brief Review of Mechanisms of Actions and Anti-cancerous Effects

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Saponins are high molecular weight glycosides with a wide variety of biological activities and pharmaceutical applications. Saponins are widely distributed in plants and interact biologically with active cellular structures. It seems that saponins in different classes may have different inter- or intra-cyto-modulating targets and their specific effective sites. In recent years, some cytotoxic activities of important phytochemical components of saponin category have been revealed, and also an apoptotic effect on some carcinomatous cells lines showed. There is a vast variety of properties that by three major mechanisms as; *Direct nuclear intervention*, *Immune system augmentation* and *Chelating effects* promotes the anti-cancerous effects of saponins and regulation of some molecules like cyclin A, promoting the immune system and also affecting on the apoptosis of cells are among them. In this review we try to classify the prominent interactions of these molecules and effects of these groups of compounds over the cellular apoptotic mechanisms, Immune system interference, and cell protection, hence trying to elucidate probable important points in future usage of natural pharmaceutical treatment of cancerous cells.

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1. INTRODUCTION

1.1 Molecular Structure

Saponins are high molecular weight glycosides and consist of a polycyclic aglycones part attached to one or more sugar side chains. This aglycone part, which is also called sapogenin, is either steroid (C_{27}) or a triterpene (C_{30}).

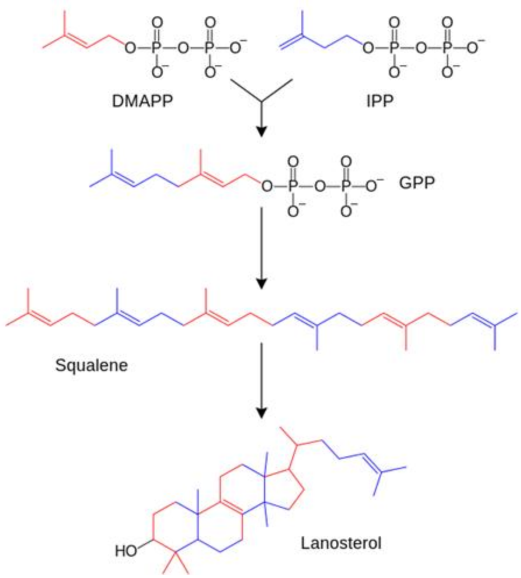

Fig. 1. Many different triterpene skeletons are known from natural sources and represent structurally cyclization products of Squalene which is the immediate biological precursor of all triterpenoids

In this figure simplified version of the steroid synthesis pathway with the intermediates isopentenyl pyrophosphate (IPP), dimethyl-allyl pyrophosphate (DMAPP), geranyl pyrophosphate (GPP) and squalene shown

The foaming ability of saponins is caused by the combination of a hydrophobic (fat-soluble) sapogenin and a hydrophilic (water-soluble) sugar part. Saponins have a bitter taste. Some saponins are toxic and are known as sapotoxin. Saponins show a wide variety of medical applications in the Eastern side of the world from ancient times up to now [1]. They exhibit a wide variety of biological activities, and throughout the history they have been investigated toward the development of new natural medicines and prove the efficacy of traditional herbal medicine. Other interesting biological applications for various specific saponins include their uses as anti-inflammatory, hypocholesterolemic and immune-stimulating agents whose properties are widely recognized and commercially utilized [2].

1.2 Distribution in Nature

Saponins are extremely distributed different parts of plants. Many of the *Allium* species, from the *Alliaceae* family, contain steroidal saponins. A lot of the research is focused on the saponins in garlic (*Allium sativum*), because of their health benefits. *Allium sativum* L. (*Liliacea*) is a perennial bulb with a tall, erect flowering stem. The bulb of the plant has been used in many parts of the world as a stimulant, carminative, antiseptic, expectorant, anthelmintic and diuretic agent [3].

Fig. 2. Garlic *(Aglio Bianco Polesano)*

The *Chenopodiaceae*, with 1500 species and 100 genera, are well represented in triterpenoid saponins, with oleanolic acid as the predominant aglycone. Oleanolic saponins are present in many edible legumes (*Leguminosae*) like soybeans (*Glycine max*), beans (*Phaseolus vulgaris*), and peas (*Pisum sativum*).

The *Fabaceae*, *Leguminosae* or *Papilionaceae*, commonly known as the legume, pea, or bean family, is a large and economically important family of flowering plants. It includes trees, shrubs, and perennial or annual herbaceous plants, which are easily recognized by their fruit (legume) and their compound, stipulated leaves. The group is widely distributed and is the third-largest land plant family in terms of number of species, behind only the *Orchidaceae* and *Asteraceae*, with 630 genera and over 18,860 species [4].

Fig. 3. Legume of *Vicia angustifolia*

A lot of S*olanaceous* plants contain saponins that have diverse biological and pharmacological activities. The best known genus of *Theaceae* family is *Camellia*, which includes the plant whose leaves are used to produce tea (*Camellia sinensis*).

Fig. 4. *Camellia sinensis* foliage leaves

Triterpenoid saponins (oleanane type) are present in seeds, roots and flowers of the tea plant. Cereals and grasses appear to be generally deficient in saponins, with the exception of some grasses, like switch grass (*Panicum virgatum*), kleingrass (*Panicum coloratum*), and oats (*Avena spp.*) [5].

1.3 Known Therapeutic Effects

One famous plant in Middle East region, *Asparagus officinalis*, is a genus of lily family and used as an appetizer with high food value and rich in vitamins like thiamine, ascorbic acid, niacin and riboflavin [6]. It is also known as a plant with antioxidant activity which seavanges free radicals and protects the human cells from oxidative stresses [7].

Asparagus Officinalis has been shown to have phyto-chemicals and bio-active Constituents and with its Flavonoid fraction, exerts strong hypo-lipidemic effects in some animal cells [8].

Fig. 5. Asparagus is a herbaceous, perennial plant growing to 100–150 centimeters tall, with stout stems with much-branched feathery foliage

One major and important phyto-constituent of *Asparagus officinallis* is asparanin saponin, which is found in high concentration in the plant. This molecule mediates the down regulation of cell cycle related proteins like cyclin A, Cdk1 and Cdk4 in association with up-regulant of p21 (WAF1/Cip1) and p-Cdk1 (Th, 14/Tyr 15) [9]. Asparanin is a steroidal saponin and Steroidal sapogenins with a C-12 carbonyl function constitute the basic structure for cortison synthesis [10].

It should be noted that natural compound therapies for cancers have gained increasing acceptance word-wide during recent years. herbal and natural medicine are generally low in cost, plentiful and also show very little toxicity to normal tissues with minimal side effects in clinical practices.

Natural medication approach may have many clinical advantages in treatment of cancerous patient as follows:

Enhancing the potency of chemo/radio therapy;

1. Reducing the inflammation of the surrounding cancerous tissues;
2. Improving the quality of patient's life;
3. Improving the Immune System Condition;

4. Prolonging the patient's life span;
5. Protecting the Normal Cell and Tissues against the damages from classic chemo/radiotherapy [11].

2. MAJOR FUNCTIONAL CLASSIFICATION

Saponins were classified as steroid or triterpenoid saponins depending on the nature of aglycone. The other classes of saponins namely the steroid saponins, containing nitrogen analogues of steroid sapogenins as aglycones [12].

Saponins have been shown to interact biologically with active cellular structures. These biological interactions well recognized and commencing from cell destruction by mechanical mechanisms like hemolysis of red blood cells which may happen as a result of their ability to form a sample with cell membrane leading to pore formation with in the membrane. On the other hand saponins exert a wide range of pharmacological activities like expectorants, anti-inflammatory, vaso-protection, and hypo-cholestrolemic, immune-modulatory, hypo-glycemic-molluscicidal, and also anti-fungal and anti-parasitic effects [13].

3. CYTOTOXIC AND ANTI-CANCEROUS EFFECTS

Many authors in their investigations referred to cyto-toxic effects of these molecules. Permeabilizing the cell membrane, immuno-modulating the cytokine interplay, cytostatic and cytotoxic effects on malignant tumor cells and also synergistical enhancement of immune-toxins toxicity are among the most important cyto-kinetic and cyto-immuno-modulating effects of the saponins [14].

It seems that saponins in different classes may have different cyto-mudulating targets and their specific effective sites with the cells or intervene with the cellular interactions. These effects may categorize as:

1. Direct anti-cancerous effects (nuclear intervention)
2. Protective effects (immune- modulating properties)
3. Inhibiting characteristics (metal-chelating effects)

Each of these functional categories may show their specific target sites within cells and also exclusive mechanism of action differing from others both in nature, intensity, and processes.

3.1 Direct Anti-cancerous Effects (Nuclear Intervention)

Evidences of interference with nuclear mechanisms come from some studies. In this field, many saponins may show direct intervention with nuclear elements of gene transcription and translation process [15]. According to some authors, saponins like AG4 (3β-O-{α-L-pyran rhamnose-(1→3)- [β-D-xylopyranose-(1→2)]-β-D- glucopyranose-(1→4)-[β-D-leucopyranose-(1→2)]-α-l-pyran arabinose}-cyclamiretin A) interact with relative expression of genes such as Box, Bad, Bid, Bd2, and Fas mRNA. This molecule markedly inhibits the growth of cancerous cells by decreasing cell proliferation and inducing apoptosis and also blocks the cell cycle in the S phase of the cell cycle [16]. In fact many saponins can affect the cancer cells proliferation in transcriptional and protein level [17].

Some saponins like zingiberensis saponin from Dioscorea zingiberensis wright (D2W) have shown apoptosis-induced effects through modulating the caspase system, a very important system in programmed cell death process. These saponins activate the two key members of this chain of interaction namely caspase-3 and caspase-9 and cleaved the poly (ADP-ribose) polymerase proteolitically [18].

Also there has been found some evidence of interaction these molecules with transcription apparatus in cells. Saponin extracted from *Gypsophila trichotoma* may showed cyto-toxicity of the tyro I ribosom- inactivating protein (RIP-I) [20].

There is also direct evidence derived from in-vitro studies, showed that natural saponins like Soya sapogenols would be directly have cytotoxicity effects on colon carcinoma cell line (HCT-116), liver Carcinoma cell line (Hep-G2) and also human breast carcinoma cell line (MCF-7). Studies showed that this effect is concentration-depended and the β-hydroxyl group at C-21 or C-22 was discovered to be aligned with marked increasing in cytotoxicity functions of the molecule.

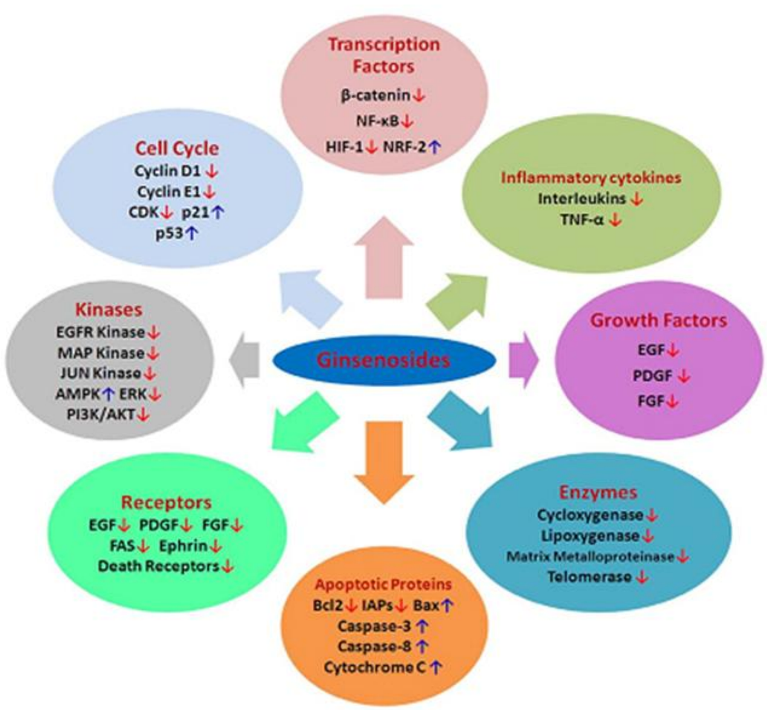

Fig. 6. Possible cellular and molecular mechanisms of Ginsenosides against cancer

CDKs, cyclin-dependent kinases; MDM2, murine double minute-2; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; PDGF, platelet derived growth factor, MMP, matrix metalloproteinase; IAP, inhibitory apoptotic protein; TNF, tumor necrosis factor; NF-κB, nuclear factor κB; PI3K, Phosphatidylinositol 3-kinase; HIF-1, hypoxia-inducible factor-1; ERK, extracellular signal-regulated kinase; NRF2, nuclear factor (erythroid-derived 2)-like; AMPK, 5′ AMP-activated protein kinase; EGF, epithelial growth factor; ↑, upregulation; ↓, downregulation [19]

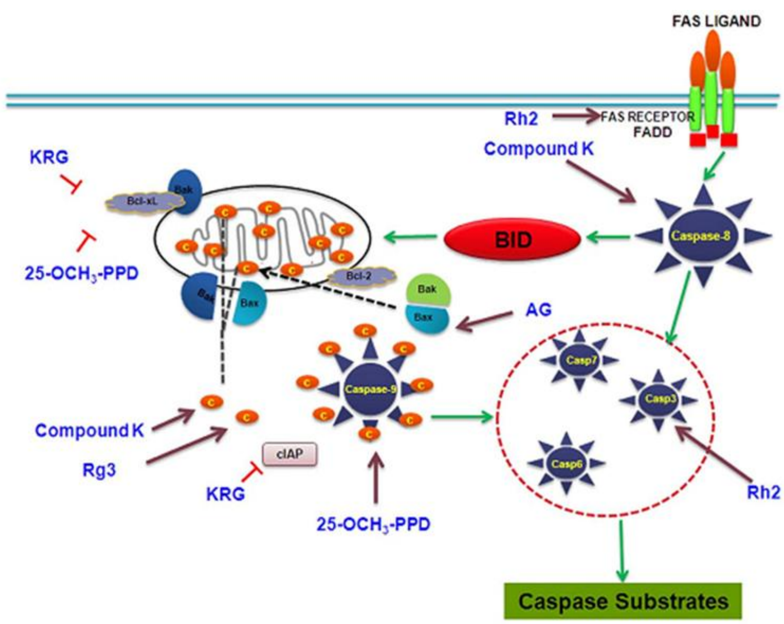

Fig. 7. A diagram of cell signaling pathways which involved in apoptotic response, targeted by selected ginsenosides

KRG: Korean Red Ginseng; AG: American Ginseng [19]

3.2 Protective Effects (Immune-modulating Properties)

It has been established that some saponins may show anti-inflammatory effects which interfere with some cellular functions. Yang and colleagues showed that proto-panaxadiol saponin diminishes the release of inflammatory mediators like nitric oxide (NO) and down-regulating the action of some enzymes like cyclooxygenase, both shows some damage on normal endothelium of vessels in body [15].

There is also another protective aspect suggested for saponins. Some studies show direct immune system interactions for some saponins like panaxadiol saponins and panaxtrol saponins. Some authors showed that these two branch of saponins improving animal immune organ weight. They also have an improving effects on interleukin 2 (IL-2), interleukin -6 (IL-6), plasma gamma-interferon (IFN-8) and tumor necrosis factor alpha (TNF-α) plasma titers which all are in the same direction of immune system fortification [21,22].

3.3 Inhibiting Effects (Metal-chelating Properties)

Phytochemical Analyses of some saponins revealed same radical scavenging activity and also anti-oxidative properties against the free radicals [23].

Some saponins showed strong protective characteristics against free radicals. Triterpene Saponins from the *chlorophytum borivilianum* are among the powerful saponin agents with antioxidant activity (2, 2-diphenyl-1-picrylhydraazol radical scavenging activity, and ion chelating and β-carotene bleaching specifications [24].

4. CONCLUSION

With all these findings considered, we shall now return to the main issue mentioned at the onset of this paper; the major functional classification of saponins specifications in cancer therapy. All these notifications showed there are a vast variety of properties that apparently by three major mechanisms as *direct cellular nuclear intervention, Immune system augmentation and metal and oxidants chelating effects* promotes the anti-cancerous effects of saponins. To make a fruitful and effective program for using the natural anticancer drugs, we should provide a very delicate and specified data bank including the types of drugs and molecular structure and exact functions besides the past medical history and gender of patients and also their demographic information to match the previous and relatively successful scenarios with the most effective compounds. In one investigation by Imran Ali and his colleagues, the perspectives of lung and breast cancer beside the other major forms of cancers in stomach, gall bladder, cervix and also oral malignancies have been planned to focus on the most prevalent ones in specific areas, which could be a suitable frame work for other scheduled treatment programs in other areas [25]. This will provide an exact clinical and demographical picture of what may happen and what should be focused on. Another important and determining aspect of natural anticancer drugs referred to their route of administration. It is critical for drugs to be selective and also get reached to the specific site of action, hence many technologies provided to enhance these two specifications.

Some nanoparticles such as dendriners, polymer, liposome and micelles could be used as the carriers of the functional molecule to its specific site of action and selecting the most suitable carrier and the route of usage, impacts deeply on the outcome of anticancer therapy with natural products [25-27]. While there are still many questions left unanswered about the nature and bio-chemical interactions between saponins and cell infra- structures, and many possible truths to be drawn from their mechanisms of actions with target sites, there would be a very fruitful and delicate landscape for futurology of the saponins in the fields of cancer therapy with effective classification of these compounds and their molecular properties and a very strong hope to promote new herbal most effective treatments for people whom involved with various types of cancer.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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