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Review Article

Plant-Derived Selected Bioactive Saponins and Tannins: An Overview of their Multi-Target Mechanisms and Diverse Biological Activities

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ABSTRACT

An extensive variety of ailments have been treated using medicinal herbs for ages. Recent research has revealed that many of these plants possess multiple therapeutic activities, rendering them interesting candidates for the creation of novel medicines. This review examines the current state of knowledge regarding the multi targeted activities of medicinal plants, including their potential for treating multiple diseases like anti-inflammatory, anti-microbial, anti-hyperglycaemic and anti-cancer activities, their ability to modulate multiple pathways, enzymes, genes and proteins. Finally, the review highlights the potential of naturally derived substances from plant material, for the development of multitargeted drugs and suggests strategies for further research. The multi-target activities will be thoroughly explored in this review of ginsenosides, platycodon D, dioscin, soyasaponins and aescin were chosen as saponins, whereas methyl gallate, chebulinic acid, tannic acid, theaflavin and punicalagins were chosen as tannins. This overview gives a brief history of the isolated natural compounds, their structures, multi-target activity, and their suggested mechanisms of action.

Keywords: Tannins, Saponins, Medicinal plants, Multi targets, Bioactive compounds, Biological activities.

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INTRODUCTION

The therapeutic benefits of plants have been extensively documented for thousands of years. They have evolved and adapted over millions of years to ward off insects, bacteria, fungi, and the environment to produce different secondary metabolic products with a diversity of structural features. Those compound's ethnopharmacological traits were used as the primary inspiration for the creation of new medications.[1,2]

Biological compounds derived from plants have been the main source of physiologically active secondary metabolites throughout the history of humanity. Plants are a vital part of human culture, whether they serve as therapeutic agent's flavours or scents, indeed, up until the commercialization of aspirin in 1899, minerals and plants have remained crucial for maintaining human health and promoting economic and social progress as the only sources of therapeutic properties and ingredients used for both the prevention and treatment of illnesses.[3] Since many of the chemical metabolites of plants have a variety of biological actions, it is uncommon for one plant extract to be utilised in traditional medicine for more than one indication. Numerous plant extracts, as well as their isolated and purified components, have received approval as pharmaceuticals and are included in pharmacopoeias all over the world. In addition, a number of different extracts and chemical components from medicinal plant species have been used to create novel and varied therapeutic approaches.[4,5]

Plant-based products continue to offer significant structural variation, although in contrast to conventional combinatorial chemistry, which has the potential to discover mostly different low molecular mass lead compounds. Less than 10% of the global biological varieties has been examined for possible biological activity, so it is challenging to access this natural chemical variation. This indicates that there are still a lot of potential natural lead compounds to be found. This indicates that there are still a lot of potential natural lead compounds to be found.[6] Two significant sub-categories of plant-derived natural

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products—saponins and tannins are highlighted in this review. Five bioactive substances with diverse structural properties were specifically chosen for each metabolic group. Ginsenosides, Platycodin D, Dioscin, soyasaponins and aescin were chosen from the saponins and from the Tannins, methyl gallate, Chebulinic acid, tannic acid, theaflavins and Punicalagins were chosen. A brief overview of the isolated, chosen natural compounds, their structures, multi-target activities, and their interpreted multi-target processes will be presented in the present article.

SAPONINS

Most often discovered within the kingdom of plants, saponins are non-volatile, surface-active chemicals that are extensively prevalent in nature.[7] According to the structure of their aglycone skeleton, saponins can be divided into two classes. The steroidal saponins, which are primarily found in monocotyledonous angiosperms, make up the first group of compounds. The second group consists of the triterpenoid saponins, which are the most prevalent and are primarily found in dicotyledonous angiosperms. The structural component of steroidal saponins is a steroidal aglycone, which typically has a six-ringed C27 spirostane skeleton. Triterpenoid saponins made up of a triterpenoid aglycone with a C30 structure that includes a pentacyclic arrangement (Figure 1).[8]

Saponin is a type of natural secondary metabolite made up of sapogenin and a sugar chain.[9] The term "saponin," which derives from the Latin "sapo" (soap), refers to the surfactant properties of saponins and their capacity to create foam. Therefore, traditional soaps have been made from a variety of saponin-containing plants.[10] Many different types of Chinese herbal remedies, including ginseng, astragalus, bupleurum, Ophiopogon japonicus, and ginseng, contain saponins as a key active ingredient.[11] Moreover, saponins possess several significant therapeutic properties against inflammation, fungal infections, bacterial infection, viral infection, cancer (Figure 2).[8]

Ginsenosides

The ginsenosides are ginseng's primary active ingredients, naturally occurring Panax species like *Panax japonica* (Japanese Ginseng), *Aralia quinquefolia* (Korean Ginseng), and *Panax notoginseng* (Indian Ginseng).[12] It is a Protopanaxadiol (PPD)-type ginsenoside with a triterpenoid of the dammarane-type as an aglycone.[13] One of the main ginsengs saponins, known as ginsenoside Rg1, has been extracted and identified. It contains the steroidal triterpene aglycone (20S)-protopanaxatriol.[12] *P. ginseng* has undergone significant studies to prove its stimulant, tonic and antifatigue effects.[14] *In vivo* research found that compound of ginsenosides (K) elevated Noradrenaline (NA) levels in particular rat brain areas, serving as an antidepressant; Rh2, Rg3, and 20(S)-proto-panaxadiol also showed similar effects.[15] A study on mice fed a lipid rich diet for 56 days revealed that an ethanol extract of wild ginseng has anti-diabetic benefits. Significantly lowering fasting blood sugar was achieved with wild ginseng ethanol extract in a dose-dependent manner.[16] Ginseng's active constituents can improve blood circulation, stimulate nitric oxide formation, prevent ROS production, modify lipid profiles, and show anti-cardiovascular activity.[17] The critical chemicals have been identified as ginsenosides. in the entire ginseng extract with adjuvanticity, and they have been used as an immunologic adjuvant.[18] The ginsenosides Rc, Rd, Rg1, and ginsan all increased NK cell and T cell activity, indicating that ginseng has a significant immunomodulatory effect on cellular immune responses.[19] G-Rb2 treatment decreased the formation of tumours and the angiogenesis of tumours connected to cancer cell metastasis in mice whose skin was implanted with melanoma cells.The crude saponin components of Korean red ginseng demonstrated HIV growth suppression efficacy.[20]

Platycodin D

One of the *Platycodi Radix* marker compounds is platycodin D, a member of the platycodon saponins.[21] The solitary species *of Platycodon grandiflorus* (*Campanulaceae*) is found mostly in Northeast Asia, which includes China, Japan, and Korea (Figure 4).[22] Studies *on Platycodon grandiflorus* in recent years have concentrated on its biological properties, such as its anti-tumour, hepatoprotective, immunoregulatory, and antioxidant actions. The results of an inflammatory experiment showed that platycodin D inhibited prostaglandin E2 synthesis in rat peritoneal macrophages activated by 12-Otetradecanoylphorbol 13-acetate at 10 and 30 μM. This was accomplished by preventing the COX-2 protein from being induced, rather than by directly inhibiting COX-1, COX-2, or phospholipase A2. A study that investigated pancreatic lipase activity demonstrated that Platycodonin D has an anti-obesity impact by preventing the activity of the pancreatic fat enzyme as well as the absorption of dietary fat.[23] platycodin D exhibit anti-cancer action by increasing the expression of P19ARF and Bax protein, reducing the expression of mutant p53 protein, and slowing the growth of U14 cervical cancer tumours in mice. Platycodin D polysaccharides may suppress the growth of tumour cells by elevating the caspase-mediated cell death of tumour cells.[24] According to a study an ethanol extract of Platycodin D lowered oral hypoglycaemic tolerance after 30 min in diabetic rats given streptozotocin. Despite receiving a combination of therapies that significantly lowered blood glucose levels in Streptozocin induced diabetic mice, the ethanol extract with Platycodin D had no impact on plasma insulin levels.[25] Studies have reported that on the liver damage brought on by CC_{l4} in mice, Platycodin D and Na_2SeO_3 exhibit variable degrees of protective effects. The highest liver-protective effects are provided by the high-dose group of Platycodin D complex nano selenium.[26] For their anti-viral properties, researchers have synthesised Platycodin D rich extracts and *P. grandiflorus* saponin components for effective treatment or prevention for hepatitis C

can be achieved using this mixture. Additionally, this mixture is safe for humans when used in therapeutic settings.[27]

Dioscin

Numerous vegetables and herbs, many of which are members of the *Dioscoreaceae* family, contain the steroidal saponin dioscin (Many underdeveloped nations around the world regularly use Dioscorea species as a source of starchy staple foods, including *Dioscorea opposita, Dioscorea alata*, and *Dioscorea japonica* (Figure 4). Dioscin's possible therapeutic benefits have drawn a lot of interest in recent times.[28]

According to study, dioscin has the ability to trigger apoptosis and cessation of cell cycle, ultimately hindering the growth of

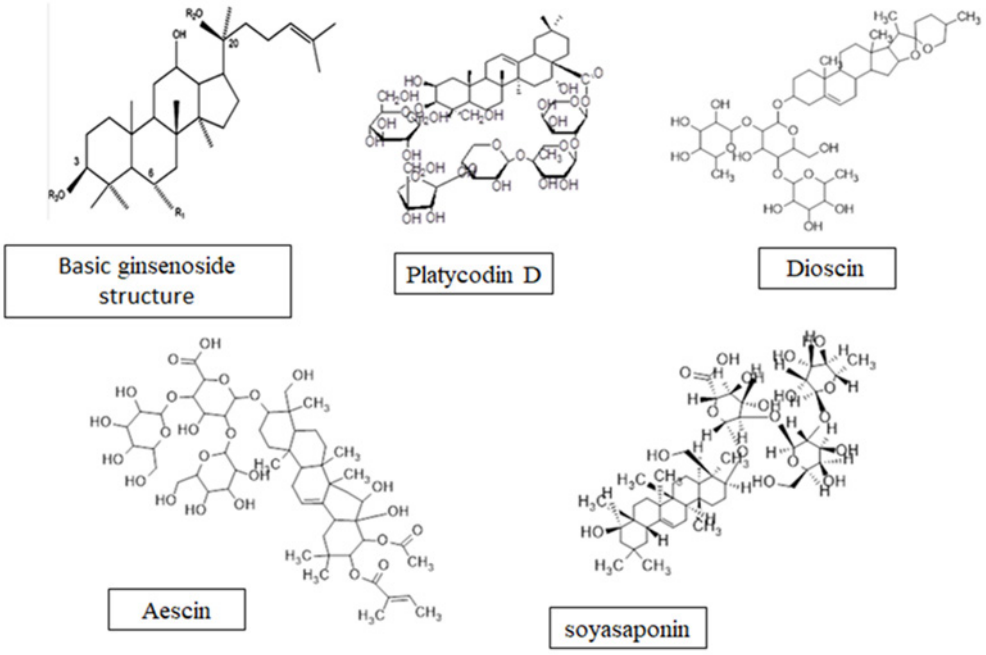

Figure 1: Chemical structures of saponin compounds

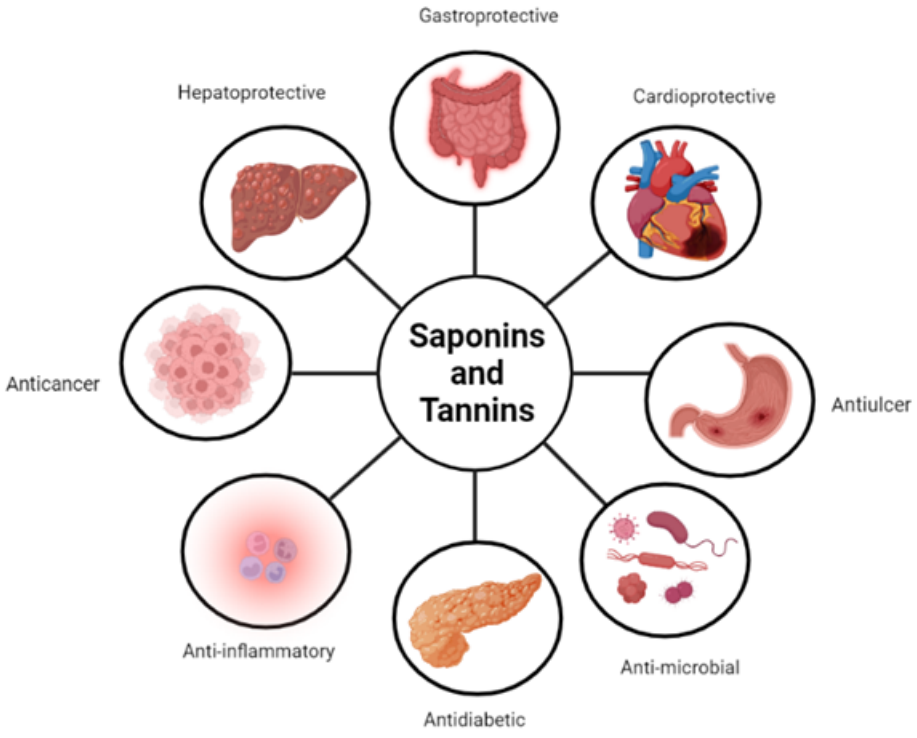

Figure 2: Common multi-target activities of saponins and tannins.

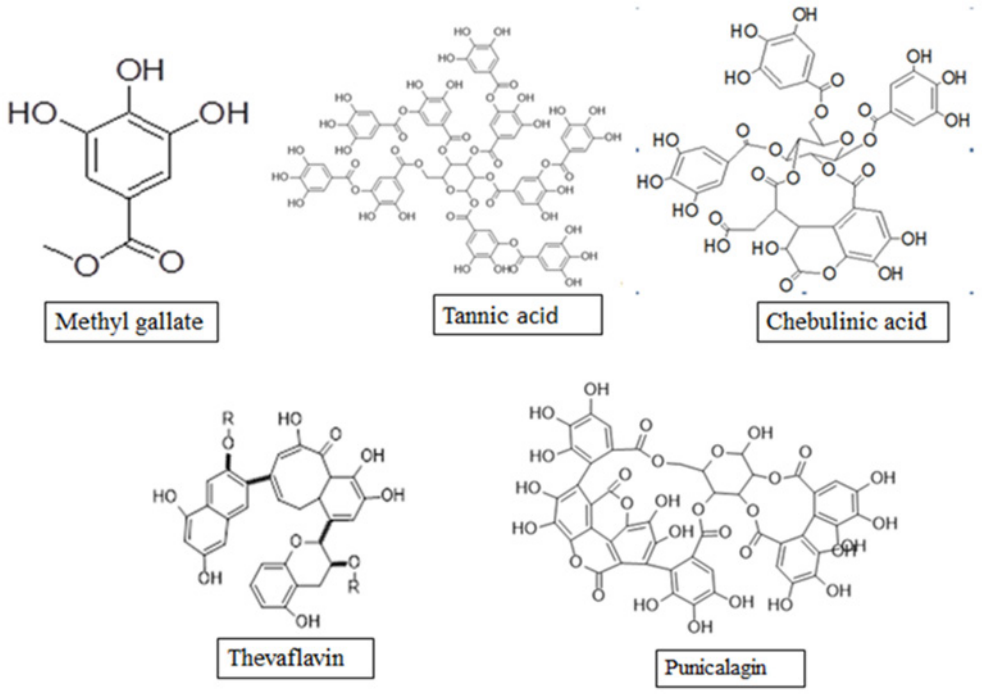

Figure 3: Chemical structures of Tannin compounds.

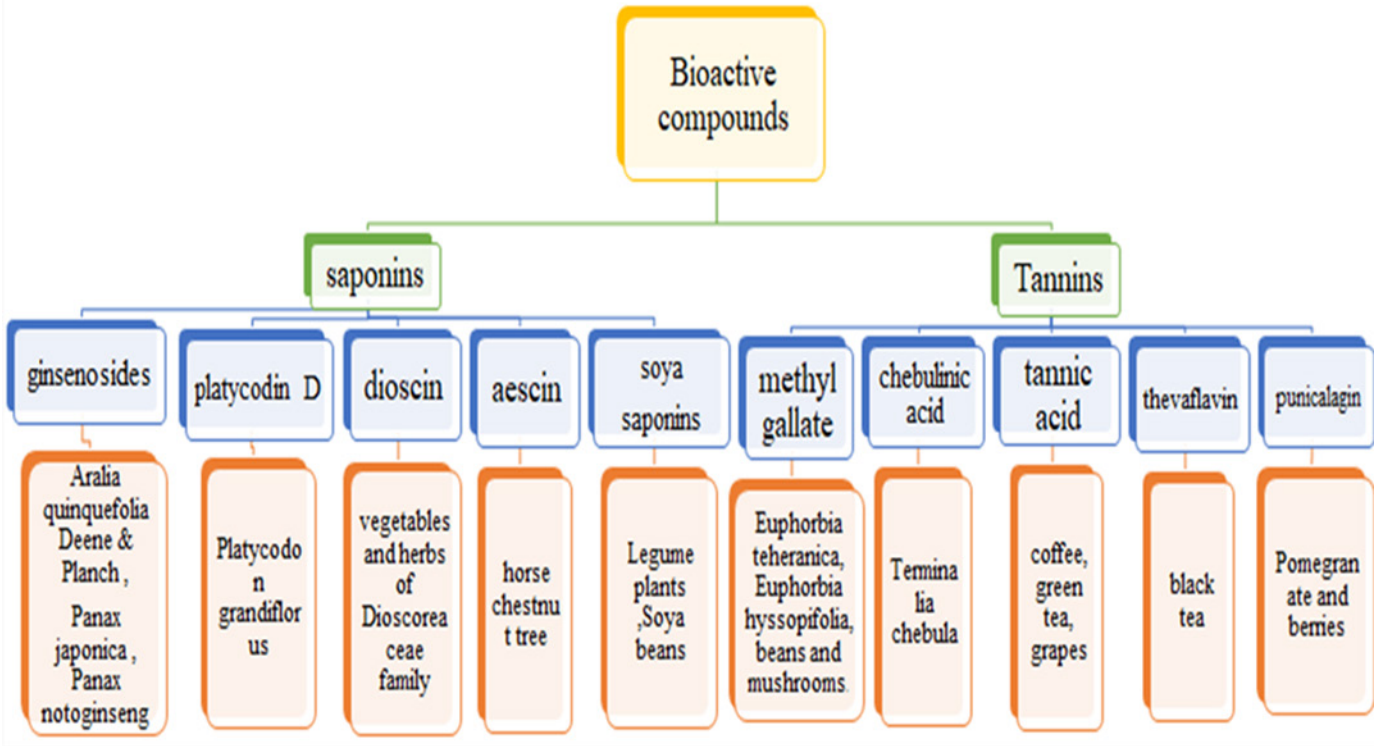

Figure 4: Sources of Bio-active saponins and tannins.

human lung cancer cells.[29] It has been observed that dioscin can inhibit the Wnt/-catenin transmission pathway, thus impeding the growth of pulmonary cancer cells.[30] Additionally, dioscin can enhance the effectiveness of chemotherapy for colorectal cancer by triggering autophagy-mediated apoptosis.[31] Moreover, it has been found that dioscin can curb the proliferation and invasion of glioma cells by suppressing the PI3K/Akt signaling pathway.[32] Another study revealed that dioscin was able to reduce inflammation and redox imbalance in a mouse model of rheumatoid arthritis by inhibiting the production of inflammatory

cytokines.[33] Moreover, dioscin was found to control the expression of genes such as COX-2 and NF-κB, which play a key role in the inflammatory response.[34] Furthermore, studies have described that dioscin can help manage diabetes by improving glucose metabolism and decreasing insulin resistance in mice.[35] It has also been suggested that dioscin's antidiabetic activities may be attributed to its ability to activate the PPAR-γ and AMPK signaling pathways, as observed in previous studies.[36] Dioscin has also been found to mitigate liver fibrosis by blockage of the TGF-β1/Smad3 signaling pathway.[37]

Soyasaponin

Soyasaponins are major compounds found in soybeans. They are a type of triterpenoid glycosides with polysaccharide chains and an oleanane-type aglycone. These have shown great potential for lowering cholesterol levels in the body.[38] Research has found that these compounds can prevent the absorption of bile acids and cholesterol in the intestines of hypercholesterolemia rats, leading to reduced serum cholesterol levels.[39] In another study, it was discovered that consuming soy protein enriched with soyasaponins for 56 days resulted in substantial reductions in the levels of triglycerides, LDL cholesterol, and total cholesterol in those with high cholesterol levels.[40]

The potential for anti-cancer capabilities of soyasaponins have also been researched. Soyasaponins have been illustrated to be able to inhibit the growth through induction of apoptosis in many cancer cell lines, including prostate, colon, and breast cancer cell lines, in *in vitro* studies.[41,42] Soyasaponins have also been linked to anti-neoplastic properties in animal experiments; one such research found that soyasaponin I consumption decreased the occurrence of colon tumours in rats.[43] Soyasaponins have been investigated for their possible anti-inflammatory qualities in addition to their low-density lipoprotein-lowering and anti-cancer benefits. Soyasaponins were added to the diet of arthritis-prone rats to reduce inflammation and enhance joint function.[44]

Another study on mice with colitis found that soyasaponin-enriched soybean extracts reduced inflammation and improved intestinal barrier function.[45] One specific soyasaponin, soyasaponin I, has been the subject of large number of studies for its potential health benefits. In addition to its anti-cancer effects mentioned above, soyasaponin I have been shown to improve glucose metabolism in diabetic mice.[46] Another study found that soyasaponin I reduced inflammation and cartilage damage in a rat model of osteoarthritis.[47] Research has shown that soyasaponins may have anti-inflammatory effects, as demonstrated by the ability of soyasaponin Bb to alleviate TNF-α-induced endothelial inflammation and dysfunction through controlling the PI3K/Akt and NF-κB pathways.[48]

Additionally, soyasaponins may have a role in improving glucose metabolism and impaired insulin sensitivity. For example, soyasaponin Bb has been found to minimised insulin resistance in rats by providing a high-lipid diet and modifying gut flora.[49] Soyasaponins also exhibit antitumor activity against colon cancer cells and may attenuate colitis by suppressing NF-κB activation. Moreover, soyasaponin Ab has been found to alleviate oxidative damage and apoptosis in cardiomyocytes through activating the PI3K/Akt pathway (Table 1).[50]

Aescin

Aescin is a significant bioactive compound present in the horse chestnut tree, also known as *Aesculus hippocastanum* that has gained considerable scientific attention for its potential therapeutic benefits. This tree species is known for its remarkable resilience in diverse environmental conditions, and it is distributed widely across the world.[51] Considerable research has been done on the Aescin, and it has been discovered to have anti-inflammatory characteristics since it can stop the synthesis of cytokines that trigger swelling, such as Interleukin-6 (IL-6) and tumour necrosis factor-alpha.[52] In clinical trials, aescin has been shown to reduce inflammation and pain levels in individuals suffering from knee osteoarthritis.[53] Aescin is also known for its potent anti-edema properties and can be beneficial in treating conditions such as Chronic Venous Insufficiency (CVI) and lymphedema.[54]

Several *in vitro* studies have suggested that aescin has apoptotic effects on different types of cancer cells, including human breast cancer cells and hepatocellular carcinoma cells.[55,56] Aescin has also been found to be protective against acetaminophen-induced hepatic damage in mice.[57] Aescin has found to attenuate osteoporosis by suppressing the RANKL-induced MAPK and NF-κB signaling pathways.[58] Furthermore, aescin has been reported to have potent anti-tumorigenic impacts through inhibiting transmission from the vascular endothelial growth factor receptor 2.[59] Finally, aescin has strong antioxidant properties and can reduce oxidative stress markers while increasing antioxidant enzyme activity, as evidenced in animal models of acetaminophen-induced liver damage (Table 1).[60]

TANNINS

The word "tannin," is derived from the old Celtic word for oak, was used in 1796 to describe how a plant extract transforms hide or skin into leather.[61] The term, however, is frequently used to refer to any major polyphenolic substance that has enough hydroxyls and other appropriate carboxyl like groups to constitute rigid complexes with proteins as well as other major molecules Tannins have a molecular weight range between 500 and more than 3000 (Figure 3).[62] In general, there are two categories of tannins: hydrolysable and condensed tannins. Condensed tannins are possessed with flavonoids as compared with hydrolyzable tannins, which are constituted of ellagic and gallic acids with a core primarily constituted of glucose.[63] Tannins shows various activities i.e. Anti-diabetic,[64] anthelmintic,[65] Anti-diarrhoeic,[66]

Table 1: Studies, biological targets and activities of saponin compounds.

Sl. No.	Bio-active compounds	*In vitro* studies on	*In vivo* studies on	Targets	Biological activity
1.	Ginsenosides	N/A	Albino wister rats	Nor-adrenaline	Anti-depressant.[15]
		N/A	ICR mice	PPAR, GIP	Anti-diabetic activity.[16]
		N/A	Albino wister rats	NK cells, T cells	Immunomodulatory effect.[19]
		N/A	Albino wister mice	Angiogenesis	Cancer metastasis.[20]
2.	Platycodin D	N/A	Albino wister rats	COX-2, COX-1, phospholipase	Anti-inflamatory activity.[23]
		N/A	Albino wister rats	Pancreatic lipase	Anti-Obesity activity.[23]
		U14 Cervical tumour cells	Albino wister mice	P19RF, BAx protein, P53 protien	Anti-cancer activity.[24]
		N/A	Albino wister mice	Plasma insulin	Anti-Hypertensive activity.[25]
		N/A	Albino wister mice	Oxidative stress	Hepatoprotective activity.[26]
3.	Dioscin	Human lung cancer cells	N/A	Apoptosis, cell cycle	Anti-tumor activity.[29]
		Pulmonary cancer cells	N/A	Wbt/catenin pathway	Anti-cancer activity.[30]
		Glioma cells	N/A	P13k/Akt signalling pathway	Anti-cancer activity.[32]
		N/A	Albino wister mice	Inflamatory cytokines	Anti-inflammatory aactivity.[33]
		N/A	Albino wister rats	PPAR, AMPK Signalling	Anti-diabetic activity.[36]
		Hepatocytes	Albino-wister rats	TGFB1/SMAD3	Liver fibrosis.[37]
4.	Soyasaponins	N/A	Hamster rats	HMG-COA reductase	Lipid lowering activity.[40]
		Prostate, colon, breast cancer cell lines		Apoptosis	Anti-cancer activity.[41,42]
		N/A	Albino wister mice	COX-2, phospholipase, PI3/akt, NF-kβ pathway	Anti-inflammatory effect.[48]
		N/A	Albino-wister rats	Gut flora	Anti-diabetic activity.[49]
		Cardinomycytes		PI3/AKT pathWays	Antioxidant activity.[50]
4.	Aescin	N/A	Albino wister rats	IL-6, TNF-α	Anti-inflammatory.[52]
		Hepatocellular carcinoma cells	N/A	Apoptosis	Anti-cancer.[55,56]
		N/A	Albino wister rats	MAPK, NF-Kβ signalling pathways	Osteoporosis.[58]
		Human Umbilical Vascular Endothelial Cells (HUVEC)	N/A	Vascular Endothelial Growth Factor (VEGF)	Anti-anti tumrogenic activity.[59]
		N/A	Albino-wister rats	Lipid peroxidation	Hepatoprotective.[60]

Table 2: Studies, biological targets and activities of tannin compounds.

Sl. No.	Bio-active compounds	*In vitro* studies on	*In vivo* studies on	Targets	Biological activity
1.	Methyl gallate	Papilloma cell lines	Albino Mice	Oxidative stress	Anti-tumerogenic activity.[74]
		Plasmodium strains	Albino mice	Protein and phosphoinositide kinases	Anti-plasmodic activity.[75]
		N/A	Albino Wister rats	Gastric secretion	Anti-ulcerogenic activity.[77]
		Escherichia coli, salmonella typhi	N/A	Protein synthesis	Anti-microbial activity.[78]
		N/A	Guinean pig, Rabbit	Calcium channels	Anti-spasmodic and anti-hypertensive activity.[79]
2.	Chebulinic acid	N/A	Albino wister rats	H^+ k^+ Atpase channels	Gastroprotective.[87]
		N/A	Albino wister rats	Langerhans cells P13-K	Anti-diabetic activity.[86]
		HOS-1 cell lines, MCF-7cell lines, S115	N/A	TNF-α	Anti-cancer activity.[88]
		Rat hepatocytes	N/A	Tetra butyl- bhd, tetra butyl hyper oxide	Hepatoprotective activity.[89]
		Helicobacter pylori	N/A	Protein synthesis	Anti-bacterial activity.[90]
		Salmonella typhi, *Salmonella typhimurium*	Albino Wister rats	Cell wall synthesis, DNA gyrase	Anti-microbial activity.[91]
3.	Tannic acid	N/A	Sprague dawley rats	MPO enzyme	Anti-infammatory activity.[96]
		Influenza A virus	N/A	Haemagglutinin	Anti-viral activity.[98]
		N/A	Albino wister rats	Calcium channels	Cardio protective activity.[99]
		HePG hepatoma cells lines	N/A	Nrf_2 / ARE signaling pathway	Anti-tumor activity.[100]
		N/A	Albino Mice	TNF-1, IL-1, IL-6	Gastroprotective effects.[101]
		N/A	Albino wister rats	Acetyl choline, oxidative stress	Memory enhancing activity.[102]
		N/A	SKH-1 Hairless Mice	TNF-α	Immunomodulatory activity.[103]
4.	Thevaflavins	MCF-7 cell lines	N/A	NH-2 terminal kinase, Activator protein kinase	Anti-carcinogenic activity.[107]
		N/A	Albino wister rats	Oxidative stress, apostosis	Antioxidant and Apoptic qualities.[108]
		P. gingivalis	N/A	Matrix metallo Protenases	Peridonstisis.[109]
		N/A	Albino mice	B-lyphocytes	Anti-hyperglycemia activity.[110]
		MCF-1 Human glioma cells	N/A	Cytochrome P450/A1	Genoprotective activity.[111]
		N/A	Sprague dawley rats	ICAM-1, COX-2, iNOS	Neuroprotective activity.[112]

Sl. No.	Bio-active compounds	*In vitro* studies on	*In vivo* studies on	Targets	Biological activity
		N/A	Albino wister rats	Amylase, lipase	Anti-hyper glycemic activity.[113]
5.	Punicalagin	Streotomyces mutans	N/A	Cell wall synthesis, Extra-cellular polysaccharide	Tooth decay.[116]
		POX-1, Beta cells of pancreas	Albino wister rats	Paraoxnase activity	Anti-diabetic activity.[117]
		N/A	Sprague dawley rats	Oxidative stress	Hepatoprotective.[118]
		N/A	Albino wister rats	Adenosine tri phosphate, melanoaldehyde, No	Neuroprotective.[120]
		SARS-CoV-2	N/A	Spike protein and ACE2	Anti-viral activity.[121]
		N/A	Albino wister rats	Gastric acid secretion	Anti-ulcerogenic activity.[122]
		Human glioma cells	N/A	Cylcic dependent kinase P27 (AMPK)	Anti-tumor activity.[123]

Anti-pyretic, anti-inflammatory and anti-nociceptive,[67] anti-viral,[68] Anti-microbial (Figure 2).[69]

Methyl gallate

Methyl gallate is gallotannin widely obtained from plant sources, one among is methyl gallate rich source is *Acacia nilotica*. It is a moderate tree that is 15–18 m tall with a stem diameter of 2-3 m. It is a member of the *Fabaceae* family (subfamily: *Mimosoideae)* of the genus Acacia, which contains around 1350 species.[70] A useful tree called *Acacia nilotica* (L.) can be found in African countries, the Middle East, and India.[71] Nearly all their parts, such as leaves, pods, roots, bark are used in medicine.[72]

The bark extract was used to isolate methyl gallate, which was then analysed using mass, UV-visible and NMR spectroscopic methods.[73] *Acacia nilotica* gum, flower, and leaf extracts demonstrate a regulating effect on the process of two-stage skin carcinogenesis. These extracts possess chemo preventive and anti-mutagenic properties, which are likely attributed to their antioxidant capabilities. They have shown the ability to hinder the development of cutaneous papilloma, induced in mice through the use of 7,12-dimethylbenz(a)anthracene (DMBA).[74] Crude root extract in aqueous and methanolic form exhibits remarkable inhibitory effect against early plasmodium infection, curative (traditional infections), in *Plasmodium berghei*-infected mice. In addition, Significant action towards chloroquine-sensitive strains is exhibithed.[75] Castor oil-induced diarrhoea has been successfully treated using an aqueous extract of *Acacia nilotica* seeds.[76] When ethanol and indomethacin were used to create gastric lesions. Root and bark extract (300 mg/kg) was studied for its anti-ulcerogenic activities. The results showed an 44.22% and 10.00%, comparatively omeprazole showed 44.06% inhibition as standard.[77] In a comparative investigation, methyl gallate rich extract of Acacia Nilotica a showed the most effectiveness against the bacteria *Escherichia coli, Staphylococcus aureus*, and *Salmonella typhi*, as well as the fungi *Candida albicans* and *Aspergillus niger* in methanolic extract.[78] In the dosage range of 3 to 30 mg/kg, the methanol extract of *Acacia nilotica* has been observed to reduce arterial blood pressure. Additionally, it exhibits an inhibitory effect on the force and rate of spontaneous contractions in paired atria of guinea pigs. Similarly, it demonstrates a concentration-dependent inhibition of spontaneous contractions in the jejunum of rabbits within the range of 0.1 to 3.0 mg/mL. Moreover, it inhibits K^+-induced contractions in rabbit jejunum at similar concentration levels. These findings suggest that the extract possesses anti-hypertensive and anti-spasmodic properties, likely achieved through the blockade of calcium channels in animal models.[79] *Acacia nilotica* extract exhibited significant dose-dependent suppressive, curative, and prophylactic effects against Plasmodium berghei NK 65, comparable to chloroquine. The extract also increased the mean survival time of treated mice and showed a safe profile with an LD_{50} of 5000 mg/kg body weight, indicating its antiplasmodial potential (Table 2).[80]

Chebulinic acid

One of the most well-known endemic multipurpose tree species is *Terminalia chebula* is also known as Haritaki, Hirda, Myrobalan, Harra and Harar.[81] The tree overall length ranges from 50 to 80 feet. It has spread branches and a rounded crown.[82] A medium to large-sized tree known as *Terminalia chebula* is found in sub-tropical and tropical Asia, including Tibet and China.[83] In fruit, Chebulinic acid and, can be found in amounts of up to 30%.[84] *Terminalia chebula* has shown a variety of therapeutic properties.[85] The *T. chebula* fruit's ethanol extract

dramatically decreased glycated hemoglobin levels and blood glucose and increased the activity of enzymes that help the body break down carbohydrates and glycogen. Additionally, it exhibits anti-hyperglycemic action by regulating PI3-K. By upregulating insulin release from the Langerhans cells, the chloroform extract helps lower blood sugar levels.[86] Chebulinic Acid (CA), a prominent component from *T. chebula's* extraction that increased mucus formation and altered H^+-K^+ ATPase function, was found to have gastroprotective properties.[87]

As per the study that investigated the inhibitory effect of phenolics on cancer cell development, chebulinic acid was discovered as the most effective growth-inhibitory constituent of *T. chebula* Retz fruit.[88] A 2:1 ratio of ethanolic extract of *T. chebula* fruits containing Chebulinic Acid (CA) and its minor isomer, neo chebulic acid, showed significant hepatoprotective activity.[89] Extracts derived from *Terminalia chebula* Retz demonstrated notable antibacterial properties, with a Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of 125 mg/L and 150 mg/L, respectively. These extracts exhibited inhibitory effects on the urease activity of *Helicobacter pylori* (*H. pylori*) a habitual bacteria connected to the the onset of tumors in the stomach, ulcers, and gastritis.[90] *Terminalia chebula* fruit extract demonstrated significant antimicrobial activity against both *S. typhi* and *S. typhimurium*, as evidenced by clear inhibition zones observed *in vitro* at concentrations ranging from 10 to 15 mg/mL. The *in vivo* study also investigated the clearance of bacteria from the liver and evaluated the levels of alanine aminotransferase and aspartate aminotransferase enzymes.[91]

Tannic acid

Tannic Acid (TA) is an profound hydrolyzable tannin, is a nutritional additive recognised by the US Food and Drug Administration.[92] A core glucose unit with ten molecules of gallic acid attached makes up the natural tannin known as tannic acid, which belongs to the phenolic acid group.[93] Tannic Acid (TA) is present in several natural sources such as coffee, green tea, grapes, and others[94] One of the earliest studies on TA was conducted in 1989, when it was discovered that TA might prevent stomach, skin, and lung tumours brought on by chemical carcinogens.[95] A formalin-induced paw oedema model has been used to research the TA's anti-inflammatory attributes. The oedema suppressing rate in the TA group was indentical to that in the indomethacin-applied group, even though the molecular mechanism is still unclear. This finding suggests that TA can suppress oedema by suppressing MPO enzyme action.[96] The quantity of phenolic hydroxyl groups determines how well tannic acid kills Staphylococcus aureus and Escherichia coli. When Tannic Acid (TA) was used as a polymer bonding agent, the resulting hydrogels exhibited anti-microbial activity on both types of bacteria, and the level of action was inversely associated with the material's TA concentration.[97] Activity of tannin against Influenza A Virus (IAV) has a 12x higher concentration than gallic acid, another phenolic acid. The anti-viral activity of galloyl depends on the overall amount of galloyl residue. Influenza A virus receptor binding and neuraminidase activity are both inhibited by TA activity. Low molecular weight tannin gallic acid, prevents hemagglutination but not neuraminidase activity. Tannic acid, hence, has greater efficacy against IAV.[98] Studies discovered that pre-treatment with TA declines structural and electrocardiographic alterations and restore cardiac shock parameters to almost normal levels in a rat model of isopreterenol-induced cardiac ischemic damage.[99] A HepG2 human hepatoma cell line was used to study the impact of TA on liver cancer cells. According to the study's findings, the use of 2 and 10 μM of TA caused the Nrf2/ARE signalling pathway to become activated. Later, antioxidant enzymes and phase II enzymes, including GST, were both inducible found.[100] By lowering free radicals and decreasing levels of pro-inflammatory cytokines including TNF-1, IL-1, and IL-6, TA has gastro-protective effects in mouse models of ulcers caused by ethanol and ethanol/HCl.[101] Therapy with TA can prevent cognition impairment in a Streptozotocin (STZ)-induced sporadic dementia model by suppressing oxidative stress and acetyl cholinesterase activity.[102] In SKH-1 hairless mice, topical administration of TA before UVB exposure significantly reduces erythema. Additionally, keratinocytes stimulated by TNF produce less IL-6 and IL-8, and TA-modified Silver Nanoparticles (AgNPs) have immunomodulatory properties.[103]

Theaflavins

The deep red colour of black tea is due to Theaflavins (TF), which have a benzotropolone skeleton and are created when certain pairs of catechins, one of which has an ortho-dihydroxy phenyl structure and the other possesses a tri hydroxyphenyl moiety, co-oxide.[104] The dry matter content of the solids in brewed black tea is known to contain 2-6% of TFs.[105] For their favourable health effects, TFs have undergone testing, and a variety of biological actions, including anti-tumor, hepatoprotective, cardioprotective, neuroprotective, anti-inflammatory effects, antioxidant, nephroprotective, and anti-microbial properties have all been studied in both *in vitro* and *in vivo* models.[106] To prevent UVR-induced photo carcinogenesis, TFs block extracellular signals that regulate protein kinase and C-Jun NH2-terminal kinase also the UVR's activator protein-1 (AP-1) activity.[107] TFs exhibit neurological benefits against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) poisoning, which causes neurodegenerative disease as Parkinson's disease, as a result of their antioxidant and anti-apoptotic qualities.[108] The influence of TFs on the infectious characteristics of *P. gingivalis* and through preventing this oral pathogen's synthesis of the matrix metalloproteinases that cause periodontitis.[109] In Japan, theaflavins are used to treat hyperglycaemia. The mechanism underlying theaflavins anti-hyperglycemic action was later the subject of numerous studies. There is evidence

that theaflavins may protect β-lymphocytes against the toxicity of STZ in Streptozotocin (STZ)-induced diabetes in mice.[110] Theaflavins' ability to prevent genotoxicity and mutagenicity by scavenging free radicals was originally demonstrated by in 1994. Theaflavins reduce DNA damage caused by carcinogens as well as oxidative stress-related cytotoxicity and cellular DNA damage by suppressing the cytochrome P450 1A1 (CYP1A1) involved in the cellular mechanism.[111] By reducing leukocyte influx and ICAM-1 formation, TFs prevented the neuronal damage in Male Sprague-Dawley rats caused by cerebral ischemia repurfusion. They also suppress the overexpression of iNOS and COX-2 in the ischemic neuronal network by mitigating STAT-1 phosphorylation.[112] TFs perform as enzyme inhibitors to limit the absorption of carbohydrates, regulate the digestion of starches, and lower postprandial hyperglycaemia.[113]

Punicalagin

Punicalagin (PUN) α and β is a form of hydrolyzable tannin consisting a high molecular weight.[114] Pomegranate and berries are the primary sources of punicalagin. Pomegranate peel often contains high levels of punicalagin, and the fruit's seed oil typically has high levels of punicic acid, both of which were reported as having profound health benefits.[115] PUN has been demonstrated to block the growth of mutagenic bacteria at higher concentration, but it also inhibits the development of biofilms and the generation of acidic and extracellular polysaccharides by *Streptococcus mutans* at sub-bactericidal concentrations, indicating that it may be able to prevent tooth decay.[116] Punicalagin has anti diabetic effects at a concentration of 50 M in both animal and *in vitro studies*, which has the effect of boosting insulin secretion. The final result of POX1 (paraoxonase-1) enzyme activity is the same as this one.

PON1 potent anti-diabetic enzyme, reduces oxidative stress and increases insulin production in beta cells, thus preventing the progression of diabetes.[117] Punicalagin shows antioxidant properties. It is a hydrolysed form of tannin found in the yellow pomegranate peel; The DPPH radical scavenger test revealed that free radical scavenging of pure Punicalagin (IC_{50} 1.9±0.2 μg/mL). was contrast to that of tannic acid (IC_{50} 1.3±0.2 μg/mL). The punicalagin content of yellowish pomegranate extract from peel produced through isolation found to be 23% PUN in 100 mg.[118] PUN can protect rats from cyclophosphamide-induced hepatotoxicity, according to research CYP is an immunosuppressive and alkylating nitrogen pyrite that is used to treat cancer. However, this substance's numerous noxious side effects reduce its potential.[119] Punicalagin exhibits neuroprotective properties at dosing of 15 and 30 mg/kg, which, based on their antioxidant capability, efficiently repair oxidative damage caused by cerebral ischemia or reperfusion through the downregulation of malondialdehyde levels, sodium-potassium adenosine triphosphatase activity, nitric oxide, and protein carbonyl content, as well as the upregulation of superoxide dismutase, catalase, glutathione peroxidase, reduced glutathione, and glutathione reductase activities.[120] Even further evidence that pomegranate extract may be used to prevent and treat SARS-CoV-2 sickness in specific study, which stated that PUN blocked the interaction between Spike protein and ACE2 and decreased viral 3CL protease activity *in vitro*.[121] Aqueous fraction of *L. pacari* and punicalagin demonstrated an antiulcerogenic effect by reducing gastric secretion volume, free acidity, and total acidity in mice after pyloric ligation for 4 hr. Additionally, it reduced the rate of gastric damage in the indomethacin induced model, indicating acid antisecretory activity as the underlying mechanism for their antiulcerogenic effects.[122] In an investigation, it was proven that PUN stimulates the phosphorylation of cyclin-dependent Kinase p27 (Kip1) on Thr198 while concurrently stimulating AMP-activated Protein Kinase (AMPK). As a consequence, human glioma cells are induced to undergo cellular autophagy through the LKB1-AMPK-p27 signalling (Table 2).[123]

CONCLUSION

The numerous studies examined here emphasize the potential of saponins and tannins as sources of bioactive substances with a range of biological effects. The combination of the *in vitro* along with *in vivo* investigations has made it possible to gain a more profound knowledge of how these compounds work and how they may be used to treat different medical conditions. The studies conducted show the versatility of saponins and tannins in treating various health conditions, from anti-inflammatory and anti-cancer capabilities to anti-hyper glycemic and anti-obesity benefits. The integration of advanced technologies, such as metabolomics and molecular modeling, will enable in-depth structure-activity relationship studies, facilitating the design of more potent and selective compounds. Moreover, the application of bio-active saponins and tannins in various fields, including medicine, agriculture, and food science, holds great potential for the development of innovative products and therapies. Continued research efforts, collaboration between multidisciplinary teams, and increased investment in this field will undoubtedly unlock the full potential of bio-active saponins and tannins, leading to significant advancements in human health and well-being.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ROS: Reactive oxygen species; **PPAR-γ:** Peroxisome proliferator-activated receptors; **AMPK:** Adenosine monophosphate-activated protein kinase; **TGF-β1:** Transforming growth factor beta 1; **Smad3:** Mothers against decapentaplegic homolog 3; **LDL:** Low-density lipoprotein; **NF-κB:** Nuclear factor kappa B; **RANKL:** Receptor activator of nuclear factor kappa-B ligand; **MAPK:** Mitogen-activated protein kinase; **NMR:** Nulclear

magnetic resonance; **PI3-K:** Phosphoinositide 3-kinases; **ATP:** Adenosine tri phosphate; **Nrf2:** Nuclear factor erythroid 2-related factor; 2**TNF-1:** Tumor necrosis factor alpha; **UVB:** Ultraviolet; **BIL:** Interlukin; **UVR:** Ultravoilet R; **iNOS:** Inducible nitric oxide synthase; **COX-2:** Cyclooxygenase-2; **PON1:** Serum paraoxonase and arylesterase1; **SARS-CoV:** Severe acute respiratory syndrome coronavirus1; **ACE2:** Angiotensin-converting enzyme 2; **LKB1:** Liver kinase B1.

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