CHAPTER 08

Saponins and Their Role in Immunomodulation and Cancer Therapy

Maryam Jameel[1], Shaista Jabeen[2*], Amsa Fatima[2], Rafia Ali[3,4], Sana Farooq[2], Muhammad Noor E Mustafa[2]

[1]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[2]University Institute of Diet and Nutritional Sciences, The University of Lahore, Lahore, Pakistan
[3]Department of Health Professional Technologies, The University of Lahore, Lahore, Pakistan
[4] Institute of Administrative Sciences, University of the Punjab, Lahore, Pakistan
*Corresponding Author: sha.jabeen4@gmail.com

ABSTRACT: Saponins represent a crucial group of plant-based secondary compounds. These macromolecules are categorized into two types: triterpenoid and steroid glycosides, whose structures vary depending on the number and position of the attached sugar units. Plant saponins benefit the immune system by stimulating organ growth and development through multiple signaling routes. Furthermore, they manage immune cell function and trigger the generation of antigen-specific antibodies and cytokines, which leads to the activation of the immune response. Saponins display anticancer effects by inhibiting cancer cell growth, preventing metastasis, blocking angiogenesis and controlling drug resistance as well as autophagy. Saponins exhibit anti-cancer activities via targeting NF-κB and PI3K/Akt signaling pathways. Furthermore, saponins used in combination treatment increase the susceptibility of chemoresistant tumor cells to chemotherapeutic drugs. Saponins, as bioactive components, have considerable potential in the development of innovative therapeutics for cancer and immune-related disorders. Overall, this chapter emphasizes the importance of saponins as prospective bioactive molecules with therapeutic applications in immunomodulation and cancer.

Keywords: Saponins, immunomodulation, anticancer activity, natural compounds, steroid glycosides

Natural substances that are biologically active have always been important, regardless of whether they come from plants or animals. Scientific research demonstrates that these substances reduce blood cholesterol levels, manage blood pressure and fight reactive oxygen species as well as reduce the risk of cancer, cardiovascular diseases, osteoporosis, inflammation, type II diabetes and other chronic degenerative diseases. Recent research on saponins has focused on characterizing their biosynthesis, structure, and distribution, while simultaneously optimizing extraction methods and assessing their economic and therapeutic benefits (El Aziz et al., 2019). Bioactive substances such as saponins hold great value since they demonstrate multiple beneficial biological activities. The commercial utilization of saponins now extends beyond their role from processing aid agents to health supplement products.

Saponins exist as chemical compounds that contain steroidal or triterpenoid aglycones joined to at least one sugar chain in their molecular structures. Saponins form a large and common category of heterosides in plants. Their structural variety is reflected in their surface-active qualities, physiological, and biological features; their ability to reduce surface tension causes them to dissolve in water and generate a foamy solution (Roopashree & Naik, 2019). They are often classified into two major categories depending on the structure of the aglycone, i.e., steroidal saponins and triterpenoid

How to Cite: Jameel M, S Jabeen, A Fatima, R Ali, S Farooq & MNE Mustafa, 2025. Saponins and Their Role in Immunomodulation and Cancer Therapy. In: Natural Products in Biomedical Research (Ijaz MU & A Ashraf, Eds.): FahumSci, Lahore, Pakistan, pp: 82-89. ISBN: 978-627-7745-15-8. https://doi.org/10.61748/NPBR.2025/08

saponins. Triterpene aglycones consist of only six rings and 30 carbon atoms in total. Steroidal aglycones include five rings and just 27 carbon atoms (Xu et al., 2023).

In nature, saponins are extensively distributed and present in a variety of plants as well as some marine organisms, such as sponges, sea cucumbers, and sea stars (Decroo et al., 2017). Consuming beans is the main dietary source of saponin intake. One of the most often ingested forms of legume saponins is found in soybeans. Variations in cultivars, growing areas, soil types, irrigation conditions, and climate can all affect the amount, structure, and composition of saponins. Numerous plant species, including *Chlorophytum borivilianum*, *Glycyrrhiza glabra*, *Panax ginseng*, *Bacopa monnieri*, and *Ilex paraguariensis*, are abundant sources of saponins. The enormous quantity of saponins found in these plants are mostly responsible for their gesticulatory, antidiabetic, immunomodulatory, antibacterial, insecticidal and androgenic traits (Kajal & Singh, 2017).

Saponins derived from a variety of plants have antibacterial effects on a range of bacterial and fungal species. According to reports, quinoa saponins that are extracted from the husks of *Chenopodium quinoa* have antibacterial properties against *Staphylococcus epidermidis*, *S. aureus* and *Bacillus cereus*. These compounds cause significant harm by breaking down the bacterial cell wall and then disrupting the cytoplasmic membrane and membrane proteins (Dong et al., 2020). The antifungal properties of *Ziziphus joazeiro* (bark) saponins demonstrate effectiveness against *Aspergillus niger* and *Candida albicans*. The antioxidant properties are shown by saponins from different plants i.e., *Agave sisalana* steroid saponins, *Z. joazeiro* triterpenic saponins, Camellia root and seed cake saponins (Hu et al., 2012). Saponins are known for their antidiabetic effects because they show potential to decrease high blood plasma glucose concentrations (Zheng et al., 2012). Total saponins extracted from *Stauntonia chinensis* stems demonstrated hypoglycemic and hypolipidemic effects, which led to potential type-2 diabetes treatment applications (Xu et al., 2018). The current chapter discusses the medicinal potentials of saponins in detail.

STRUCTURAL CLASSIFICATION AND BIOAVAILABILITY CHALLENGES

Saponins consist of non-sugar aglycones attached to sugar chain units to form their complex structure. The sugar chain length of saponins determines their classification into monodesmoside, bidesmoside or tridesmoside based on their single, double, or triple sugar chains. Saponins belong to two different classes according to their triterpene or steroidal aglycone composition i.e., sapogenins. Multiple functional groups (-OH, -COOH, -CH3) exist within triterpene and steroidal aglycones. The natural diversity of saponin structures emerges from multiple functional groups and various sugar chain compositions, as well as attachment options. Different parts of the same plant species produce saponins with unique structural compositions.

Saponins, i.e., triterpenoid saponins and steroidal saponins, stem from 30 carbon atoms that begin with squalene oxide (Yao et al., 2020). The main difference between the two types of saponins lies in the fact that triterpenoid saponins contain 30 carbon atoms, but steroidal saponins contain 27 carbon atoms. These compounds share common characteristic because they possess one or more sugar chains that connect to aglycones through glycoside ether or ester linkages. The glycochain in monosaccharide saponins attaches to the aglycone through a glycosidic bond at position C-3. Glycosidic bonds can form connections not only at C-3 but also at C-6, C-26, and C-28. Saponin aglycones have distinct structural differences (Cui et al., 2023).

The bioactivity of dietary ingredients is dependent on their release, digestion, absorption, distribution, and metabolism. During digestion and absorption, a small number of ingested saponins enter the bloodstream, undergo phase I/II reactions, and are distributed throughout the body. Saponins, like many other phytochemicals such as polyphenols and flavonoids, have been shown to have low bioavailability (Navarro del Hierro et al., 2020), which means they do not enter the circulation or target organs in their natural form. The metabolism of gut flora has a crucial role in improving saponin bioavailability and pharmacological action. The majority of pentacyclic triterpenes, including lupeol, betulinic acid, oleanolic acid, and ursolic acid, have moderate to poor bioavailability due to adverse solubility. The bioavailability of sapogenins can be enhanced by making them more water-soluble in intestinal fluid, which proves to be a simpler for saponin bioavailability improvement (Furtado et al., 2017).

The structural complexity of saponins increases following glycosylation, which can hinder their extraction and isolation. Research has shown that aglycon compounds exhibit stronger cardioprotective effects than their glycoside counterparts (Zhang et al., 2013). Wang et al. (2010) analyzed the relationship between structural elements of 20(S)-protopanaxadiol and its synthetic counterparts (20S,24S)-epoxydammarane-3β,12β,25-triol and (20S,24R)-epoxydammarane-3β,12β,25-triol and their functional characteristics. The administration of 20(S)-protopanaxadiol, as well as its 24(R)-epoxy epimeric derivatives protected heart tissue from ischemic damage through antioxidant system strengthening (Singh et al., 2018).

IMMUNOMODULATORY PROPERTIES OF SAPONINS

The immune system utilizes various types of immune cells to achieve its functional operations. Research indicates that saponins boost the phagocytic function of macrophages together with the cytotoxic function of natural killer cells, thus controlling the innate immune response. Saponins increase dendritic cell antigen presentation while activating different T lymphocyte subsets including Th1, Th2 and CTL. Moreover, they trigger B lymphocytes to become plasma cells which then produce specific antibodies, thus strengthening the adaptive immune response (Shen et al., 2023).

Mechanisms of Immune Activation

Saponins serve to enhance the body's humoral immunity through their ability to boost B lymphocyte antibody production to antigens while regulating immune cell movement and intracellular pathways as well as promoting T lymphocyte development into $CD4^+$ Th cells for multiple immune functions and enhancing cytokine and chemokine secretion throughout immune response processes. The stimulation of T lymphocytes occurs through three distinct signals that antigen-presenting cells (APC) exchange with T lymphocytes. The immune response begins when APCs present antigen fragments via MHC class II molecules, which are recognized by T cell receptors. Concurrently, APCs provide a crucial second signal by using co-stimulatory molecules to engage T lymphocytes. Additionally, APCs release cytokines that regulate and shape the overall immune process (Wang et al., 2016). The initial activation of primary T lymphocytes leads to their differentiation into multiple effector T cell types which include Th1, Th2 and Th17 (Yang et al. 2015). Ginseng saponin immunomodulators boost cytokine production through their influence on Th1 cells which results in increased TNF-α levels and enhanced antibacterial activity and other effects (Wang et al., 2020).

Quillaja saponin-21 (QS-21) is a component of Quil A and is an acylated triterpene glycoside saponin (a combination of saponins) isolated from the bark of the *Quillaja saponaria* Molina tree. Quil-A combination and QS-21 are adjuvants capable of stimulating both cellular and humoral immunity (Zhu & Tuo, 2015). Among the saponins in the Quil A combination, QS-21 possesses excellent adjuvant properties while being low in toxicity. The adjuvant QS-21 was recently used in clinical research for therapeutic vaccination against certain cancers. QT-0101, a deacylated version of QS-21, increased IgG1 antibodies while decreasing IgG2a antibodies and IFN-γ cytokine levels when injected with ovalbumin antigen in mice (Marciani, 2014). The QT-0101 adjuvant demonstrates potential to adjust immune responses while controlling inflammation caused by auto-antigens (Heidari et al., 2019).

Regulation of Th1/Th2 Balance and Dendritic Cell Function

Dendritic cells (DCs) function as professional antigen-presenting cells, which connect innate immunity to adaptive immune responses. These cells play a fundamental role during both the initiation and control phases of immune responses. The ability of DCs to carry tumor antigens to draining lymph nodes activates T cells, which serve as a fundamental process for T cell-dependent immunity and immune checkpoint blockade (ICB) therapy (Zhou et al., 2020). Mature DCs discharge IL-12, which stimulates Th1 cell growth. The activation of DCs in tumor patients proves to be an effective anti-tumor immunotherapy approach for T cell activation (Sabado et al., 2017). Research demonstrates that polysaccharides along with terpenoids and flavonoids, promote DC maturation while enhancing antigen-presenting function and controlling tumor immune microenvironments through direct influence on DC surface proteins, MyD88 pathway modulation and immunogenic cell death (ICD) induction (Han et al., 2022). The mechanism of immune activation by saponins has been illustrated in Fig. 1.

Anti-inflammatory vs. Pro-inflammatory Dual Roles Based on Dose and Structure

Research interest in natural compounds for therapeutic applications continues to grow mainly because these substances could potentially regulate inflammation which serves as a fundamental factor in sustaining numerous prolonged disorders. The natural bioactive chemical saponins stand out as potential therapeutic agents because researchers have identified their anti-inflammatory effects. IL-1 together with IL-6 and TNF-α trigger inflammatory processes while IL-10 functions to terminate these processes (Docherty et al., 2022).

The chemokine family which includes CCL2 (monocyte chemoattractant protein-1) and interleukin-8, functions to guide immune cells toward affected regions of damage or infection to support their defensive operations. Pattern recognition receptors (PRRs), including toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) detect specific molecular patterns from infections or dangers to trigger potent inflammatory reactions (Ostrycharz & Hukowska-Szematowicz, 2022). The combination of these molecular elements forms an intricate network that enables precise and adaptable inflammatory regulation (Vu et al., 2013). Medical drugs provide advantages, but they produce adverse effects and have limited capabilities (Moura et al., 2018). People use pharmaceuticals extensively to handle inflammation, but recent trends indicate increasing interest in natural and nutritional strategies for inflammation management. The use of saponins as anti-inflammatory agents aligns with the current movement which focuses on alternative medicines to maintain health and inhibit diseases (Khan et al., 2022).

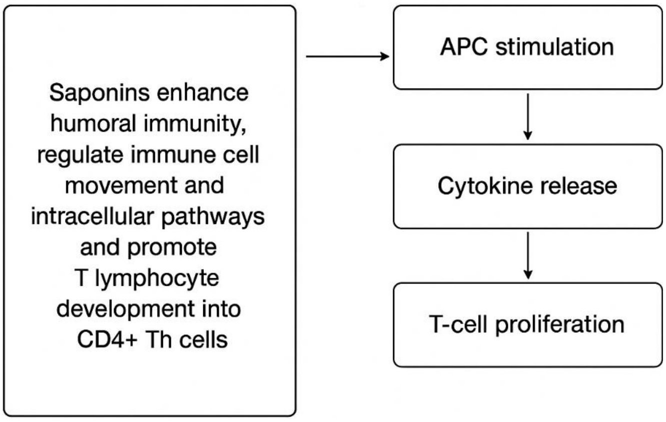

Fig 1. Mechanism of immune activation by saponins

Applications for Immunotherapy and Autoimmune Disorders

The immune cell activation along with cytokine release by saponins occurs through several immune-related signaling pathways that include nuclear factor-kappa B (NF-κB), TLR and hippo-Yes-associated protein (hippo-YAP). They initiate innate immune responses and enhance antigen-specific immune responses. TLRs function as transmembrane receptors that detect foreign microorganisms such as bacteria and viruses; their triggering and subsequent immune responses enable immune cells to detect microorganisms and release immunomodulatory factors via their signaling pathways. The TLRs have the capacity to identify plant-based molecules such as saponins and polysaccharides as well as flavonoids which trigger downstream signaling pathways. The stimulation of TLRs signaling pathway through ginseng stem leaf saponins enables immune cells to migrate more effectively, while promoting antigen-presenting cells to express higher levels of MHC class I and II molecules and better capture and process antigens (Shen et al., 2023).

ANTICANCER PROPERTIES AND CYTOTOXIC MECHANISMS

Saponins have a diverse range of biological actions, the most well-studied of which are their cytotoxic and antitumor activities.

Induction of Apoptosis: Caspase Activation

Apoptosis, or programmed cell death, is a highly controlled process that is activated by either the death receptor route (the extrinsic) or the mitochondrial system (the intrinsic). Thus, targeting programmed cell death has emerged as a viable technique in cancer treatment. Saponins promote apoptosis by activating a protease family of enzymes known as caspase. Saponin-induced cell death through apoptosis operates through multiple caspase-independent pathways in addition to the caspase-dependent mechanisms. The enzymes known as caspases function as cysteine-dependent aspartate-specific proteases which control both the beginning and final stages of apoptotic cell death. These enzymes exist as inactive pro-enzymes or zymogens which become active through receptor-mediated or mitochondria-dependent activation mechanisms. The activation of caspase-8 by saponins through intrinsic pathways cannot independently start apoptosis so some saponins depend on BCl-2 protein family to link with intrinsic apoptosis pathways for cell death induction. Cancer cells that contain p53 mutations block apoptosis through the intrinsic pathway so this alternative cell death mechanism can kill p53 mutant cancer cells (Stefanowicz-Hajduk et al., 2015).

Inhibition of Cancer Cell Proliferation and Metastasis

Malignant tumor cells start in one area and spread through lymphatic vessels and blood vessels to distant tissues. The majority of cancer patients experience death because their tumors spread throughout their bodies which results in 90% of cancer fatalities. Genetic changes within metastatic cancer cells allow them to maintain their survival when they spread to faraway areas. The extracellular matrix (EM) functions as a barrier that tumor cells must traverse during their metastatic spread. Cancer cell invasion relies on this fundamental mechanism which requires the destruction of EM through proteolytic enzymes, including MMP2 and MMP9. Cancer cells generate elevated levels of MMP-2 and MMP-9 during their progression. Saponins demonstrate their ability to block cancer metastasis through their interference with multiple proteins involved in tissue remodeling pathways during *in vitro* and *in vivo* studies. Saponins have been discovered to possess outstanding abilities to selectively target matrix degeneration proteins, including MMP-2 together with vimentin and MMP-9. Ginsenoside Rd specifically decreases the production levels of MMP-1, MMP-2 and MMP-7 (Wang et al., 2014).

Notable Examples

Saponins exhibit the capability to stop the formation of blood vessels within tumor cells. The dammarane saponin Ginsenoside-Rb2 demonstrates its ability to prevent tumor-related blood vessel formation which results in slowed tumor progression in B16-BL6. According to the study by Chan et al. (2011), polyphyllin D controls endothelial cell growth and movement during *in vitro* tests and affects intersegmental vessel (ISV) formation in zebrafish. The compound *Panax notoginseng* demonstrates an ability to restore proper ISV development within zebrafish larvae (Yang et al., 2016).

Yang et al. (2015) demonstrated that Paris saponin II (PSII) prevents cancer cell angiogenesis at minimal doses and does not harm endothelial cells which are normal. PSII exerts its anti-angiogenic effects through controlling NF-κB expression levels. The reduction of NF-κB expression by PSII resulted in lowered protein activity for VEGF, Bcl-2 and Bcl-xL.

Chemoprevention is defined as the use of natural or synthetic substances to prevent, reverse, or suppress the process of carcinogenesis before the development of invasive, clinical cancer. Saponins demonstrate their chemopreventive properties through anti-inflammatory effects and redox potential control as well as multiple pathways to restrict cell growth. The study by Xie et al. (2017) revealed Paris saponins from *Paris polyphyllae* trigger autophagy in breast cancer cells by reducing Akt/mTOR signaling. Triterpenoid glycosides demonstrate their ability to induce apoptosis in hepatocellular carcinoma through their effects on PI3K/Akt/mTOR signaling (Xue et al., 2019). The inhibition of mTOR to stimulate autophagy represents a promising cancer chemoprevention technique that helps decrease metabolic stress accumulation.

SAPONINS AS VACCINE ADJUVANTS AND PHARMACEUTICAL AGENTS

QS-21 and other triterpene saponin adjuvants are made up of amphiphilic glycosides with a lipophilic triterpene nucleus that usually comprises one or two hydrophilic saccharide chains formed by O-heterosidic bonds and ester linkages, resulting in monodesmosidic or bidesmosidic glycosides. The oligosaccharide chains attach to QS-21 triterpene aglycone at positions C-3 and C-28 with the C-28 oligosaccharide containing an acylated fucopyranosyl residue which differs between glycosides. The fucopyranosyl unit in QS21 forms an ester bond with the C-28 triterpene aglycone carboxyl group through its 1-hydroxyl group and carries a rhamnosyl unit at position 2 and 3,5-dihydroxy-6-methyl octanoic acids at position 4 in a continuous sequence (Marciani, 2014). Different saponins contain imine-forming carbonyl groups at various positions, including acyl chain regions which can transform into ketone or other molecular structures. The scientists revealed the full chemical synthesis process of GPI-0100 in their recent publication which shows the compound produces Th1 responses at doses that exceed QS-21 by a factor of five to ten (Wang et al., 2016). The new alkyl chain replacement with cyclohexyl compounds results in the loss of GPI-0100's ability to produce Th1 immune responses. The production of QS-21 and new saponin derivatives with adjuvant properties will help scientists understand how these saponins work as adjuvants (Fernández-Tejada et al., 2016).

Mechanisms of Adjuvanticity

Saponins have become popular vaccine adjuvants because they produce multiple biological and immune system effects. The saponin adjuvant Quil-A together with its purified component QS-21 represent the most extensively used adjuvant because they maximize antibody responses while activating cytotoxic T lymphocytes cells and T helper cells through dendritic cell stimulation (Chen et al., 2023). The adjuvant shows its effectiveness through the combination of branched sugar chains, an acyl residue and aldehyde groups which exists on the aglycone structure (Detienne et al., 2016). Research indicates that the aldehyde group on triterpene molecules serves as an essential factor for saponin adjuvanticity because QS-21 derivatives which lost their aldehyde groups, failed to demonstrate any adjuvant activity in stimulating antibodies and inducing CTL responses. The acyl chains of QS-21 demonstrate a relationship with cytotoxic T-cell proliferation because removing the acyl chain shows no effect on antibody and CTL response stimulation. Soyasaponins and lablabosides function as effective adjuvants even though they do not contain acyl residues. Saponins exhibit their adjuvant properties through their amphiphilic design that consists of a hydrophobic aglycone core and hydrophilic sugar chains. The triterpene needs to bind with cholesterol to perform antigen cross-presentation and QS-21 activates lysosomal membrane disruption through cholesterol-dependent cytocytosis which activates innate immunity (Marciani, 2018).

Role in Mucosal and Intranasal Vaccine Platforms

Nasal vaccinations provide an effective method to create antigen-specific immune defenses which protect mucosal surfaces and offer protection to the entire body. The respiratory system operates with distinct physical and immune features which allow the nasopharyngeal-associated lymphoid tissue to function as a primary mucosal immune activation zone during nasal vaccine delivery. The nasal vaccine method produces superior mucosal immune responses than standard injection vaccines because it activates particular T cell responses and produces secretory immunoglobulin A. The body dispatches IgA to identify pathogens which allows for their elimination before infections start to take hold. Vaccine formulation requires adjuvants to enhance antigen immunogenicity, so they create enduring protective immunity. Experiments demonstrate that saponins when used as adjuvants in nasal vaccines, produce strong immune protection across mucosal surfaces and throughout the entire body (Chen et al., 2023).

Emerging Delivery Systems for Enhanced Immunogenicity and Stability

The major goal of vaccine adjuvant design and development is to guarantee that vaccination preparations efficiently activate the immune system, induce protective or therapeutic immunological responses, and are safe (Kumar et al., 2018). The continuous optimization of vaccine development procedures stands as a vital step to reach this goal. The scientific community actively investigates adjuvants together with delivery carriers, which serve as essential components for eliciting strong and long-lasting immune responses during acquired immunodeficiency syndrome treatment. The use of delivery vectors represents a necessary alternative because unmodified antigens typically fail to trigger powerful immune reactions. The delivery system of nanocarriers executes multiple operational tasks. The combination of nanoparticles with antigens and adjuvants enables them to protect these substances from enzymatic degradation within the body, thus extending their stability. In vivo, APCs demonstrate enhanced efficiency when they phagocytize and digest nanoparticles (AbdelAllah et al., 2020). The design of targeting ligands on nanoparticle surfaces enables the achievement of specific targeting for immune organs or immune cells by directing them towards lymph nodes or APCs (Saraf et al., 2020).

CONCLUSION

Saponins represent a group of chemical substances from plants and herbs that demonstrate promising immunomodulatory and anticancer capabilities. The immunomodulatory effects of saponins emerge through multiple signaling pathways to boost immune organ development and maturation, increase immunological cytokines and antigen-specific antibodies also regulate immune cell behavior. Despite advances in the application of saponin for cancer therapy, toxicity and limited bioavailability remain key challenges. Furthermore, the relevance of various saponin scaffolds shows uncertain anticancer activity, making medication optimization problematic. So far, the most promising approaches to saponin research have been combination treatment and more efficient drug delivery systems. Plant saponins have a unique chemical structure that, while providing immune-boosting benefits, also has hemolytic and cytotoxic properties, limiting their use. As a result, saponins offer enormous potential due to their immunomodulatory and anticancer activities.

REFERENCES

AbdelAllah NH, Y Gaber, ME Rashed et al., 2020. Alginate-coated chitosan nanoparticles act as effective adjuvant for hepatitis A vaccine in mice. International Journal of Biological Macromolecules 152:904-12.

Chan JYW, JCM Koon, X Liu et al., 2011. Polyphyllin D, a steroidal saponin from *Paris polyphylla*, inhibits endothelial cell functions in vitro and angiogenesis in zebrafish embryos in vivo. Journal of Ethnopharmacology 137:64-9.

Chen K, N Wang, X Zhang et al., 2023. Potentials of saponins-based adjuvants for nasal vaccines. Frontiers in Immunology 14:1153042.

Cui X, X Ma, C Li et al., 2023. A review: structure–activity relationship between saponins and cellular immunity. Molecular Biology Reports 50:2779-93.

Decroo C, E Colson, M Demeyer et al., 2017. Tackling saponin diversity in marine animals by mass spectrometry: Data acquisition and integration. Analytical and Bioanalytical Chemistry 409:3115-26.

Detienne S, I Welsby, C Collignon et al., 2016. Central role of CD169+ lymph node resident macrophages in the adjuvanticity of the QS-21 component of AS01. Scientific Reports 6:39475.

Docherty S, R Harley JJ McAuley et al., 2022. The effect of exercise on cytokines: Implications for musculoskeletal health: a narrative review. BMC Sports Science, Medicine and Rehabilitation 14:5.

Dong S, X Yang, L Zhao et al., 2020. Antibacterial activity and mechanism of action saponins from *Chenopodium quinoa* Willd. husks against foodborne pathogenic bacteria. Industrial Crops and Products 149:112350.

El Aziz MMA, AS Ashour & ASG Melad, 2019. A review on saponins from medicinal plants: chemistry, isolation, and determination. Journal of Nanomedicine Research 8:6-12.

Fernández-Tejada A, DS Tan & DY Gin, 2016. Development of improved vaccine adjuvants based on the saponin natural product QS-21 through chemical synthesis. Accounts of Chemical Research 49:1741-1756.

Furtado NAJC, L Pirson, H Edelberg et al., 2017. Pentacyclic triterpene bioavailability: An overview of in vitro and in vivo studies. Molecules 22:400

Han, S, S Bi, T Guo et al., 2022. Nano co-delivery of Plumbagin and Dihydrotanshinone I reverses immunosuppressive TME of liver cancer. Journal of Controlled Release 348:250-63.

Heidari AR, S Boroumand-Noughabi, R Nosratabadi et al., 2019. Acylated and deacylated quillaja saponin-21 adjuvants have opposite roles when utilized for immunization of C57BL/6 mice model with MOG35-55 peptide. Multiple Sclerosis and Related Disorders 29:68-82.

Hu JL, SP Nie, DF Huang et al., 2012. Extraction of saponin from *Camellia oleifera* cake and evaluation of its antioxidant activity. International Journal of Food Science and Technology 47:1676-87.

Kajal M & K Singh, 2017. Small RNA profiling for identification of miRNAs involved in regulation of saponins biosynthesis in *Chlorophytum borivilianum*. BMC Plant Biology 17:265.

Khan MI, G Karima, MZ Khan et al., 2022. Therapeutic effects of saponins for the prevention and treatment of cancer by ameliorating inflammation and angiogenesis and inducing antioxidant and apoptotic effects in human cells. International Journal of Molecular Sciences 23:10665.

Kumar A, TS Meldgaard & S Bertholet, 2018. Novel platforms for the development of a universal influenza vaccine. Frontiers in Immunology 9:600.

Marciani DJ, 2014. New Th2 adjuvants for preventive and active immunotherapy of neurodegenerative proteinopathies. Drug Discovery Today 19:912-20.

Marciani DJ, 2018. Elucidating the mechanisms of action of saponin-derived adjuvants. Trends in Pharmacological Sciences 39:573-85.

Moura MDG, LC Lopes, MT Silva et al., 2018. Use of steroid and nonsteroidal anti-inflammatories in the treatment of rheumatoid arthritis: Systematic review protocol. Medicine 97:12658.

Navarro del Hierro J, G Reglero & D Martin, 2020. Chemical characterization and bioaccessibility of bioactive compounds from saponin-rich extracts and their acid-hydrolysates obtained from fenugreek and quinoa. Foods 9:1159.

Ostrycharz E & B Hukowska-Szematowicz, 2022. New insights into the role of the complement system in human viral diseases. Biomolecules 12:226.

Roopashree KM & D Naik, 2019. Saponins: properties, applications and as insecticides: a review. Bioscience Trends 8:1-14.

Sabado RL, S Balan & N Bhardwaj, 2017. Dendritic cell-based immunotherapy. Cell Research 27:74-95.

Saraf S, S Jain, RN Sahoo et al., 2020. Lipopolysaccharide derived alginate coated Hepatitis B antigen loaded chitosan nanoparticles for oral mucosal immunization. International Journal of Biological Macromolecules 154:466-76.

Shen L, H Luo, L Fan et al., 2023. Potential immunoregulatory mechanism of plant saponins: a review. Molecules 29:113.

Singh D & PK Chaudhuri, 2018. Structural characteristics, bioavailability and cardioprotective potential of saponins. Integrative Medicine Research 7:33-43.

Stefanowicz-Hajduk J, R Bartoszewski, S Bartoszewska et al., 2015. Pennogenyl saponins from *Paris quadrifolia* L. induce extrinsic and intrinsic pathway of apoptosis in human cervical cancer HeLa cells. PLoS ONE 10:e0135993.

Vu D, DB Huang, A Vemu et al., 2013. A structural basis for selective dimerization by NF-κB RelB. Journal of Molecular Biology 425:1934-45.

Wang H, X Zhang, X Zheng et al., 2016. Prevention of allograft rejection in heart transplantation through concurrent gene silencing of TLR and kinase signaling pathways. Scientific Reports 6:33869.

Wang P, DA Devalankar, Q Dai et al., 2016. Synthesis and evaluation of QS-21-based immunoadjuvants with a terminal-functionalized side chain incorporated in the west wing trisaccharide. The Journal of Organic Chemistry 81:9560-6.

Wang P, J Cui, X Du et al., 2014. Panax notoginseng saponins (PNS) inhibits breast cancer metastasis. Journal of Ethnopharmacology 154:663-71.

Wang T, Q Meng, J Zhang et al., 2010. Study on the structure–function relationship of 20(S)-panaxadiol and its epimeric derivatives in myocardial injury induced by isoproterenol. Fitoterapia 81:783-7.

Wang Y, X Cui, L Yuan et al., 2020. A Solution with ginseng saponins and selenium as vaccine diluent to increase Th1/Th2 immune responses in mice. Journal of Immunology Research 20:2714257.

Xie ZZ, MM Li, PF Deng et al., 2017. Paris saponin-induced autophagy promotes breast cancer cell apoptosis via the Akt/mTOR signaling pathway. Chemico-Biological Interaction 264:1-9.

Xu C, B Xia, Z Zhang, Y Lin et al., 2023. Research progress in steroidal saponins from the genus *Polygonatum*: chemical components, biosynthetic pathways and pharmacological effects. Phytochemistry 213:113731.

Xu J, S Wang, T Feng et al., 2018. Hypoglycemic and hypolipidemic effects of total saponins from *Stauntonia chinensis* in diabetic db/db mice. Journal of Cellular and Molecular Medicine 22:6026-38.

Xue S, Y Zhou, J Zhang et al., 2019. Anemoside B4 exerts anti-cancer effect by inducing apoptosis and autophagy through inhibiton of PI3K/Akt/mTOR pathway in hepatocellular carcinoma. American Journal of Translational Research 11:2580-9.

Yang BR, KK Cheung, X Zhou et al., 2016. Amelioration of acute myocardial infarction by saponins from flower buds of *Panax notoginseng* via pro-angiogenesis and anti-apoptosis. Journal of Ethnopharmacology 181:50-8.

Yang M, J Zou, H Zhu et al., 2015. Paris saponin II inhibits human ovarian cancer cell-induced angiogenesis by modulating NF-κB signaling. Oncology Reports 33:2190-8.

Yang M, Y Liu, G Ren et al., 2015. Increased expression of surface CD44 in Hypoxia-Dcs skews helper T Cells toward a Th2 polarization. Scientific Reports 5:13674.

Yao L, J Lu, J Wang et al., 2020. Advances in biosynthesis of triterpenoid saponins in medicinal plants. Chinese Journal of Natural Medicine 18:417-24.

Zhang W, X Wang, H Tang et al., 2013. Triterpenoid saponins from *Clematis tangutica* and their cardioprotective activities. Fitoterapia 84:326-31.

Zheng T, G Shu, Z Yang et al., 2012. Antidiabetic effect of total saponins from *Entada phaseoloides* (L.) Merr. in type 2 diabetic rats. Journal of Ethnopharmacology 139:814-21.

Zhou Y, N Slone, T Chrisikos et al., 2020. Vaccine efficacy against primary and metastatic cancer with in vitro-generated CD103+ conventional dendritic cells. The Journal for Immunotherapy of Cancer 8:e000474.

Zhu D & W Tuo, 2015. QS-21: a potent vaccine adjuvant. Natural Products Chemistry Research 3:1-11.