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REVIEW

IMMUNOMODULATORY PROPERTIES OF PHYTOCOMPOUNDS

Blanca Liliana Sánchez-Rodríguez[1,2], David Pedroza-Escobar*[1], Lisset-Esmeralda González-Manjarrez[2], Alejandra Torres-Flores[2], Irais Castillo-Maldonado[1], DealmyDelgadillo-Guzmán[2], Tania González-Cortés[1], Cecilia Hernández-Morales[3], Pedro IV González-Luna[3], Erika Flores-Loyola[4], Agustina Ramírez-Moreno[4], Joaquín Avalos-Soto[5] and Miguel Ángel Téllez-López[5]

[1]Centro de Investigacion Biomedica. Universidad Autonoma de Coahuila. Unidad Laguna. Torreon, Coahuila, 27000, Mexico
[2]Facultad de Medicina. Universidad Autonoma de Coahuila. Unidad Laguna. Torreon, Coahuila, 27000, Mexico
[3]Facultad de Odontologia. Universidad Autonoma de Coahuila. Unidad Laguna. Torreon, Coahuila, 27000, Mexico
[4]Facultad de Ciencias Biologicas, Unidad Laguna. Torreon, Coahuila, 27087, Mexico
[5]Cuerpo Académico Farmacia y Productos Naturales, Facultad de Ciencias Químicas, Universidad Juárez del Estado de Durango, Gómez Palacio, Mexico.
Email: dpedroza@uadec.edu.mx

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Abstract: Phytocompounds are naturally occurring bioactive molecules synthesized by plants that have demonstrated diverse pharmacological properties, including immunomodulatory effects. These compounds are classified into several categories such as polyphenols, alkaloids, saponins, terpenoids, glycosides, and phytosterols. Phytocompounds can modulate immune responses through mechanisms involving cytokine regulation, immune cell activation, enhancement of antigen presentation, and modulation of inflammatory signaling pathways. This review aims to provide a comprehensive overview of the immunomodulatory properties of several notable phytocompounds, including quercetin, tannic acid, curcumin, vincristine, *Quillaja saponaria*, ginsenosides, betulinic acid, and resveratrol. The therapeutic potential of these compounds is described in contexts such as vaccine adjuvants, treatment of autoimmune and inflammatory disorders, cancer therapy, and infectious disease management. Despite their promising biological activities, challenges remain in terms of standardization, bioavailability, and understanding of their precise mechanisms of action. Future research should focus on improving phytocompound formulations, elucidating their immunomodulatory mechanisms, and conducting rigorous clinical trials to optimize their therapeutic applications.

Keywords: Phytocompounds, Immunomodulation, *Curcumin*, Vincristine, *Quillaja saponaria*, Ginsenosides, Resveratrol

INTRODUCTION

Phytocompounds, also known as phytochemicals, are naturally occurring bioactive substances found in plants. These molecules are of significant interest for researchers due to their potential health benefits and therapeutic properties (Ramos Mendonça-Filho, 2006). Although these compounds are not essential nutrients like vitamins or minerals, they are synthesized by plants to serve various physiological and ecological functions, including defense mechanisms against pathogens, herbivores, and environmental stressors (Ahmad *et al*., 2014). In recent decades, the study of phytocompounds has expanded beyond their ecological roles to encompass their pharmacological properties and applications in medicine (Esmeeta *et al*., 2022; Çoban *et al*., 2020; Diniz do Nascimento *et al*., 2020).

The historical use of plants for medicinal purposes can be traced back to ancient civilizations across the world. Traditional medical systems such as Ayurveda, Traditional Chinese Medicine, and Indigenous healing practices have long utilized plant-based remedies for the treatment of various ailments (Kataria& Singh, 2024; Wang *et al*., 2021; Elendu, 2024). Many of these traditional practices have been supported by scientific evidence in recent years, which has led to a resurgence of interest in phytocompounds as potential therapeutic agents (Almutairi *et al*., 2022; Mohanty *et al*., 2023; Razavi *et al*., 2021). Moreover, analytical techniques and molecular biology have facilitated the identification and characterization of numerous phytocompounds with promising biological activities (Mondal *et al*., 2024).

Phytocompounds are broadly classified into several categories based on their chemical structure and

*Corresponding Author

properties (Reyna-Margarita et al, 2019). These categories include polyphenols, alkaloids, saponins, terpenoids, glycosides, and phytosterols. Among these, polyphenols are the most extensively studied due to their potent antioxidant and anti-inflammatory properties (Khan & Mukhtar, 2018). Polyphenols include flavonoids, phenolic acids, tannins, and stilbenes, which are commonly found in fruits, vegetables, tea, coffee, wine, and various medicinal plants (Luca *et al*., 2020). Notable polyphenols such as quercetin, resveratrol, curcumin, and tannic acid have demonstrated a wide range of biological activities, including antimicrobial, anti-inflammatory, antioxidant, and immunomodulatory effects (Georgiou *et al*., 2023; Galiniak *et al*., 2019; Nelson *et al*., 2017; Jing *et al*., 2022).

Alkaloids represent another major class of phytocompounds known for their diverse pharmacological properties. These nitrogen-containing compounds are predominantly found in plants and exhibit a broad spectrum of biological activities, ranging from analgesic and anti-inflammatory to anticancer and antimicrobial effects (Bhambhani *et al*., 2021). One of the most well-known alkaloids with immunomodulatory properties is vincristine, a chemotherapeutic agent derived from the plant *Catharanthus roseus* (Shukla *et al*., 2023). Vincristine has been used effectively for the treatment of various cancers and is known to modulate immune responses by targeting specific cellular pathways.

Saponins are glycosidic compounds commonly found in a variety of plants, particularly in legumes and certain medicinal herbs. They are characterized by their surfactant-like properties, which allow them to form complexes with cholesterol and other lipids. This characteristic has made saponins valuable not only in the food industry but also in pharmaceutical applications (Timilsena *et al*., 2023). One of the most prominent examples of saponins with immunomodulatory properties is *Quillaja saponaria*, a plant native to South America. Saponins derived from *Quillaja saponaria* have been extensively studied for their ability to enhance immune responses, particularly in the context of vaccine adjuvants (Fleck *et al*., 2019). Furthermore, ginsenosides, a group of saponins derived from various species of ginseng, have demonstrated immunomodulatory effects through their interaction with cytokine production, immune cell activation, and inflammatory responses (Li *et al*., 2023).

Terpenoids, also known as isoprenoids, constitute another important category of phytocompounds with immunomodulatory potential. These compounds are synthesized via the mevalonate and methylerythritol phosphate pathways and are characterized by their structural diversity and wide-ranging biological activities (Bergman *et al*., 2019). Terpenoids such as betulinic acid, which is derived from the bark of *Betula* species, have attracted considerable attention for their anti-inflammatory, anticancer, and immunomodulatory properties (Lou *et al*., 2021). Current publications report that betulinic acid can modulate immune cell activity, enhance cytokine production, and inhibit inflammatory pathways, making it a potential candidate for therapeutic applications in immune-related disorders.

Despite the diverse chemical structures and mechanisms of action associated with phytocompounds, their application in immunomodulation remains a rapidly evolving field of study. Immunomodulation refers to the regulation or alteration of the activity of the immune system through the enhancement or suppression of immune responses. While traditional immunotherapies often involve synthetic drugs or biologics, phyto-compounds offer a natural and potentially safer alternative for modulating immune function (Gasmi *et al*., 2023). This concept has become increasingly relevant in the context of chronic inflammatory diseases, autoimmune disorders, infectious diseases, and even cancer.

The aim of this review is to provide a comprehensive overview of the immunomodulatory properties of phytocompounds, with a particular emphasis on their mechanisms of action, therapeutic applications, and potential for integration into modern medical practices.

PHYTOCOMPOUNDS: CLASSIFICATION, PROPERTIES, AND APPLICATIONS

Definition and Classification of Phytocompounds

Phytocompounds are considered secondary metabolites because they are not directly involved in the basic growth, development, or reproduction of plants, but instead play critical roles in defense mechanisms against pathogens, herbivores, and environmental stressors (Li *et al*., 2020). Additionally, phytocompounds contribute to plant pigmentation, flavor, and scent, which can aid in pollination and seed dispersal (Erb & Kliebenstein, 2020). Despite their auxiliary functions in plant physiology, phytocompounds have been extensively studied for their pharmacological properties, particularly their antioxidant, anti-inflammatory, antimicrobial, anticancer, and immunomodulatory activities (Pant *et al*., 2021). The diverse chemical structures and biological functions of phyto-compounds make them promising candidates for various therapeutic applications.

The classification of phytocompounds is primarily based on their chemical structure and biosynthetic origin. This classification system enables researchers to systematically study their properties and potential applications. Phytocompounds are commonly categorized into several major groups, including polyphenols, alkaloids, saponins, terpenoids, glycosides, and phytosterols (Zheng *et al*., 2022).

Polyphenols are among the most extensively studied groups of phytocompounds due to their potent

antioxidant properties and ability to modulate various biological pathways. They are characterized by the presence of one or more aromatic rings bearing hydroxyl groups (Reyna-Margarita, 2019). This category includes flavonoids, phenolic acids, tannins, and stilbenes. Flavonoids, which are widely distributed in fruits, vegetables, and medicinal plants, are known for their anti-inflammatory, antioxidant, and immunomodulatory activities. Phenolic acids, such as tannic acid, exhibit strong antioxidant properties and have been studied for their effects on immune modulation and inflammation. Stilbenes, such as resveratrol, are known for their anti-inflammatory and anticancer activities.

Alkaloids are nitrogen-containing compounds that often exhibit pronounced pharmacological effects. They are typically derived from amino acids and are found in various plant families. Alkaloids are known for their diverse biological activities, including analgesic, anti-inflammatory, anticancer, antimicrobial, and immunomodulatory effects. Vincristine, a well-known alkaloid derived from *Catharanthus roseus*, has been used effectively as a chemotherapeutic agent for various cancers. Its mechanism of action involves interference with microtubule formation during cell division, which also influences immune cell proliferation (Bhambhani *et al*., 2021; Shukla *et al*., 2023).

Saponins are glycosidic compounds characterized by their surfactant-like properties, which allow them to interact with cell membranes and cholesterol. They are commonly found in legumes, herbs, and certain medicinal plants. Saponins exhibit various biological activities, including immunomodulatory, anti-inflammatory, and anticancer effects. They have been used as adjuvants in vaccines to enhance immune responses. For example, saponins derived from *Quillaja saponaria* have been extensively studied for their ability to enhance the immunogenicity of vaccines by promoting antigen presentation and cytokine production (Timilsena *et al*., 2023; Fleck *et al*., 2019; Li *et al*., 2023).

Terpenoids are classified based on the number of isoprene units they contain for instance monoterpenes (10), sesquiterpenes (15), diterpenes (20), triterpenes (30) and so on. Terpenoids are known for their wide range of biological activities, including antimicrobial, anti-inflammatory, anticancer, and immunomodulatory effects (Bergman *et al*., 2019). Betulinic acid, a terpenoid derived from the bark of *Betula* species, has been shown to possess immunomodulatory properties through its interaction with immune cells and modulation of cytokine production.

Other notable groups of phytocompounds include glycosides and phytosterols. Glycosides are compounds that consist of a sugar moiety bonded to a non-sugar component known as an aglycone (Yulvianti & Zidorn, 2021). They are widely distributed in the plants and exhibit a broad spectrum of biological activities, including anti-inflammatory, antimicrobial, and immunomodulatory effects. Saponins, previously mentioned, are a type of glycoside characterized by their amphipathic nature (Güçlü-Ustündağ & Mazza, 2007). Phytosterols, which are structurally like cholesterol, are found in plant cell membranes and have been studied for their potential to modulate immune responses and lower cholesterol levels. Their structural similarity to cholesterol allows them to compete for absorption in the digestive system, thereby reducing blood cholesterol levels (Sohn *et al*., 2021).

Properties of Phytocompounds

The diverse chemical structures of phytocompounds contribute to their wide range of biological properties. General properties of phytocompounds include antioxidant, anti-inflammatory, anticancer, antimicrobial, and immunomodulatory activities. The antioxidant activity of phytocompounds is largely attributed to their ability to scavenge free radicals and reduce oxidative stress. This property is particularly significant because oxidative stress is implicated in the pathogenesis of numerous diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions (Zeb, 2020).

The anti-inflammatory properties of phytocompounds are primarily mediated through the inhibition of inflammatory enzymes, modulation of cytokine production, and suppression of pro-inflammatory transcription factors (Conte *et al*., 2017). This makes them valuable in the treatment of chronic inflammatory conditions and autoimmune diseases. Additionally, many phytocompounds exhibit antimicrobial activity, making them potential candidates for developing novel antimicrobial agents (Nik Mohamad Nek Rahimi *et al*., 2022).

Current Medical Applications of Phytocompounds

In the context of cancer therapy, certain phytocompounds have demonstrated the ability to induce apoptosis, inhibit tumor growth, and modulate immune responses (Bozzuto *et al*., 2014). Furthermore, the immunomodulatory properties of phytocompounds are of particular interest due to their potential to enhance or suppress immune functions, depending on the therapeutic objective. The ability of phytocompounds to modulate immune responses through various mechanisms, including the activation of immune cells, regulation of cytokine production, and enhancement of antigen presentation, underscores their potential as natural immunomodulators (Cherian *et al*., 2021).

The broad range of properties exhibited by phytocompounds highlights their potential applications in various therapeutic contexts. Understanding their classification, properties, and mechanisms of action is essential for developing effective strategies to harness their therapeutic potential.

PHYTOCOMPOUNDS AS IMMUNOMODULATORS

Immunomodulation refers to the process by which certain substances can enhance or suppress the immune response (Holland &Vizi, 2002). Phytocompounds have diverse chemical structures, and many biological activities have been attributed to them. These compounds are a promising natural approach to modulate immune function. Unlike synthetic drugs, which often target a single pathway or receptor, phytocompounds frequently exhibit multifaceted effects through their interaction with multiple cellular targets (Cherian *et al*., 2021). This characteristic is particularly valuable in immunomodulation, where the immune response often involves a complex network of cells, cytokines, and pathways.

Mechanisms of Immunomodulation by Phytocompounds

The immunomodulatory effects of phytocompounds occur through various mechanisms, which may involve direct interaction with immune cells, modulation of cytokine production, or inhibition of pro-inflammatory pathways (Balasubramaniam *et al*., 2024). One of the primary mechanisms by which phytocompounds modulate the immune response is through the activation or suppression of specific immune cells, including macrophages, T cells, B cells, dendritic cells, and natural killer cells. For instance, certain phytocompounds such as thymol enhance the activity of macrophages, thereby promoting phagocytosis and antigen presentation (Merecz-Sadowska, 2020; Chauhan *et al*., 2013). This activation can subsequently stimulate adaptive immune responses, such as T cell and B cell activation, which are essential for generating long-term immunity.

The regulation of cytokine production is another important mechanism through which phytocompounds modulate immune responses. Cytokines are signaling molecules that play a central role in regulating immune and inflammatory responses. Phytocompounds can influence the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ), as well as anti-inflammatory cytokines like interleukin-10 (IL-10). The ability to modulate cytokine production allows phytocompounds to exhibit both immunostimulatory and immunosuppressive effects depending on the therapeutic context. For example, quercetin and curcumin have been reported to inhibit the production of pro-inflammatory cytokines, making them potential candidates for the treatment of inflammatory and autoimmune diseases (Sadeghi *et al*., 2023; Safarzadeh *et al*., 2024).

Additionally, phytocompounds often exert their immunomodulatory effects through the modulation of signaling pathways involved in inflammation and immune responses. Notable pathways include the nuclear factor-kappa B (NF-κB) pathway, mitogen-activated protein kinase (MAPK) pathway, and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway (Ren *et al*., 2013; Zhang *et al*., 2021; Porro *et al*., 2019). By inhibiting or activating these pathways, phytocompounds can effectively alter the transcription of genes involved in inflammation and immune regulation. For example, resveratrol inhibits the NF-κB pathway, thereby reducing the expression of pro-inflammatory cytokines and promoting anti-inflammatory effects (Ren *et al*., 2013).

Moreover, phytocompounds can enhance immune responses by promoting the maturation and activation of dendritic cells, which are essential for antigen presentation and the initiation of adaptive immunity. Saponins, such as those derived from *Quillaja saponaria*, have been extensively studied for their ability to enhance antigen presentation and stimulate robust immune responses when used as vaccine adjuvants (Fleck *et al*., 2019). This adjuvant activity is attributed to their capacity to interact with cell membranes, enhance antigen uptake, and promote the production of cytokines that favor adaptive immunity.

Applications of Phytocompounds in Immunomodulation

The immunomodulatory properties of phytocompounds makes them useful for several applications in therapeutic areas, including vaccines, inflammatory disorders, autoimmune diseases, cancer therapy, and infectious diseases. One of the most prominent applications of phytocompounds as immunomodulators is their use as adjuvants in vaccines (Reyna-Margarita *et al*., 2019). Adjuvants are substances that enhance the immune response to an antigen, thereby improving the efficacy of vaccines. Saponins derived from *Quillaja saponaria* have been utilized as adjuvants in several commercial vaccines due to their ability to enhance both humoral and cellular immune responses (Fleck *et al*., 2019).

Phytocompounds have potential use in the treatment of autoimmune and inflammatory disorders. Conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis are characterized by dysregulated immune responses and chronic inflammation. Phytocompounds with anti-inflammatory and immunosuppressive properties, such as curcumin, resveratrol, and ginsenosides, have demonstrated efficacy in modulating inflammatory pathways and reducing the production of pro-inflammatory cytokines (Guo *et al*., 2021; Lin *et al*., 2022). By targeting key signaling pathways such as NF-κB and MAPK, these compounds can effectively suppress excessive immune activation and restore immune homeostasis (Ren *et al*., 2013; Zhang *et al*., 2021; Porro *et al*., 2019).

In cancer therapy, some phytocompounds exhibit immunostimulatory effects that can enhance the

immune ability to recognize and eliminate tumor cells. Betulinic acid promotes the activation of natural killer cells and enhance cytokine production, thereby facilitating an antitumor immune response (Wang *et al*., 2021). Additionally, vincristine, an alkaloid commonly used as a chemotherapeutic agent, has demonstrated immunomodulatory properties by influencing immune cell proliferation and promoting apoptosis in cancer cells (Hiser *et al*., 2008).

Furthermore, phytocompounds have shown promise in the management of infectious diseases by enhancing immune responses and providing antimicrobial effects (Orozco-Nunnelly *et al*., 2021). For example, quercetin and tannic acid have demonstrated antiviral activity through their ability to inhibit viral replication and modulate immune responses (Kaczmarek, 2020; Di Petrillo *et al*., 2021).

EXAMPLES OF IMMUNOMODULATORY PHYTOCOMPOUNDS

Some phytocompounds have been identified as effective immunomodulators due to their ability to influence different aspects of the immune response. These compounds are derived from diverse plant sources and belong to multiple categories, including polyphenols, alkaloids, saponins, and terpenoids. Each group exhibits own mechanisms of action, which contribute to their immunomodulatory properties.

Polyphenols

Polyphenols are a large and diverse group of phytocompounds that include flavonoids, phenolic acids, tannins, and stilbenes. Many polyphenols are known for their antioxidant, anti-inflammatory, and immunomodulatory activities. Quercetin, a flavonoid commonly found in fruits, vegetables, and tea, has been extensively studied for its ability to modulate immune responses (Di Petrillo *et al*., 2021). It exerts immunomodulatory effects by inhibiting the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while enhancing the activity of natural killer cells and T lymphocytes (Georgiou *et al*., 2023; Safarzadeh *et al*., 2024; Zhang *et al*., 2021). Tannic acid has demonstrated potent anti-inflammatory and antioxidant activities (Wang *et al*., 2023). Its immunomodulatory effects are primarily mediated through the inhibition of pro-inflammatory pathways such as NF-κB and MAPK (Wang *et al*., 2023). Resveratrol, a stilbene found in grapes, berries, and peanuts, has shown significant potential as an immunomodulator (Galiniak *et al*., 2019). It regulates immune responses by modulating cytokine production, enhancing antioxidant defenses, and suppressing inflammatory signaling pathways (Ren *et al*., 2013). Curcumin, the active component of turmeric, also exhibits immunomodulatory properties by inhibiting pro-inflammatory cytokines and promoting anti-inflammatory responses (Porro *et al*., 2019). In Figure 1 some notable phytocompounds with immunomodulatory properties are shown.

Alkaloids

Alkaloids are nitrogen-containing compounds that possess a wide range of biological activities, including immunomodulation. Vincristine, an alkaloid derived from the plant *Catharanthus roseus*, is primarily known for its antitumor properties (Hiser *et al*., 2008). However, it also exhibits immunomodulatory effects by influencing immune cell proliferation and promoting apoptosis in cancer cells (Shukla *et al*., 2024). The ability of vincristine to disrupt microtubule formation affects not only cancer cells but also immune cells, thereby modulating immune responses (Becker *et al*., 2020).

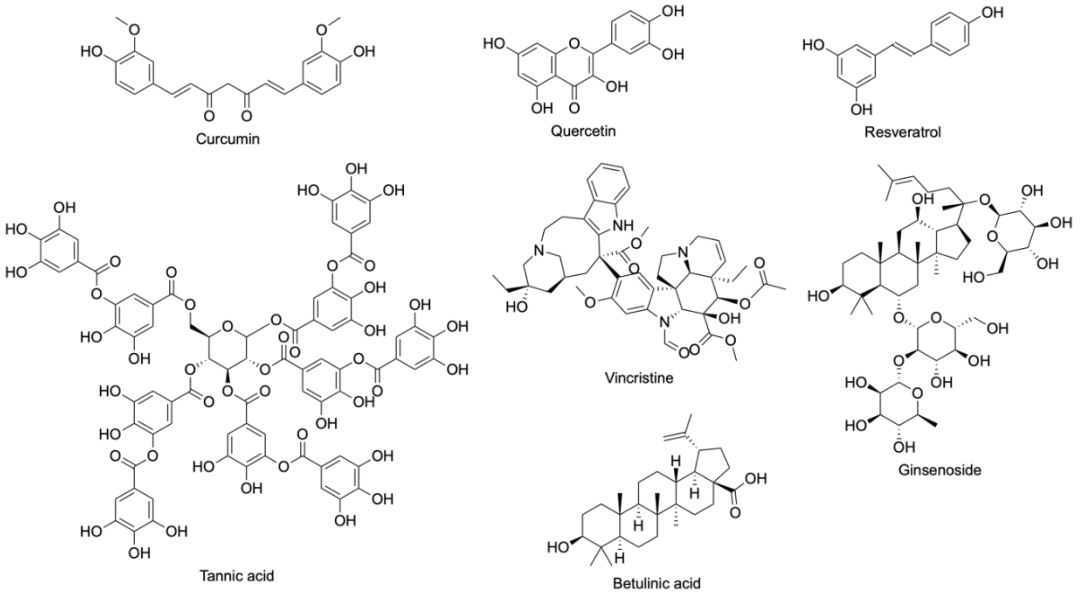

Figure 1. Notable phytocompounds with immunomodulatory properties.

Saponins

Saponins are glycosidic compounds with immunomodulatory effects, particularly as adjuvants in vaccines. *Quillaja saponaria*, a plant native to South America, produces saponins that have been studied for their ability to enhance immune responses (Güçlü-Ustündağ& Mazza, 2007). These saponins promote antigen presentation, stimulate cytokine production, and enhance the proliferation of immune cells such as T lymphocytes and macrophages (Fleck *et al*., 2019). Ginsenosides, a group of saponins derived from ginseng species, have also demonstrated immunomodulatory properties (Fan *et al*., 2024). They exert their effects through various mechanisms, including the modulation of cytokine production, activation of natural killer cells, and enhancement of phagocytic activity (Jang *et al*., 2024). Depending on the dose and specific ginsenoside, these compounds can exhibit either immunostimulatory or immunosuppressive effects.

Terpenoids

Terpenoids, also known as isoprenoids, are a diverse group of phytocompounds that exhibit a wide range of biological activities. Among them, betulinic acid exhibits immunomodulatory effects (Lou *et al*., 2021). Derived from the bark of Betula species, betulinic acid has demonstrated significant anti-inflammatory and antitumor properties (Wang *et al*., 2022). It modulates immune responses by enhancing cytokine production, promoting the activation of natural killer cells, and inhibiting inflammatory signaling pathways (Olanlokun, 2022).

CHALLENGES AND FUTURE PERSPECTIVES

Despite the potential of phytocompounds as immunomodulatory agents, several challenges must be addressed before using them in medicine. One of the primary challenges is the lack of standardization in the isolation, characterization, and quantification of phytocompounds. Due to their natural origin, the concentration and composition of phytocompounds can vary significantly depending on factors such as plant species, cultivation conditions, harvesting methods, and extraction techniques (Stanisz *et al*., 2024). This variability poses difficulties in ensuring consistency, reproducibility, and efficacy in therapeutic applications.

Another major challenge is related to the bioavailability and pharmacokinetics of phytocompounds. Many phytocompounds exhibit low solubility, stability, and absorption, which can limit their therapeutic efficacy when administered orally or through other conventional routes (Gayathiri *et al*., 2024). Improving the bioavailability of these compounds through novel delivery systems such as nanoparticles, liposomes, or encapsulation techniques is an area that requires further investigation.

Additionally, the mechanisms of action of many phytocompounds remain not completely understood, particularly when considering their complex interactions with multiple targets and pathways within the immune system. More comprehensive studies are needed to elucidate their precise mechanisms of immunomodulation and to identify the most effective therapeutic combinations. Furthermore, clinical trials evaluating the safety, efficacy, and optimal dosage of phytocompounds are limited, which hinders their translation from experimental research to clinical practice.

Future research should focus on addressing these challenges by developing standardized extraction and formulation protocols, improving bioavailability through advanced delivery systems, and conducting rigorous clinical trials.

CONCLUSION

Phytocompounds represent a promising class of natural bioactive molecules with significant immunomodulatory potential. Through various mechanisms such as cytokine regulation, immune cell activation, enhancement of antigen presentation, and modulation of inflammatory signaling pathways, phytocompounds have demonstrated their capacity to modulate both innate and adaptive immune responses. The immunomodulatory effects of compounds such as quercetin, tannic acid, curcumin, vincristine, *Quillaja saponaria*, ginsenosides, betulinic acid, and resveratrol have been well-documented in numerous preclinical studies. These compounds have shown potential in enhancing vaccine efficacy, managing autoimmune and inflammatory disorders, combating cancer, and addressing infectious diseases.

Despite their promising applications, several challenges remain, particularly related to standardization, bioavailability, and understanding of their complex mechanisms of action. Inconsistencies in extraction and quantification methods, combined with limited clinical studies, have hindered their medical applications. Future research should focus on addressing these challenges by developing standardized protocols, improving bioavailability through advanced delivery systems, and conducting rigorous clinical trials. Overall, the immunomodulatory properties of phytocompounds hold great potential for developing novel therapeutic strategies.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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