DOI: 10.22319/rmcp.v17i1.6865
Vol. 17(1) | 2026 | e1716865

https://cienciaspecuarias.inifap.gob.mx/

Role of curcumin, resveratrol, and glycyrrhizinic acid as immunomodulatory and antiviral agents in animal health. Review

García-Cambrón, José Bryan[ab]

Cuevas-Romero, Julieta Sandra[b]

Blancas-Flores, Gerardo[c]

Cerriteño-Sánchez, José Luis[b]*

[a]Universidad Autónoma Metropolitana. Posgrado en Biología Experimental. Ciudad de México, México.

[b]Centro Nacional de Investigación Disciplinaria en Salud Animal e Inocuidad. Instituto Nacional de Investigaciones Forestales Agrícolas y Pecuarias. Laboratorio de Epizootiología. Ciudad de México, México.

[c] Universidad Autónoma Metropolitana. División de Ciencias Biológicas y de la Salud. Ciudad de México, México.

Corresponding author: cerriteno.jose@inifap.gob.mx

Abstract

In recent years, interest in studying plant-based compounds for therapeutic purposes has increased significantly, driven by numerous studies demonstrating their properties at the molecular, cellular, and physiological levels. These compounds, commonly present in human and animal diets, tend to be little harmful to the body. In particular, certain polyphenols, such as resveratrol and curcumin, and triterpenoids, such as glycyrrhizinic acid (GA), have exhibited promising qualities for the prevention and treatment of infectious diseases. These compounds have been shown to have pleiotropic effects that reduce the pathogen load and improve the body's immune responses. This review addresses the physiological, immunological, and antiviral roles of resveratrol, curcumin, and GA, highlighting their potential use in the treatment and control of infectious diseases, particularly viral diseases, and their possible applications in animal health. Additionally, the bioactivity of the compounds in the body is described, emphasizing the most relevant findings and noting their antiviral and immunomodulatory effects for the treatment and protection against viral infectious diseases.

Keywords: Polyphenols; Triterpenoids; Immunomodulators; Antivirals; Anti-inflammatories

Received: February 18, 2025

Accepted: October 27, 2025

Published: March 06, 2026

Introduction

Recently, polyphenols and triterpenoids derived from natural products have gained significant importance in the field of health due to their antioxidant[1], anti-inflammatory[2], and antiviral[3] properties,

among others. This has increased interest in studying them. Polyphenols can be classified into various categories, including flavonoids, phenolic acids, tannins, lignans, stilbenes, and simpler derivatives[4]. Their use in animal health has been shown to have benefits, as their properties help prevent and control diseases associated with oxidative damage, inflammation, and physiological disorders associated with various pathologies[5,6]. Thus, polyphenols and triterpenoids are recognized as compounds with the potential to improve animal health.

Typically, these compounds play a crucial role in antioxidant activity through mechanisms such as hydrogen atom transfer, single-electron transfer, and metal chelation, which protect the body from free radical attacks and thus modulate associated inflammatory responses[7]. In addition, polyphenols and triterpenoids have been shown to influence the maturation and function of immune response cells. Recent studies have focused on understanding their role in activating dendritic cells and on their ability to modulate their function, especially in their interactions with T lymphocytes, which are essential for regulating the immunomodulatory effects of these compounds[2,8]. These types of effects are important during the pathogenesis of viral infections, where they not only play a key role in inducing the immune response but also act as agents that can inhibit or block viral replication. This makes them promising candidates for developing biologics that can be used to control viral infections[3].

This review describes the roles of two phenolic compounds-resveratrol and curcumin-and a triterpenoid, glycyrrhizinic acid (GA), which have recently attracted scientific interest. In addition, their influence on the activation and modulation of the immune response is mentioned, along with their ability to inhibit viral infection progression both *in vitro* and *in vivo*, aspects that could potentially be applied to animal health.

Resveratrol

Resveratrol (3,5,4'-trihydroxy-trans-stilbene, RSV, $C_{14}H_{12}O_3$) is a stilbenoid polyphenol (a phytoalexin) isolated from the root of *Polygonum cuspidatum* and *Veratrum grandiflorum*. It is also found in high concentrations in red wines, red grapes, berries, strawberries, raspberries, tomatoes, and some other nuts[9]. It is interesting to note that resveratrol can also be produced by biotechnological means, through stilbene biosynthesis pathways in some microorganisms, such as bacteria of the genus *Lactococcus*, *E. coli*, and *Cephalosporium*, as well as in yeasts of the genera *Yarrowia* and *Saccharomyces*[10].

Pharmacological characteristics

After ingestion, resveratrol has an approximate bioavailability of 70 %. Nevertheless, its high rate of hepatic and intestinal metabolism, including glucuronidation and sulfation processes, as well as the susceptibility of conversion from the *trans* to *cis* form by oxidation, light, enzymes, and temperature, results in the formation of compounds less active than resveratrol itself, so its systemic availability is considered to be reduced by an additional 5 %[11]. Its low water solubility (0.03 mg/mL) also complicates the creation of a dosable formulation for therapeutic use[12]. Human evaluations have shown that only 2 % of resveratrol, in its *trans* form, is excreted in the urine after 12 h[13]. Interestingly, animal studies indicate that *trans*-resveratrol and its glycosylated and glucuronized forms achieve better tissue distribution when administered gastrointestinally; however, they are rapidly excreted, with up to 52.8 % detected in 72 h[14].

Antiviral effects

Resveratrol has been recognized for its inhibition or blocking effects on various viruses, which is why it has been considered a promising candidate for developing useful biological treatments aimed at controlling various viral pathologies. Nonetheless, in most related publications or works, viral inhibition is not only related to the characteristic antioxidant capacity of resveratrol, but also to the ability to modulate gene expression and the translation of proteins responsible for antiviral activity, including TRAIL-R2/DR5, TRAIL-R2/DR4, p53, Bim, Noxa, PUMA, Bak, Bax, Mcl-1, survivin, Bcl-XL, and Bcl-2,

which are linked to apoptotic cellular effects, as well as the activity of nuclear factor kappa β (NF-κβ), procyclooxygenase-2, and the production of prostaglandins, responsible for acute inflammatory activity[15]. An example of this is its application as an adjuvant; together with the pseudorabies virus (PRV), resveratrol was shown to induce the cellular antiviral response through the production of key proteins, such as TLR4, Ikk, IκBa, NF-κB, and JNK, in addition to inducing the activity of peritoneal macrophages through the presentation of CD86 and MHC-II molecules[16]. Resveratrol-induced cellular antiviral responses effectively help combat viral pathologies caused by coronavirus. *In vitro* studies have demonstrated that the application of resveratrol reduces pro-apoptotic effects by inhibiting apoptotic pathways, such as PUMA/JNK, mediated by MERS-CoV infection[17]. Interestingly, in cases of infection with the alphacoronavirus of porcine epidemic diarrhea (PEDV), triacetylated resveratrol (TCRV) promotes early apoptosis in small intestinal enterocytes through the early release of mitochondrial cytochrome C, compared to the apoptotic effect generated by PEDV infection, a crucial factor for the elimination of the virus and its viral particles[18].

Independently, resveratrol can influence the expression and transit of viral proteins within the cell, which affects virion formation. This is a particular case observed in influenza virus infection, where resveratrol has been shown to inhibit the cytoplasmic-nuclear translocation of ribonucleoproteins *in vitro* by inhibiting the expression of proteins involved in inhibiting protein kinase C (PKC)-related pathways[15]. Assays of resveratrol's antiviral response to African swine fever virus (ASFv) have found that it can lead to a decrease in the expression of the virus's p72 and p30 proteins (structural proteins) by inhibiting viral DNA replication, which decreases viral replication sites in the perinuclear area of cells[19]. In addition, the activity of resveratrol at the nuclear level is associated with the acetylation of nuclear proteins, such as histones, resulting in an inhibitory effect on the DNA synthesis of herpes simplex virus (HSV)[20]. Additionally, resveratrol has been shown to induce autophagy and lysosomal production in cells, mechanisms that contribute to controlling infection by porcine hemagglutinating encephalomyelitis virus (PEV)[21]. These examples highlight how resveratrol modulates the expression and production of viral proteins, which is linked to cellular antiviral activity modulated by its presence, which could control viral infection.

Immunomodulatory activity

Resveratrol effectively regulates inflammation by interacting with T cells, modulating their differentiation, and inhibiting the release of proinflammatory cytokines and other inflammatory mediators[22]. Part of its activity is attributed to the activation of sirtuin-1 (SIRT-1), which inhibits the acetylation of the target protein p65/relA, thereby reducing NF-κB activity and decreasing the expression of inflammatory factors such as TNF-α, IL-1β, IL-6, metalloproteases (MMP)-1, MMP-3, and cyclooxygenase-2 (Cox-2)[23]. In addition, SIRT-1 activation promotes deacetylation of STAT3, blocking its translocation to the nucleus and interrupting the activation of RORγt and IL-17A, which affects the balance between Treg and Th17 cells[24]. Because it can be incorporated into cells, resveratrol has demonstrated a modulatory effect on some cellular immune response receptors. Associated with its ability to inhibit inflammatory mediators, treatment with resveratrol reduces the tolerance of certain cell receptors involved in immune responses in T cells and macrophages, such as lipopolysaccharide receptors (LPS) and Toll-like receptors (TLRs), thereby modulating cellular immune reactivity[23,24]. In the same sense, it has been observed that resveratrol allows the modulation of cell differentiation and response. In macrophages, treatments with resveratrol allow the intracellular restoration of glutathione (GSH) due to its antioxidant activity, decreasing the activity of cytokines/chemokines and the inducer phorbol-myristate-acetate (PMA), which are responsible for the M1/M2 differentiation of macrophages, thereby causing an anti-inflammatory effect[25]. On the other hand, resveratrol has been observed to modulate the production of autoantibodies in B cells or plasma cells, an effect that holds promise for the treatment of autoimmune diseases and for reducing autoreactogenic effects in the presence of antigens[21].

Curcumin

Curcumin ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione, $C_{21}H_{20}O_6$) is a polyphenolic compound that has been widely used for nutraceutical, dietary, and gastronomic purposes for more than 20 years in regions such as South Asia, China, and Latin America, in addition to being known for its beneficial effects on health[26]. This aromatic compound, isolated from *Curcuma longa* L., is known for its use in food and as a natural colorant (food, cosmetic, and textile), as a repellent of different insects, and as an antimicrobial agent, the latter being important for its application as a therapeutic agent[27].

Pharmacological aspects

Much of the knowledge about curcumin has been obtained from animal trials; however, its pharmacological effects in both animals and humans have recently been evaluated *in vitro* and in clinical trials. Tests on rats have shown that curcumin absorption ranges from 60 % orally. In addition, due to its low solubility, blood recirculation, hepatic and intestinal metabolism, and rapid elimination[28], it is reported that 50 % of curcumin and its metabolites end up being excreted in bile, 75 % in excrement, and only 2 % is usually found in plasma[29,30,31]. Interestingly, it has been determined that when curcumin is coupled with piperine, a constituent of black pepper, and dosed orally, curcumin bioavailability increases by up to 150 % in mice and up to 2,000 % in humans due to piperine inhibiting glucuronidation, which prevents curcumin metabolism[32].

The main transformation pathways of curcumin are glucuronidation and sulfation in the intestine, which are the main reasons for its low solubility and, therefore, low bioavailability[28]. Nevertheless, trials in colorectal cancer patients who were treated with 36 mg of curcumin for four months showed a decrease in antioxidant lymphocyte function (at least 45 % compared to the control), as well as the inhibition of inflammatory mediators, such as NF-κB, which showed a low presence of COX2, an important marker of chemoprevention[33]. These assays indicate that therapeutic cellular effects can be achieved at low curcumin concentrations.

Antiviral activity

As mentioned, curcumin has demonstrated antimicrobial effects, and in the recent decade, antiviral effects have been identified. Due to its anti-inflammatory effects, curcumin has been shown to have the ability to decrease the alteration of the structural proteins ZO-1 and occludin in epithelial tissue, which generates trans-epithelial resistance when HIV comes into contact with genital mucous membranes, because the epithelial cells, which line the genital tract, do not show a typical inflammatory effect when it comes into contact with the virus, a condition that reduces infection[34,35]. In some enveloped viruses, curcumin has been observed to impact the function of viral anchor proteins and proteins with RNA-dependent polymerase activity, inhibiting virus replication[36,37]. Plaque assays have found that curcumin can inhibit the activity of some enveloped viruses, such as ZIKA viruses and pseudorabies virus, by disrupting the viral membrane, decreasing lytic plaque formation, and reducing the presence of the virus in cells[38]. This effect has been characteristic, especially with viruses with hemagglutinating activity, such as influenza A virus, which decreases adsorption to the cell by disrupting the activity of the virus's hemagglutination (HA) protein, mediated by the direct interaction of curcumin with the protein[39,40], in addition to exerting immunomodulatory effects via TLR2/4, p38/JNK MAPK, and NF-κB, triggering cellular mechanisms that inhibit viral infection[41]. These effects have been evaluated in enveloped viruses, such as Newcastle virus, herpes simplex virus, pseudorabies virus, Japanese encephalitis virus, and dengue virus type II, where it was not only shown that curcumin can inhibit the entry of the virus into the cell by disruption of the membrane and viral liposomes but that it also promotes immunomodulatory activity associated with the antiviral response, capable of conferring resistance to infection in cells. However, this effect was not observed in exposed viruses, such as enterovirus 71[42]. A similar case occurs with some coronaviruses, such as the transmissible gastroenteritis virus (TGEV), where it has

been evaluated that curcumin can generate inhibitory adsorption effects on cells and virucidal effects[43]. Taking into account the previous cases, it is summarized that curcumin promotes the inhibition of enveloped viruses by interrupting the activity of key proteins associated with viral adsorption, which can be directly (binding of curcumin with the key protein) or indirectly (activation of antiviral and antioxidant pathways in the cell)[44].

Immunomodulatory effects

Some of its beneficial properties on some of the diseases mentioned above are directly linked to curcumin's effects on the immune system. Studies carried out in rats show the role of curcumin in the inhibition of proinflammatory agents, an increase in reactive oxygen species (ROS) and nitric oxide (NO) in macrophages and NK cells, a decrease in cytotoxic effects and apoptosis, as well as an increase in the potential proliferation of T cells[45]. In particular, it has been observed that this compound can affect the change of polarization in macrophages, from the M1 to M2 phenotype, being a compensatory effect on tissue inflammation[46]. Likewise, studies in RAW264.7 cells treated with lipopolysaccharides (LPS), which were treated with curcumin at non-lethal concentrations (< 50 µM), showed a decrease in proinflammatory factors such as IL-1β, IL-6, IL-12, TNF-α, metalloproteinases-M, and reactive oxygen and nitrogen species, a chronic modulatory effect of the early cellular immune response[47]. At the genetic level, curcumin has been shown to inhibit histone (H3) acetylation in autoimmune pathologies, such as rheumatoid arthritis, thereby reducing the expression of genes involved in the disease, such as IL-6[48,49]. With the recent SARS-CoV-2 pandemic, and through molecular docking assays, it was possible to understand more widely that curcumin has effects associated with the inhibition of ligand-receptor interaction, through the binding of curcumin with the C-terminal portion of the spike (S) protein of the virus[50] and, on the other hand, it presents agonist and antagonistic effects on mediators of the antiviral response, such as NRF2 or HMGB1, respectively, responsible for mediating the response of inflammation caused by viral pathology, due to dose-dependent inhibition associated with the antioxidant capacity of curcumin[51,52]. In rat models with severe lung inflammation, curcumin was found to reduce inflammation by inhibiting HMGB1-regulated PPAR-γ/RAGE pathways[53].

Various studies on the beneficial properties of curcumin are associated with study models of liver diseases. A model of liver cirrhosis in rats showed that curcumin can increase the plasma concentration of IL-10, an interleukin that participates in the modulation of inflammation, and, at the same time, decrease the concentration of inflammatory factors such as TNF-α and TGF-1β, so the use of curcumin is considered a prospect for the control of chronic inflammation in liver pathologies[54]. Other liver evaluations have also reported that curcumin reduces the activity of pathways such as MAPK/ERK, which are not only associated with the cellular immune response but also with oxidative activity[55].

Glycyrrhizinic acid

18-β-glycyrrhizinic acid ((2S,4aS,6aR,6aS,6bR,8aR,10S,12aS,14bR)-10-hydroxy-2,4a,6a,6a,9,9,12a-heptamethyl-13-oxo-3,4,5,6,6a,7,8,8a,10,11,12,14b-dodecahydro-1H-picene-2-carboxylic acid, GA) is a triterpenoid compound obtained from the root of the Licorice plant (*Glycyrrhiza glabra*), with amphiphilic characteristics, which has been widely used in traditional medicine and gastronomy of the Asian continent[56]. Various studies show its antiviral, anticancer, and antimicrobial biological activities[57] and its high capacity for inclusion in therapeutic compounds[58]; in addition, because it shows low toxic effect[59], the interest in its use is related to the development and application of delivery systems for therapeutic agents.

Pharmacological activity

GA, being a compound derived from Licorice, is part of the group of phytocomponents approved by the FDA (Food and Drug Administration, USA) for use in over-the-counter foods and cosmetics[58]. Experiments in murine models have identified that the median lethal dose (LD50) of GA in mice via intraperitoneal administration is 308 mg/kg, and orally, it is >610 mg/kg. In rats, the LD50 was 610 mg/

kg orally. On the other hand, an experiment involving 39 volunteers did not show a toxic effect when they were administered 2 mg/kg/day for 8 weeks[60,61]. Based on this, in 2015, the European Food Safety Authority (EFSA) published that the safe concentration of GA for all species, except chickens, is 1 mg/kg[62]. Despite this, the only undesirable effect of GA is its ability to inhibit 11β-hydroxysteroid dehydrogenase, leading to a cortisol-cortisone imbalance that affects alkalosis, hypokalemia, water and sodium retention, thereby generating a tendency to hypertension, kaliuresis, and suppression of the renin-angiotensin-aldosterone axis. It is worth mentioning that this effect has been observed when high concentrations of GA are used (800 mg < daily), so its use, in humans and animals, would be limited to therapeutic and safe concentrations[60].

GA is obtained metabolically when glycyrrhizin (a compound obtained directly from the plant) is ingested and is glucuronized enterically by β-glucuronidase, an enzyme present in bacteria of the strains *Eubacterium* sp, *Ruminococcus* sp, and *Clostridium innocuum* ES2406[63]. In rats, enteral administration of 200 mg/kg GA resulted in low bioavailability (14 %)[64]. Nonetheless, a periodic enteral administration of 25 mg/kg GA in rats showed better absorption[65]. At different concentrations, GA is excreted mainly via the biliary tract and part of it via the urinary tract[66].

Uses as an antiviral

Publications on the potential antiviral effect of GA have shown interest in this compound for the treatment of various pathologies caused by viruses. One example is the use of GA as a therapeutic agent for coronavirus-associated diseases. Two isolated SARS-CoV strains (FFM1 and FFM2) were exposed to 300 mg/ml GA *in vitro* in VERO cells, and the compound was found to inhibit viral replication, as well as viral adsorption and entry into the cell[67]. Nevertheless, in infected patients, the administered dose did not reach the ideal plasma concentration for biological effects (>400 µg/ml)[68].

Aminated GA conjugates have been evaluated, of which two amino acid-associated conjugates (Glycine-Leucine) show up to 70-fold cytopathic inhibition effects of SARS-CoV *in vitro*. Although GA can form these amide interactions, increasing the concentration could generate cytotoxic effects[69]. With respect to other viruses, GA has been shown to generate an inhibitory effect on the replication of the Epstein-Barr virus (herpesvirus type 4) when used *in vitro* at 0.04-4.8 mM, showing a selectivity index twice as high as the antiviral drug zidovudine, and twice as low as acyclovir[70]. Given its ability to associate with amino acids, GA has exhibited proliferative and cytopathic inhibitory effects caused by the ZIKA virus, which could be used as a therapeutic agent in diseases caused by some flaviviruses[71].

In animal health, GA has also been of great interest due to its potential therapeutic effects that could be used for prophylactic purposes against viral diseases. Early trials in poultry infected with influenza and Newcastle viruses showed that GA can inhibit viral proliferation by inhibiting the activity of viral hemagglutinins, which are of vital importance for virion infection[72]. A 2014 study assessed GA's ability to decrease viral titers and infect porcine parvovirus (PPV) in porcine testicular cells[73]. A 2020 publication showed that glycyrrhizin (a precursor of GA) can inhibit HMGB1 activity via TLR4/MAPK/p38, which are essential factors for the secretion of proinflammatory cytokines present in porcine epidemic diarrhea virus (PEDV) infection, allowing it to inhibit viral proliferation[74].

Immunomodulatory effects

GA has recently been characterized as modulating the immune response by different pathways. At the cellular level, GA was able to decrease VEGF, ICAM-1, GM-CSF, and GRO/KC in rat models of alcoholic hepatitis[75]. Likewise, *in vitro* experiments and clinical trials have demonstrated that GA can inhibit pathways such as PLA2/ARA and their respective metabolites, PGE2, TXA2, and LTB4, in different pathological models, including infectious diseases[76,77]. A recent study evaluated, in mice, the ability of GA to inhibit NF-κβ via PI3K or MAPK in a model of myocardial hypertrophy[78]. In addition, *in vitro*, it was shown that GA can inhibit the expression of the cascade of cytokines IL-1β, IL-3, IL-5, IL-6, IL-10, IL-12, IL-13, eotaxin, and TNF-α[79]. However, interestingly, some studies show that GA can increase IL-12

production in macrophages, which, in other study models, has suggested that this allows the increase of IFN-γ in infectious processes[80,81,82]. Based on this evidence, GA is considered an agent that can inhibit cytokine storms during infectious processes and, at the same time, modulate inflammation[83].

Potential therapeutic applications in animal health

Polyphenolic and triterpenoid compounds have been used in animal health care because their antioxidant and anti-inflammatory properties are beneficial for the gastrointestinal system; therefore, they are often used as additives in animal feed, particularly in the livestock sector[84]. Nonetheless, there has been recent interest in developing therapeutic and prophylactic models associated with immunomodulatory and antiviral effects, which could generate novel tools for maintaining health in animals.

Delivery systems for therapeutic purposes

Delivery systems have emerged as novel mechanisms for transport and coupling, improving the bioavailability and durability of molecules for nutritional and food transport purposes[85], as well as for therapeutic purposes, for drugs[86] or antigens for prophylactic purposes[87]. Their development enables better control of diseases, being tools that are currently necessary to guarantee health.

Resveratrol, curcumin, and GA are compounds that have recently been used for designing organic nanoparticles (lipid-solid, liposomes, polymeric, virosomal, and micellar) and inorganic nanoparticles (mesoporous silica and carbon nanotubes) useful in the transport of drugs and antigens[88]. As mentioned, due to its low solubility, the direct use of resveratrol is limited, so coupling it to nanoparticles allows the increase of the compound's bioavailability and would reduce its use in high concentrations, in addition to maintaining its therapeutic properties[89]. These delivery system models have been used to control infectious pathologies, particularly viral pathologies[90], in the transport of drugs and therapeutic molecules, also guaranteeing the reduction of their toxic and reactogenic risks[91]. In particular, recent research has highlighted the use of resveratrol in small pigs and sows in order to maintain the health of these animals, taking advantage of its antioxidant and immunomodulatory capacities[92]. Recent studies have shown that the administration of resveratrol in piglets allows the inhibition of expression and production of proinflammatory cytokines such as IL-1β and TNF-α, as well as an increase in IL-10 in jejunum and ileum, despite intestinal malabsorption, so its application in delivery systems would allow its application in enteric viral pathologies[93]. Curcumin has also benefited from its incorporation into nanoparticles, increasing its bioavailability through the evasion of plasma proteins, so its interaction and effects with target cells are improved, and it has been evaluated in a large number of pathologies, including cancer[94]. In its nano- and microemulsion forms, antioxidant and immunomodulatory effects have been exploited, with low cytotoxic effects[95]. Recent studies emphasize the role of curcumin encapsulation models, underscoring its antiviral role against enveloped viruses and its lower toxicity compared to the compound alone, improving cell viability by 80 % versus 15 %, respectively[96]. Most of the formulations evaluated are lipid-based, which offer benefits when incorporating different molecules, such as proteins, nucleic acids, surfactants, polysaccharides, and different types of phospholipids, as well as different types of drugs[97]. Evaluations in animal models show that the effects of these curcumin-containing nanoparticles can be at the genetic, cellular, and molecular levels, with a wide distribution via blood and lymphatic system, acting extensively on the immune system with modulating effects on inflammation and oxidative stress, which, in some viral pathologies, results in a potential antiviral agent[98]. Regarding GA, this triterpenoid has been used and evaluated in multiple nanoparticle formulations. Some tests have determined that, in liposomal form, GA can be retained longer, increasing its solubility and interaction with cells; likewise, the particle shape is preserved for longer, allowing it to infiltrate more easily between tissues[99]. In addition, due to their amphiphilic characteristics, nanoparticle models with GA can be coupled to both soluble and insoluble drugs, increasing the possibilities of their use[100]. Some studies have evaluated the coupling of antigens to GA-loaded liposomes and have

described their ability to enhance the immune response, opening the possibility of being applied as adjuvants in immunization systems[99,101].

Adjuvants

Due to their immunoregulatory properties, polyphenolic and triterpenoid agents have been used as adjuvants in therapeutic processes, improving the prognosis in multiple pathologies. Resveratrol has been used in clinical trials with cancer patients as an immune facilitator, being a reducing agent of cell invasion, and as an enhancer of the effects of other therapies[102]. In addition to the above, the periodic use of resveratrol has shown an increase in the sensitization of tissues and cells against oxidative and inflammatory effects, which would allow the body to resist potential pathologies[103]. Resveratrol can be introduced into cells via passive diffusion, being superior in its nanoparticle form, or by protein transport via integrins[104], a route by which the modulation of the immune response can be carried out, particularly with first-line cells, such as antigen-presenting cells[105]. Curcumin plays an important role when taken up by target cells, reducing the inflammatory effects of various metabolic[106] and autoimmune pathologies[107], as well as the sensitization of first-line defense cells through the stimulation of surface receptors and the formation of T-cell subpopulations[108]. On the other hand, GA has exhibited the ability to increase cellular and humoral responses *in vivo* when incorporated in the form of liposomes and coupled to viral antigens[109]. Recently, two studies demonstrated that lipid nanoparticles with GA can be incorporated with recombinant antigens of viruses that affect animal health, can satisfactorily increase the humoral response, and generate a modulating effect on cellular responses[110,111].

Conclusions

The *in vitro* and in animal health connections between these compounds remain unclear, and understanding in laboratory animals and humans is poor compared with production animals. This review points out the effects of these compounds that could be used in animal health, taking into account the most relevant needs of this sector. In most evaluations, both in humans and animals, the compounds' antioxidative effects, the reduction of inflammation, the antimicrobial and antiviral effects, with low systemic accumulation, little retention in excretory organs, and the presence of poorly active metabolites are highlighted, which together translate into desirable effects in their therapeutic use. Nonetheless, it is important to bear in mind that the antiviral and immunomodulation properties of these compounds have an impact under the pathological conditions associated with the type of pathogen, since some infectious agents can use these effects to enhance their proliferation, counterposing their use as therapeutic agents, so their application must be specifically targeted.

However, more work is needed on the effects of these compounds on viral agents that affect farm animals. Likewise, it is necessary to explore the mechanisms of viral proliferation inhibition, the decrease in inflammatory activity alongside the increase in the humoral response, as well as the associative capacity of new delivery systems with other therapeutic molecules. Similarly, it is relevant to investigate, in depth and in a comparative way, the bioavailability of these compounds in production animals, considering the physiological differences and their conditions that can be taken as advantages or disadvantages in their use.

Funding:

This work was funded by "fiscal projects: evaluation of immunomodulatory compounds and antiviral compounds for the treatment of porcine blue eye disease" [no. 2192136578] of CENID-SAI/INIFAP, Mexico City, Mexico. José Bryan García-Cambrón receives a scholarship from CONAHCYT (CVU: 992190).

Conflict of interest:

The authors declare that there are no conflicts of interest.

License:

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Literature cited:

1. Lang Y, Gao N, Zang Z, Meng X, Lin Y, Yang S, Yang Y, Jin Z, Li B. Classification and antioxidant assays of polyphenols: A review. J Future Foods 2024;4(3):193-204. https://doi.org/10.1016/j.jfutfo.2023.07.002.

2. Islam T, Albracht-Schulte K, Ramalingam L, Schlabritz-Lutsevich N, Park OH, Zabet-Moghaddam M, Kalupahana NS, Moustaid-Moussa N. Anti-inflammatory mechanisms of polyphenols in adipose tissue: Role of gut microbiota, intestinal barrier integrity and zinc homeostasis. J Nutr Biochem 2023;(115): 109242. https://doi.org/10.1016/j.jnutbio.2022.109242.

3. Montenegro-Landívar MF, Tapia-Quirós P, Vecino X, Reig M, Valderrama C, Granados M, Cortina JL, Saurina J. Polyphenols and their potential role to fight viral diseases: An overview. Sci Total Environ 2021; (801):149719. https://doi.org/10.1016/j.scitotenv.2021.149719.

4. Grosso G. Effects of polyphenol-rich foods on human health. Nutrients 2018;10(8):1089. https://doi.org/10.3390/nu10081089.

5. Stover MG, Watson RR. Polyphenols in foods and dietary supplements. In: Polyphenols in human health and disease. 2014. Elsevier. https://doi.org/10.1016/B978-0-12-398456-2.00001-3.

6. Frei B, Higdon JV. Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. J Nutr 2003;133(10):3275S-3284S. https://doi.org/10.1093/jn/133.10.3275S.

7. Gülçin İ. Antioxidant activity of food constituents: An overview. Arch Toxicol 2012;86(3):345-391. https://doi.org/10.1007/s00204-011-0774-2.

8. Francisco V, Costa G, Neves BM, Cruz MT, Batista MT. Anti-inflammatory activity of polyphenols on dendritic cells. In: Polyphenols: prevention and treatment of human disease. 2018:395-415. Elsevier. https://doi.org/10.1016/B978-0-12-813008-7.00031-X.

9. Constantinescu T, Mihis AG. Resveratrol as a privileged molecule with antioxidant activity. Food Chem 2023;(3):100539. https://doi.org/10.1016/j.focha.2023.100539.

10. Braga A, Faria N. Biotechnological production of specialty aromatic and aromatic-derivative compounds. World J Microbiol Biotechnol 2022;38(5):80. https://doi.org/10.1007/s11274-022-03263-y.

11. Robertson I, Wai Hau T, Sami F, Sajid Ali M, Badgujar V, Murtuja S, et al.. The science of resveratrol, formulation, pharmacokinetic barriers and its chemotherapeutic potential. Int J Pharm 2022;(618): 121605. https://doi.org/10.1016/j.ijpharm.2022.121605.

12. Wang X, Parvathaneni V, Shukla SK, Kulkarni NS, Muth A, Kunda NK, Gupta V. Inhalable resveratrol-cyclodextrin complex loaded biodegradable nanoparticles for enhanced efficacy against non-small cell lung cancer. Int J Biol Macromol 2020;(164):638-650. https://doi.org/10.1016/j.ijbiomac.2020.07.124.

13. Calvo-Castro LA, Schiborr C, David F, Ehrt H, Voggel J, Sus N, Behnam D, Bosy-Westphal A, Frank J. The oral bioavailability of trans -resveratrol from a grapevine-shoot extract in healthy humans is significantly increased by micellar solubilization. Mol Nutr Food Res 2018;(62):1701057.

14. Su M, Dong C, Wan J, Zhou M. Pharmacokinetics, tissue distribution and excretion study of trans-resveratrol-3-O-glucoside and its two metabolites in rats. Phytomedicine 2019;(58):152882. https://doi.org/10.1016/j.phymed.2019.152882.

15. Abba Y, Hassim H, Hamzah H, Noordin MM. Antiviral activity of resveratrol against human and animal viruses. Adv Virol 2015:1-7. https://doi.org/10.1155/2015/184241.

16. Chen M, Chen X, Song X, Muhammad A, Jia R, Zou Y, et al.. The immune-adjuvant activity and the mechanism of resveratrol on pseudorabies virus vaccine in a mouse model. Int Immunopharmacol 2019; (76):105876. https://doi.org/10.1016/j.intimp.2019.105876.

17. Benedetti F, Sorrenti V, Buriani A, Fortinguerra S, Scapagnini G, Zella D. Resveratrol, rapamycin and metformin as modulators of antiviral pathways. Viruses 2020;12(12):1458. https://doi.org/10.3390/v12121458.

18. Wang X, Liu Y, Li K, Yang M, Wang Q, Hao Z. Triacetyl resveratrol inhibits PEDV by inducing the early apoptosis in vitro. Int J Mol Sci 2022;23(23):14499. https://doi.org/10.3390/ijms232314499.

19. Galindo I, Hernáez B, Berná J, Fenoll J, Cenis JL, Escribano JM, Alonso C. Comparative inhibitory activity of the stilbene's resveratrol and oxyresveratrol on African swine fever virus replication. Antivir Res 2011;91(1):57-63. https://doi.org/10.1016/j.antiviral.2011.04.013.

20. Chen X, Song X, Zhao X, Zhang Y, Wang Y, Jia R, Zou Y, Li L, Yin Z. Insights into the anti-inflammatory and antiviral mechanisms of resveratrol. Mediators Inflamm 2022:1-1. https://doi.org/10.1155/2022/7138756.

21. Liu Y, Song D, Liu X, Wang Y, Wang G, Lan Y. Suppression of porcine hemagglutinating encephalomyelitis virus replication by resveratrol. Virol J 2022;19(1):226. https://doi.org/10.1186/s12985-022-01953-5.

22. Malaguarnera L. Influence of resveratrol on the immune response. Nutrients 2019;11(5):946. https://doi.org/10.3390/nu11050946.

23. Harikumar KB, Aggarwal BB. Resveratrol: a multitargeted agent for age-associated chronic diseases. Cell Cycle 2008;7(8):1020-1035. https://doi.org/10.4161/cc.7.8.5740.

24. Delmas D, Limagne E, Ghiringhelli F, Aires V. Immune Th17 lymphocytes play a critical role in the multiple beneficial properties of resveratrol. British Industrial Biological Research Association 2020;137:111091. https://doi.org/10.1016/j.fct.2019.111091.

25. Vasamsetti SB, Karnewar S, Gopoju R, Gollavilli PN, Narra SR, Kumar JM, Kotamraju S. Resveratrol attenuates monocyte-to-macrophage differentiation and associated inflammation via modulation of intracellular GSH homeostasis: Relevance in atherosclerosis. Free Radic Biol Med 2016;96:392-405. https://doi.org/10.1016/j.freeradbiomed.2016.05.003.

26. Kotha RR, Luthria DL. Curcumin: Biological, pharmaceutical, nutraceutical, and analytical aspects. Molecules 2019;24(16):2930. https://doi.org/10.3390/molecules24162930.

27. Fu YS, Chen TH, Weng L, Huang L, Lai D, Weng CF. Pharmacological properties and underlying mechanisms of curcumin and prospects in medicinal potential. Biomed Pharmacother 2021;(141): 111888. https://doi.org/10.1016/j.biopha.2021.111888.

28. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. Mol Pharm 2007;4(6):807-818. https://doi.org/10.1021/mp700113r.

29. Ravindranath V, Chandrasekhara N. Absorption and tissue distribution of curcumin in rats. Toxicology 1980;16(3):259-265. https://doi.org/10.1016/0300-483x(80)90122-5.

30. Ravindranath V, Chandrasekhara N. Metabolism of curcumin--studies with [3H] curcumin. Toxicology 1981;22(4):337-344. https://doi.org/10.1016/0300-483x(81)90027-5.

31. Sharma RA, Ireson CR, Verschoyle RD, Hill KA, Williams ML, Leuratti C, et al.. Effects of dietary curcumin on glutathione s-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug levels. Clin Cancer Res 2001;(7):1452-1458.

32. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998;64(4):353-356. https://doi.org/10.1055/s-2006-957450.

33. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, et al.. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 2004;10(20):6847-6854. https://doi.org/10.1158/1078-0432.CCR-04-0744.

34. Ferreira VH, Nazli A, Dizzell SE, Mueller K, Kaushic C. The anti-inflammatory activity of curcumin protects the genital mucosal epithelial barrier from disruption and blocks replication of HIV-1 and HSV-2. PloS One 2015;10(4):e0124903. https://doi.org/10.1371/journal.pone.0124903.

35. Nazli A, Chan O, Dobson-Belaire WN, Ouellet M, Tremblay MJ, Gray-Owen SD, et al.. Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. PLoS Pathog 2010;6(4):e1000852. https://doi.org/10.1371/journal.ppat.1000852.

36. Sui Z, Salto R, Li J, Craik C, Ortiz de Montellano PR. Inhibition of the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Bioorg Med Chem 1993;1(6):415-422. https://doi.org/10.1016/s0968-0896(00)82152-5.

37. Mazumder A, Raghavan K, Weinstein J, Kohn KW, Pommier Y. Inhibition of human immunodeficiency virus type-1 integrase by curcumin. Biochem Pharmacol 1995;49(8):1165-1170. https://doi.org/10.1016/0006-2952(95)98514-a.

38. Mounce BC, Cesaro T, Carrau L, Vallet T, Vignuzzi M. Curcumin inhibits Zika and Chikungunya virus infection by inhibiting cell binding. Antivir Res 2017;(142):148-57. https://doi.org/10.1016/j.antiviral.2017.03.014.

39. Chen DY, Shien JH, Tiley L, Chiou SS, Wang SY, et al.. Curcumin inhibits influenza virus infection and haemagglutination activity. Food Chem 2010;(119):1346-135. https://doi.org/10.1016/j.foodchem.2009.09.011.

40. Ou JL, Mizushina Y, Wang SY, Chuang DY, Nadar M, Hsu WL. Structure-activity relationship analysis of curcumin analogues on anti-influenza virus activity. FEBS J 2013;280(22):5829-5840. https://doi.org/10.1111/febs.12503.

41. Dai J, Gu L, Su Y, Wang Q, Zhao Y, Chen X, Deng H, Li W, Wang G, Li K. Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-κB pathways. Int Immunopharmacol 2018;(54):177-187. https://doi.org/10.1016/j.intimp.2017.11.009.

42. Chen TY, Chen D, Wen HW, Ou JL, Chiou SS, Chen JM, Wong ML, Hsu WL. Inhibition of enveloped viruses infectivity by curcumin. PloS One 2013;8(5):e62482. https://doi.org/10.1371/journal.pone.0062482.

43. Li Y, Wang J, Liu Y, Luo X, Lei W, Xie L. Antiviral and virucidal effects of curcumin on transmissible gastroenteritis virus in vitro. J Gen Virol 2020;101(10):1079-1084. https://doi.org/10.1099/jgv.0.001466.

44. Praditya D, Kirchhoff L, Brüning J, Rachmawati H, Steinmann J, Steinmann E. Anti-infective properties of the golden spice curcumin. Front Microbiol 2019;(10):912. https://doi.org/10.3389/fmicb.2019.00912.

45. Varalakshmi Ch, Ali AM, Pardhasaradhi BVV, Srivastava RM, Singh S, Khar A. Immunomodulatory effects of curcumin: In-vivo. Int Immunopharmacol 2008;8(5):688-00. https://doi.org/10.1016/j.intimp.2008.01.008.

46. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A. Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. J Nutr Biochem 2019;(66):1-16. https://doi.org/10.1016/j.jnutbio.2018.12.005.

47. Makuch S, Więcek K, Woźniak M. The immunomodulatory and anti-inflammatory effect of curcumin on immune cell populations, cytokines, and in vivo models of rheumatoid arthritis. Pharma 2021;14(4): 309. https://doi.org/10.3390/ph14040309.

48. Conigliaro P, Triggianese P, De Martino E, Fonti GL, Chimenti MS, Sunzini F, Viola A, Canofari C, Perricone R. Challenges in the treatment of rheumatoid arthritis. Autoimmun Rev 2019;18(7):706-713. https://doi.org/10.1016/j.autrev.2019.05.007.

49. Bright JJ. Curcumin and autoimmune disease. In: Aggarwal BB, Surh YJ, Shishodia S. The molecular targets and therapeutic uses of curcumin in health and disease. 2007:425-451. Springer US. https://doi.org/10.1007/978-0-387-46401-5_19.

50. Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, Ray S. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in-silico study for drug development. J Biomol Struct Dyn 2021;39(16):6306-6316. https://doi.org/10.1080/07391102.2020.1796811.

51. Shen T, Jiang T, Long M, Chen J, Ren D-M, Wong PK, Chapman E, Zhou B, Zhang D. A curcumin derivative that inhibits vinyl carbamate-induced lung carcinogenesis via activation of the nrf2 protective response. Antioxid Redox Signa 2015;23(8):651-664. https://doi.org/10.1089/ars.2014.6074.

52. Da W, Zhang J, Zhang R, Zhu J. Curcumin inhibits the lymphangiogenesis of gastric cancer cells by inhibiton of HMGB1/VEGF-D signaling. Int J Immunopathol Pharmacol 2019;(33):205873841986160. https://doi.org/10.1177/2058738419861600.

53. Cheng K, Yang A, Hu X, Zhu D, Liu K. Curcumin attenuates pulmonary inflammation in lipopolysaccharide induced acute lung injury in neonatal rat model by activating peroxisome proliferator-activated receptor γ (pparγ) pathway. Med Sci Monit 2018;(24):1178-1184. https://doi.org/10.12659/MSM.908714.

54. Abo-Zaid MA, Shaheen ES, Ismail AH. Immunomodulatory effect of curcumin on hepatic cirrhosis in experimental rats. J Food Biochem 2020;44(6). https://doi.org/10.1111/jfbc.13219.

55. Farzaei M, Zobeiri M, Parvizi F, El-Senduny F, Marmouzi I, Coy-Barrera E, Naseri R, Nabavi S, Rahimi R, Abdollahi M. Curcumin in liver diseases: a systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients 2018;10(7):855. https://doi.org/10.3390/nu10070855.

56. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. Phytother Res 2018;32(12):2323-2339.

57. Selyutina OY, Polyakov NE. Glycyrrhizic acid as a multifunctional drug carrier - From physicochemical properties to biomedical applications: A modern insight on the ancient drug. Int J Pharm 2019;(559): 271-279.

58. Polyakov NE. Glycyrrhizic acid as a novel drug delivery vector: synergy of drug transport and efficacy. Open Conf Proc J 2011;2(1):64-72. https://doi.org/10.2174/2210289201102010064.

59. Ming LJ, Yin AC. Therapeutic effects of glycyrrhizic acid. Nat Prod Commun 2013;8(3):415-418.

60. Omar HR, Komarova I, El-Ghonemi M, Fathy A, Rashad R, Abdelmalak HD, et al.. Licorice abuse: Time to send a warning message. Ther Adv Endocrinol Metab 2012;3(4):125-138. https://doi.org/10.1177/2042018812454322.

61.Cosmetic Ingredient Review Expert Panel. Final report on the safety assessment of glycyrrhetinic acid, potassium glycyrrhetinate, disodium succinoyl glycyrrhetinate, glyceryl glycyrrhetinate, glycyrrhetinyl stearate, stearyl glycyrrhetinate, glycyrrhizic acid, ammonium glycyrrhizate, dipotassium glycyrrhizate, disodium glycyrrhizate, trisodium glycyrrhizate, methyl glycyrrhizate, and potassium glycyrrhizinate. Int J Toxicol 2007;26(2):79-112. https://doi.org/10.1080/10915810701351228.

62. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). (2015). Scientific opinion on the safety and efficacy of glycyrrhizic acid ammoniated (chemical group 30, miscellaneous substances) when used as a flavouring for all animal species. EFSA J 2015;13(1):3971. https://doi.org/10.2903/j.efsa.2015.3971.

63. Hattori M, Sakamoto T, Yamagishi T, Sakamoto K, Konishi K, Kobashi K, Namba T. Metabolism of glycyrrhizin by human intestinal flora. II. Isolation and characterization of human intestinal bacteria capable of metabolizing glycyrrhizin and related compounds. Chem Pharm Bull 1985;33(1):210-217. https://doi.org/10.1248/cpb.33.210.

64. Wang Z, Nishioka M, Kurosaki Y, Nakayama T, Kimura T. Gastrointestinal absorption characteristics of glycyrrhizin from glycyrrhiza extract. Biol Pharm Bull 1995;18(9):1238-1241. https://doi.org/10.1248/bpb.18.1238.

65. Parke DV, Pollock S, Williams RT. The fate of tritium-labelled beta-glycyrrhetic acid in the rat. J Pharm Pharmacol 1963;(15):500-506. https://doi.org/10.1111/j.2042-7158.1963.tb12825.x.

66. Ploeger B, Mensinga T, Sips A, Seinen W, Meulenbelt J, DeJongh J. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. Drug Metab Rev 2001;33(2):125-147. https://doi.org/10.1081/dmr-100104400.

67. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 2003;361(9374):2045-2046. https://doi.org/10.1016/s0140-6736(03)13615-x.

68. Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, et al.. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31(1):69-75. https://doi.org/10.1016/j.jcv.2004.03.003.

69. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, Doerr HW, Cinatl J Jr. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J Med Chem 2005;48(4): 1256-1259. https://doi.org/10.1021/jm0493008.

70. Lin JC. Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication in vitro. Antivir Res 2003;59(1):41-47. https://doi.org/10.1016/s0166-3542(03)00030-5.

71. Baltina LA, Hour MJ, Liu YC, Chang YS, Huang SH, Lai HC, Kondratenko RM, Petrova SF, Yunusov MS, Lin CW. Antiviral activity of glycyrrhizic acid conjugates with amino acid esters against Zika virus. Virus Res 2021;(294):198290. https://doi.org/10.1016/j.virusres.2020.198290.

72. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, Bielenberg J. Antiviral effects of Glycyrrhiza species. Phytother Res 2008;22(2):141-148. https://doi.org/10.1002/ptr.2295.

73. Li P, Zou H, Ren Y, Zarlenga DS, Ren X. Antiviral effect of diammonium glycyrrhizinate on cell infection by porcine parvovirus. Curr Microbiol 2014;69(1):82-87. https://doi.org/10.1007/s00284-014-0540-9.

74. Gao R, Zhang Y, Kang Y, Xu W, Jiang L, Guo T, Huan C. Glycyrrhizin Inhibits PEDV Infection and proinflammatory cytokine secretion via the HMGB1/TLR4-MAPK p38 pathway. Int J Mol Sci 2020;21(8): 2961. https://doi.org/10.3390/ijms21082961.

75. Huo X, Sun X, Cao Z, Qiao J, Yang S, Meng X, Zhao Y. Optimal ratio of 18α- and 18β-glycyrrhizic acid for preventing alcoholic hepatitis in rats. Exp Ther Med 2019;18(1):172-178. https://doi.org/10.3892/etm.2019.7572.

76. Xie C, Li X, Wu J, Liang Z, Deng F, Xie W, Zhu M, Zhu J, Zhu W, Geng S, Zhong C. Anti-inflammatory activity of magnesium isoglycyrrhizinate through inhibition of phospholipase a2/arachidonic acid pathway. Inflammation 2015;38(4):1639-1648. https://doi.org/10.1007/s10753-015-0140-2.

77. Yang R, Yuan B-C, Ma Y-S, Zhou S, Liu Y. The anti-inflammatory activity of licorice, a widely used Chinese herb. Pharm Biol 2017;55(1):5-18. https://doi.org/10.1080/13880209.2016.1225775.

78. Ma D, Zhang J, Zhang Y, Zhang X, Han X, Song T, Zhang Y, Chu L. Inhibition of myocardial hypertrophy by magnesium isoglycyrrhizinate through the TLR4/NF-κB signaling pathway in mice. Int Immunopharmacol 2018;(55):237-244. https://doi.org/10.1016/j.intimp.2017.12.019.

79. Zhao L, Ju-ying Z, Er-ning G, Hong Y. Effects of glycyrrhizin acid and licorice flavonoids on LPS-induced cytokines expression in macrophage. Zhongguo Zhong Yao Za Zhi 2014;39(19).

80. Dai JH, Iwatani Y, Ishida T, Terunuma H, Kasai H, Iwakula Y, Fujiwara H, Ito M. Glycyrrhizin enhances interleukin-12 production in peritoneal macrophages. Immunology 2001;103(2):235-243. https://doi.org/10.1046/j.1365-2567.2001.01224.x.

81. Bhattacharjee S, Bhattacharjee A, Majumder S, Majumdar SB, Majumdar S. Glycyrrhizic acid suppresses Cox-2-mediated anti-inflammatory responses during Leishmania donovani infection. J Antimicrob Chemother 2012;67(8):1905-1914. https://doi.org/10.1093/jac/dks159.

82. Bordbar N, Karimi MH, Amirghofran Z. The effect of glycyrrhizin on maturation and T cell stimulating activity of dendritic cells. Cell Immunol 2012;280(1):44-49. https://doi.org/10.1016/j.cellimm.2012.11.013.

83. Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids. Med Inflamm 2021;1-15. https://doi.org/10.1155/2021/6699560.

84. Scott MB, Styring AK, McCullagh JSO. Polyphenols: bioavailability, microbiome interactions and cellular effects on health in humans and animals. Pathogens 2022;11(7):770. https://doi.org/10.3390/pathogens11070770.

85. Sampathkumar KTKX, Loo SCJ. Developing nano-delivery systems for agriculture and food applications with nature-derived polymers. iScience 2020;23(5):101055. https://doi.org/10.1016/j.isci.2020.101055.

86. Adepu S, Ramakrishna S. Controlled drug delivery systems: current status and future directions. Molecules 2021;26(19):5905. https://doi.org/10.3390/molecules26195905.

87. Ding Y, Li Z, Jaklenec A, Hu Q. Vaccine delivery systems toward lymph nodes. Adv Drug Deliv Rev 2021;(179):113914. https://doi.org/10.1016/j.addr.2021.113914.

88. Jia W, Zhou L, Li L, Zhou P, Shen Z. Nano-based drug delivery of polyphenolic compounds for cancer treatment: progress, opportunities, and challenges. Pharmaceuticals 2023;16(1):101. https://doi.org/10.3390/ph16010101.

89. Vasconcelos T, Araújo F, Lopes C, Loureiro A, das Neves J, Marques S, Sarmento B. Multicomponent self-nano emulsifying delivery systems of resveratrol with enhanced pharmacokinetics profile. Eur J Pharm Sci 2019;(137):105011. https://doi.org/10.1016/j.ejps.2019.105011.

90. Bohara RA, Tabassum N, Singh MP, Gigli G, Ragusa A, Leporatti S. Recent overview of resveratrol's beneficial effects and its nano-delivery systems. Molecules 2022;27(16):5154. https://doi.org/10.3390/molecules27165154.

91. Singh G. Resveratrol: nanocarrier-based delivery systems to enhance its therapeutic potential. Nanomedicine 2020;15(28):2801-2817. https://doi.org/10.2217/nnm-2020-0289.

92. Meng Q, Li J, Wang C, Shan A. Biological function of resveratrol and its application in animal production: a review. J Anim Sci Biotechnol 2023;14(1):25. https://doi.org/10.1186/s40104-022-00822-z.

93. Gan Z, Wei W, Li Y, Wu J, Zhao Y, Zhang L, Wang T, Zhong X. Curcumin and resveratrol regulate intestinal bacteria and alleviate intestinal inflammation in weaned piglets. Molecules 2019;(24):1220. https://doi.org/10.3390/molecules24071220.

94. Dei Cas M, Ghidoni R. Dietary curcumin: Correlation between bioavailability and health potential. Nutrients 2019;11(9):2147. https://doi.org/10.3390/nu11092147.

95. Józsa L, Vasvári G, Sinka D, Nemes D, Ujhelyi Z, Vecsernyés M, et al.. Enhanced antioxidant and anti-inflammatory effects of self-nano and microemulsifying drug delivery systems containing curcumin. Molecules 2022;27(19):6652. https://doi.org/10.3390/molecules27196652.

96. Witika BA, Makoni PA, Matafwali SK, Mweetwa LL, Shandele GC, Walker RB. Enhancement of biological and pharmacological properties of an encapsulated polyphenol: curcumin. Molecules 2021;26(14):4244. https://doi.org/10.3390/molecules26144244.

97. Kharat M, McClements DJ. Recent advances in colloidal delivery systems for nutraceuticals: A case study - Delivery by design of curcumin. J Colloid Interface Sci 2019;(557):506-518. https://doi.org/10.1016/j.jcis.2019.09.045.

98. Huang M, Zhai BT, Fan Y, Sun J, Shi YJ, Zhang XF, Zou JB, Wang JW, Guo DY. Targeted drug delivery systems for curcumin in breast cancer therapy. Int J Nanomed 2023;(18):4275-4311. https://doi.org/10.2147/IJN.S410688.

99. Liu T, Zhu W, Han C, Sui X, Liu C, Ma X, Dong Y. Preparation of glycyrrhetinic acid liposomes using lyophilization monophase solution method: Preformulation, optimization, and in vitro evaluation. Nanoscale Res Lett 2018;13(1):324. https://doi.org/10.1186/s11671-018-2737-5.

100. Polyakov NE. Glycyrrhizic acid as a novel drug delivery vector: synergy of drug transport and efficacy. OCP 2011;2(1):64-72. https://doi.org/10.2174/2210289201102010064.

101. Zhao X, Liu J, Hu Y, Fan Y, Wang D, Yuan J, Xu L, Cui L, Jing Z. Optimization on condition of glycyrrhetinic acid liposome by RSM and the research of its immunological activity. Int J Biol Macromol 2012;51(3):299-304. https://doi.org/10.1016/j.ijbiomac.2012.05.005.

102. Dionigi L, Ragonese F, Monarca L, Covino S, de Luca A, Iannitti RG, et al.. Focus on the use of resveratrol as an adjuvant in glioblastoma therapy. Curr Pharm Des 2020;26(18):2102-2108. https://doi.org/10.2174/1381612826666200401085634.

103. Mortezaee K, Najafi M, Farhood B, Ahmadi A, Shabeeb D, Musa AE. Resveratrol as an adjuvant for normal tissues protection and tumor sensitization. Curr Cancer Drug Targets 2020;20(2):130-145. https://doi.org/10.2174/1568009619666191019143539.

104. Delmas D, Lin HY. Role of membrane dynamics processes and exogenous molecules in cellular resveratrol uptake: consequences in bioavailability and activities. Mol Nutr Food Res 2011;55(8): 1142-1153. https://doi.org/10.1002/mnfr.201100065.

105. Alesci A, Nicosia N, Fumia A, Giorgianni F, Santini A, Cicero N. Resveratrol and immune cells: A link to improve human health. Molecules 2022;27(2):424. https://doi.org/10.3390/molecules27020424.

106. Maithilikarpagaselvi N, Sridhar MG, Swaminathan RP, Sripradha R, Badhe B. Curcumin inhibits hyperlipidemia and hepatic fat accumulation in high-fructose-fed male Wistar rats. Pharm Biol 2016;54(12):2857-2863. https://doi.org/10.1080/13880209.2016.1187179.

107. Huang G, Xu Z, Huang Y, Duan X, Gong W, Zhang Y, Fan J, He F. Curcumin protects against collagen-induced arthritis via suppression of BAFF production. J Clin Immunol 2013;33(3):550-557. https://doi.org/10.1007/s10875-012-9839-0.

108. Zhao HM, Xu R, Huang XY, Cheng SM, Huang MF, Yue HY, Wang X, Zou Y, Lu AP, Liu DY. Curcumin improves regulatory T cells in gut-associated lymphoid tissue of colitis mice. World J Gastroenterol 2016;22(23):5374-5383. https://doi.org/10.3748/wjg.v22.i23.5374.

109. Zhao X, Fan Y, Wang D, Hu Y, Guo L, Ruan S, Zhang J, Yuan J. Immunological adjuvant efficacy of glycyrrhetinic acid liposome against Newcastle disease vaccine. Vaccine 2011;29(52):9611-9617. https://doi.org/10.1016/j.vaccine.2011.10.053.

110. Castañeda-Montes MA, Cuevas-Romero JS, Cerriteño-Sánchez JL, de María Ávila-De la Vega L, García-Cambrón JB, Ramírez-Álvarez H. Small ruminant lentivirus capsid protein (SRLV-p25) antigenic structural prediction and immunogenicity to recombinant SRLV-rp25-coupled to immunostimulatory complexes based on glycyrrhizinic acid. BBB 2023;87(3):267-278. https://doi.org/10.1093/bbb/zbac206.

111. García-Cambrón JB, Cerriteño-Sánchez JL, Lara-Romero R, Quintanar-Guerrero D, Blancas-Flores G, Sánchez-Gaytán BL, et al.. Development of glycyrrhizinic acid-based lipid nanoparticle (LNP-GA) as an adjuvant that improves the immune response to porcine epidemic diarrhea virus spike recombinant protein. Viruses 2024;16(3):431. https://doi.org/10.3390/v16030431.