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REVIEW ARTICLE

Saponins and Their Role as Vaccine Adjuvant Against Coccidiosis in Poultry

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Abstract

Coccidiosis, induced by various *Eimeria* species, has been one of the most important health threats and performance of poultry around the world. Other than the current treatment, successful vaccination approaches have been realized. Advances in saponin biochemistry, from *Quillaja saponaria* and *Yucca schidigera* plants, have supported the development of vaccine adjuvants based on these natural glycosides. Saponins also activate innate immune pathways and can assist with antigen presentation, enhancing humoral and cell-mediated responses. Saponin-based adjuvants, including QS-21 and Quil A, can enhance adjuvant efficacy by inducing higher antibody responses and promoting long-lasting protective immunity privation. Nonetheless, challenges including toxicity issues about the saponin fractions and the variable adjuvant activity among different saponins, have also been reported. Future studies aim to improve saponin adjuvant formulations, determine their harmlessness, and investigate new transport systems, such as immunostimulating complexes. By enhancing poultry health, such advancements contribute to safer meat and egg products, directly supporting food safety. Moreover, reducing disease-related losses in poultry farms promotes food security by ensuring stable and efficient protein production. The focus of this review article is to highlight the role of saponins as vaccine adjuvants to enhance immunity against *Eimeria* species in poultry.

Keywords: Coccidiosis, *Eimeria*, Food safety, Phytochemicals, Quil A, Saponins, Vaccine adjuvants

INTRODUCTION

Coccidiosis is one of the most important health problems [1] affecting animals worldwide, causing disease with major economic losses [2]. It is caused by obligate intracellular parasitic protozoa known as *Eimeria*, belonging to the order Apicomplexa [3]. *Eimeria* remains one of the most economically important species that cause disease in livestock globally [4]. *Eimeria* is remarkably receptive in the poultry industry [5], this is because the transmission of parasites is highly favored by the bulk number of susceptible birds [6,7]. *Eimeria* spp. results in coccidiosis disease that hinders the expansion of the poultry industry [8]. The infection may get worse because of poor management techniques such as excessive stocking densities, contaminated feeders, drinkers, and damp litter that encourage oocyst sporulation, and inadequate ventilation facilities [9]. Among the most virulent *Eimeria* spp., *E. tenella* is the most common, followed by *E. acervulina* and *E. maxima* [10]. Due to increased mortality, stunted growth, and a low feed conversion ratio, the disease directly affects the production potential of affected livestock, resulting in significant financial losses [11,12]. In the poultry industry, globally there was a huge economic loss of more than 3 billion US$ annually [13]. Such economic losses not only reduce profitability but also threaten food security by limiting the availability of affordable protein sources. Additionally, disease-related contamination in meat and eggs poses a serious risk to food safety across the supply chain.

The coccidial parasites can enter various animal hosts and effectually exploit the immune system [4]. This creates a serious dispute against the action of control. Many drugs have been developed against the coccidia parasite [8]. In avian coccidiosis, *Eimeria* species develop frequent resistance when new and effective drugs are detected in the body [14]. Alongside commercial losses, using chemotherapeutics in poultry can also generate harmful residues in eggs and meat [15]. According to studies, the use of vaccines is the most efficient way to prevent and reduce the prevalence of infectious diseases [16,17]. Though there is an emerging line of action as prophylactic vaccines, these are said to be a successful approach against coccidia, but these vaccines are minimal and in short supply [4]. Anticoccidial drugs have successfully prevented coccidiosis over the decades, with certain restrictions related to production costs [18]. There are various kinds of vaccines: live attenuated, inactivated vaccines (killed), and recombinant vaccines (subunits) [19]. Mostly, the commercial vaccines against coccidiosis are based on killed or live virulent organisms [20]. Nonetheless, the assurance of a live attenuated vaccine is uncertain because of the possibility of severe regression [21]. When comparing, it shows that a durable solution and safer options are provided by subunit vaccines [22,23]. However, isolated antigens from different host systems can be less antigenic and immune stimulating than killed or live attenuated vaccine variants [24]. To stimulate an effective immune response by delivering these antigens to the immune system is a challenging task [25]. In this matter, it is generally acknowledged that to increase efficacy and immunity, we need further components to be added to vaccines. These components are macromolecules and their complexes, either compounds or molecules, commonly known as adjuvants [26,27].

Adjuvants were first discovered in 1920 by Gaston Ramon [28], a French scientist who observed that if aluminum salts are included in a vaccine, they increase its potential [29]. It is derived from the Latin word "Adjuvare" which means to aid [30,31]. Vaccine adjuvants are used to increase the potential of the immune system response to combined antigens [32]. Most adjuvants are chemicals, macromolecules, or compounds that improve innate immunity by combining with the antigens, and enhance the immune response [16,33]. Many efforts have been made to reduce the intricacy of antigens, such as pure antigens, recombinants [34], artificially manufactured peptides, and proteins, as an alternative use of whole inactive organisms without adjuvants to induce immunity [35,36]. The non-toxic adjuvants can boost and direct immune response. Certain adjuvants, including mineral gels or water in oil emulsions, regulate the antigen at the injection site [37]. Adjuvants increase the secondary type of immune response by slowly releasing the restrained antigen into the immune system [38, 39]. The enhancement in the action of vaccines using adjuvants is shown in *Fig. 1*.

Although the mechanism of action of adjuvants is still under investigation, significant progress has been made in recent years to identify them [40]. The potential and virulent nature of adjuvants should be maintained in order to provide protected stimulants with very fewer reactions [41], it depends on how adjuvants are being used [36,42]. In several years, adjuvants have been used in many experimental subunit vaccines that are often too weak to stimulate

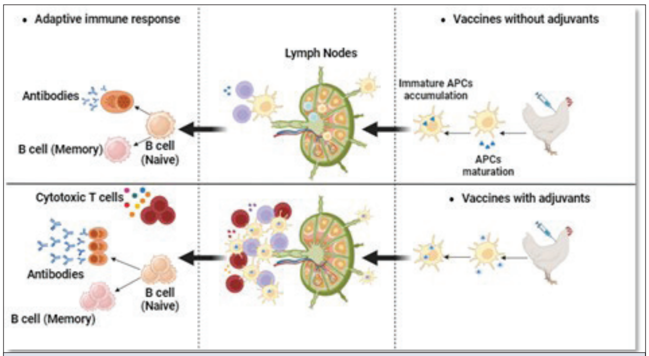

Fig 1. Vaccine enhancement using adjuvants

immune response alone [31], however, not all vaccines need adjuvants [36].

Many studies have shown that the plant-derived compounds of herb spices known as phytochemicals, play a vital role in antimicrobial, coccidiostat activities in animals [43-46], as they improve gut health, immunity, growth enhancement, and adsorption of nutrients [47,48]. Adjuvants derived from phytochemistry, such as saponins, carbohydrates,protein lectins, and heat-shock proteins, are efficient immune stimulants with little toxicity [49]. Different studies marked the effectiveness of phytochemicals as adjuvants against various diseases. These have proved to be useful as potential adjuvants against coccidiosis. Saponins are the most significant phyto-biotics for use as adjuvants in vaccines among all other phytochemicals [50]. They are natural compounds produced by plants that play an important role in defense mechanisms due to their antimicrobial, fungicidal, and insecticidal properties. Furthermore, many plant saponins can activate the immune system, which leads to considerable interest in their potential as vaccine adjuvants [3]. This review deliberates the potential application of plant-derived saponin compounds in the development of vaccines against poultry coccidiosis. It also comprehensively explains the immunological effects, functions, constraints, and postulated mechanisms of action of saponins.

Saponins

Saponins are amphiphilic, heat-stable, and glycosidic secondary metabolites derived from plants [51]. These steroidal aglycones and triterpenoids are significantly used in the pharmaceutical industry [52]. They have immunomodulatory and antioxidant qualities that mainly make them useful as immunizing adjuvants against coccidiosis [53,54]. The bark, roots, leaves, and seeds of the *Quillaia Saponaria* tree yield an extract known to have immune-modulatory qualities. This tree is widely distributed throughout South America [3,52,55]. Non-polar

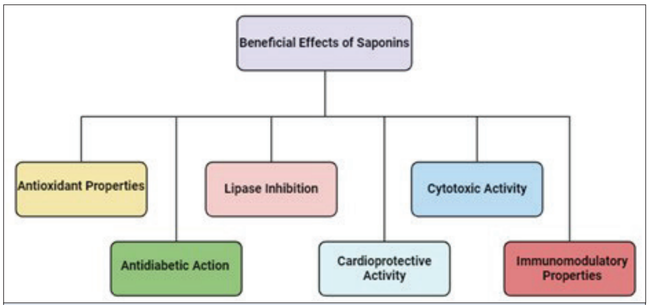

Fig 2. Properties of Saponins

Table 1. *Adjuvant active saponins*

Source	Adjuvant	Poultry	*Eimeria* spp.	Antigen	Route	Results	Ref.
Saponins	QCDC/RT	Broiler	*E. acervulina*	rProfilin	Subcutaneous	Weight gain, antibody production, and intestinal lesions were reduced	[63]
Saponins	QCDC-R	Chicken	*E. acervulina*	rProfilin	Subcutaneous	Mitogen-induced lymphocyte production and increased body weight Reduced intestinal lesions. No impact on oocyst shedding.	[64]
QS-21	QS-21	Chicken	*E.* spp.	IgG2a	Intramuscular and Intranasal	Purified saponin from *Quillaja saponica*, used to stabilize lipid emulsions	[65]
Saponins	QCDC	Chicken Embryo	*E. maxima*	rProfilin	Non-encapsulated	Increased growth. Reduced oocyst shedding	[66]
Anemone radiant Saponins	3- monodesmoside, 3,28-bisdesmoside	Chicken	*E.* spp.	IgGs	Subcutaneous	The serum antibody titer in chicken activates macrophages	[55, 67]
Saponins	QCDC	Broiler	*E. acervulina*	rProfilin	Subcutaneous	No effect on oocyst, IgG increased	[68]
Saponins	ISCOMs from endemic plants	Broiler	*E. tenella*	*E. tenella* all antigens	Intranasal	Increased IgGs protected against infection	[69]
Saponins	ISCOMs	Broiler	*E. tenella*	Antigens from sporozoite	Intranasal	Decreased lesion score and oocyst shedding	[70]
Saponins	ISCOMs	Broiler	*E. tenella*	AgP27	Diet Supplement	Increased total body weight Conferred partial protection against infection	[71]

aglycones make up the chemical structure of saponins, which is connected with chains of carbohydrates (polar) [56,57]. The presence of both polar and non-polar groups provides surface-active properties [58]. Saponins have a lot of beneficial effects as shown in *Fig. 2*.

They can stimulate a broad range of cytokine secretions [59], thereby enhancing both humoral and cellular immune responses [60]. Their ability to modulate innate immunity suggests that they could be used to design new vaccines that induce specific immune responses tailored to various pathogens and can reduce the drug resistance problem [61,62]. Adjuvant active saponins are shown in *Table 1*.

Saponin-Derived Compounds

Summarized in *Table 2*.

Immunostimulating Complexes (ISCOMs)

One innovative approach in utilizing saponins while mitigating their toxicity involves formulating them into Immunostimulating complexes "ISCOMs" [72]. ISCOMs are particulate adjuvant systems that combine saponins with cholesterol and phospholipids [73], significantly reducing toxicity while retaining potent adjuvant properties [74]. They provide a sophisticated approach to coccidiosis vaccination in poultry, taking advantage of their unique structure and composition to efficiently boost immune responses [3]. It mimics the immune system's innate detection of bacterial and viral structures to trigger potent humoral and cellular immune responses in poultry [75]. It is essential to activate both immune systems while treating intracellular parasites such as *Eimeria* species [76].

Table 2. *Saponin-Derived Compounds*

Source	Common Name	Adjuvant	Mode of Action	Benefits	Ref.
Peptasan	Sikakai	*Acacia concinna*	Immune modulation enhances adaptive and innate immune reactions Antioxidant and anti-inflammatory characteristics	Enhanced immune response Reduced parasite load Natural and safe for poultry	[91]
Yucca schidigera	Yucca	*Y. schidigera*	Saponins boost the immune response by boosting cytokine synthesis and T-cell proliferation Antioxidant characteristics	Improved gut health Reduced ammonia levels Enhanced vaccine efficacy	[92]
Quillaja Saponaria	Soapbark	*Q. Saponaria*	Saponins boost the immune response by boosting dendritic cell development and antigen presentation Adjuvant for vaccinations	Increased vaccine efficacy Enhanced antibody production Natural adjuvant	[50]
Norponin XO2	Yucca and Fenugreek	*Yucca schidigera* and *Trigonella foenum-graecum*	Yucca and Fenugreek saponins work together to enhance immunological response Improved intestinal health and decreased parasite load	The synergistic effect enhances immune response Improved gut health	[93]

Research has demonstrated encouraging outcomes in terms of improving vaccination efficacy and offering a more comprehensive defense against many *Eimeria* strains that are common in the production of chickens [45,77,78].

Quil A

Dalsgaard purified an adjuvant derived from *Q. saponaria* called Quil A containing a mixture of saponins in 1978 [79]. The mixture is enriched to use as an adjuvant for immunity induction via other isotypes of antibodies [80]. It is also used commercially in many vaccines [81,82]. The toxicity differs significantly between the components of Quil A [83,84]. The efficacy of Quil A as an adjuvant has been hindered by its apparent toxicity [85], which has been found in small animals following parenteral immunization with this adjuvant, and such toxicity may limit its utility [86]. However, nontoxic immunostimulatory fractions of Quil A have been identified, which may reduce or eliminate this issue [87]. While Quil A does not appear to be an effective mucosal adjuvant, its use as part of ISCOMs appears to be critical to the system's efficacy [88]. Structural and functional relationships of Saponin-adjuvant compounds are of interest because various fractions are used in immunological research.

QS-21

It can play an important role in poultry coccidiosis by improving antigen presentation and helping in T cells and antibody development [75]. Regardless of its efficacy, it is linked to formulation stability issues and some toxicity problems [89], which has prompted ongoing research to address these issues. The goal of continuing research is to create QS-21 variations that are less toxic while maintaining immunostimulatory activity to maximize its potential as an adjuvant in vaccines against coccidiosis [90]. QS-21 shows promising results as an adjuvant in boosting immune responses against coccidiosis. However, their efficacy and safety profiles in this setting necessitate additional research and optimization for their efficient application in poultry vaccination programs [44].

Mechanism of Action

Immunomodulatory Effects and Immune Boosting

In poultry, saponins enhance the immune response by affecting immune organ maturation, increasing antibody levels, and providing better defense against coccidiosis [94]. They are well-recognized for their potent immune modulatory effects [95]. The primary mechanism involves their interaction with immune cells, leading to the enhancement of the immune response [96]. They attract a variety of cells including macrophages, DCs (dendritic cells), and lymphocytes [55]. Saponins activate DCs by enhancing their capacity to process T lymphocytes. Maturation of DCs and upregulation of co-stimulatory chemicals allow for the efficient activation of T-cells [73,95]. B cells can create large amounts of antibodies. Saponins do this by boosting antibody isotype switching, resulting in a more effective immune response to pathogens.

Antioxidant Properties

Saponins have a great antioxidant capacity, which helps to manage reactive oxygen species and minimize diseases linked with oxidative stress, a major role in coccidiosis [97,98]. Reactive oxygen species (ROS) are produced during coccidia infection, resulting in oxidative stress and tissue damage. Saponins' antioxidant activities serve to neutralize ROS, lowering oxidative stress and its related diseases [99]. This antioxidant activity not only protects the host from ROS-induced damage but also improves the immune response by lowering pro-inflammatory cytokine production and increasing overall antioxidant levels [100-102].

Mechanisms at the Cellular Level

Saponins regulate several essential systems that underpin the immune response. These include the effects on antigen presentation and cytokine generation [103]. Saponins have a crucial role in antigen presentation, which initiates the adaptive immune response [104]. When antigen-presenting cells (APCs) are enhanced, dendritic cells (DCs) and macrophages can efficiently process and present antigens, thereby initiating immune responses [78,105]. It involves the upregulation of major histocompatibility complex (MHC) molecules on the surface of APCs, that are important for presenting antigens to T-cells. Boosting antigen presentation by APCs leads to activation of helper T cells (Th cells) and cytotoxic T cells [106].

Comparative Studies with Other Adjuvants

Comparative studies help to position saponins within the broader context of coccidiosis control strategies and highlight their advantages and limitations. A comparative study by [107] assessed the efficacy of saponins compared to synthetic anticoccidial drugs in broiler chickens. The results demonstrated that saponins were as effective as synthetic drugs in controlling coccidiosis, with the added benefit of being natural and reducing the risk of resistance development. This study also emphasized the potential of saponins to be used in combination with other control methods to enhance their efficacy [107]. In another study, saponins were compared with ionophore anticoccidials, which are widely used in the poultry industry. The findings indicated that saponins were comparable to ionophores in reducing lesion scores and oocyst shedding. Moreover, saponins exhibited a more favorable safety profile, with fewer side effects reported in treated birds. This highlights the potential of saponins as safer alternatives to traditional anticoccidials [78,105].

Limitations of Phytochemical Adjuvant Vaccination of Coccidiosis

Phytochemicals may have anti-nutritional qualities, resulting in decreased feed intake, growth suppression, and negative effects on body growth [108]. Some may be harmful at high quantities but harmless at lower levels [109]. The effectiveness of phytochemicals in treating coccidiosis varies depending on the specific plant compounds employed, their quantities, and their ratios [110-112]. The lack of standardization has the potential to undermine the dependability and efficacy of phytochemical adjuvants [113]. The extensive use of phytochemicals, like anticoccidial chemical compounds, has the potential to cause resistance in *Eimeria* spp. [108]. As a result, it is critical to apply techniques to prevent resistance development, such as alternating phytochemical adjuvants with other management methods and employing them in conjunction with other interventions [114,115]. More research is needed to understand the mechanisms of action of phytochemical adjuvants and to identify the most effective chemicals for coccidiosis reduction.

Prospects

Advances in biotechnology and synthetic biology offer exciting opportunities for producing saponins with enhanced properties [112], genetic engineering techniques can be used to modify microorganisms to produce saponins with specific structural features that enhance their stability and immunostimulatory effects. Moreover, the integration of saponins with advanced delivery systems, such as nanocarriers and immunostimulating complexes, holds great potential. These delivery systems can protect saponins from degradation, enhance their targeting of immune cells, and provide a controlled release of antigens [115]. The task at hand involves developing standardized animal models that replicate the illnesses of the intended species for use in vaccination regimens and determining the parameters that must be assessed accurately to determine the effectiveness of vaccines [3].

Conclusion

In summary, the reviewed data suggest that saponins as adjuvants allow the opportunity to achieve the main objective of adjuvant research in vaccines, as a safe option that is mostly non-toxic and able to boost immune response as it may be included in many vaccine formulations against coccidiosis. However, the difficulty lies in choosing the best adjuvant that is most suitable for immunization protocols. Despite that, their decreased immunogenicity eventually became a crucial component as a refined antigen of several vaccinations. In addition to their amazing qualities, the non-toxic nature of most saponins eases the main worry about manufactured compounds having severe effects. Saponins can increase the efficacy of coccidiosis vaccines, which are made using live attenuated, inactivated, and recombinant techniques by increasing immune response. Formulations such as Quil A, QS-21, and ISCOMs have shown considerable promise in increasing vaccine efficacy while minimizing toxicity when appropriately modified. Unlike synthetic adjuvants, saponins are derived from plants and often exhibit fewer side effects, with added antioxidant and immunomodulatory benefits. However, comparative studies suggest that saponins can be as effective as conventional anticoccidials, while also reducing the risk of drug resistance. It is demonstrated that they can dramatically boost the immune response, increasing protection against illness and saponins are safer substitutes for traditional adjuvants. All things considered, the use of saponins in vaccines is an essential tactic in the prevention and control of coccidiosis, and future research should concentrate on the creation of safer and more effective adjuvants and vaccines to tackle this serious health issue.

Declaration

Availability of Data and Materials: Data and materials for this research are available upon request.

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