



Application of Nanotechnology in Enhancing the Anticoccidiosis Effect of Herbal Extracts in Poultry: A Systematic Review

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ABSTRACT

Background/Objective- Coccidiosis, a disease caused by *Eimeria* protozoa, is a major challenge in the poultry industry worldwide, causing significant economic losses annually. Long-term dependence on chemical anticoccidial drugs has led to widespread drug resistance and concerns about drug residues in poultry products. Hence, the search for safe and effective alternatives, such as plant extracts, has intensified. However, the clinical application of these extracts often faces limitations such as poor solubility, low bioavailability, and instability. This systematic review aims to investigate the superiority of nanoencapsulation technology in overcoming these obstacles and increasing the therapeutic efficacy of anticoccidial plant extracts.

Method- This study was conducted as a systematic review with a comprehensive search of electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords related to nanotechnology, plant extracts, coccidiosis, and poultry were used. Inclusion criteria were articles published in English between January 2018 and December 2024 that evaluated the effects of plant nanoformulations in *in vitro*, *in vivo*, or clinical trials on poultry. Data were extracted and analyzed according to the PRISMA protocol.

Results- Of the 557 identified articles, 18 studies met the inclusion criteria for this review. The findings conclusively demonstrated that nanoencapsulation of plant extracts (using carriers such as lipid and polymer nanoparticles and nanoemulsions) significantly increased solubility, improved stability, controlled release, and ultimately increased bioavailability and therapeutic potency of these compounds. Compared to traditional forms of extracts, nanoformulations showed a significant reduction in the number of excreted oocysts, improved growth indices, and reduced intestinal lesions in infected chickens. These formulations also had comparable or even superior efficacy to conventional chemical drugs at lower doses.

Conclusion- Nanoformulations appear to be a promising strategy to enhance the therapeutic efficacy of anticoccidial plant extracts. This technology has great potential to provide a potent and natural alternative to chemical drugs that can help reduce drug resistance and safety concerns. However, further toxicological research, pharmacokinetic studies, and the development of cost-effective methods for industrial-scale production are necessary to enable the widespread application of these nanocarriers in the poultry industry.

Keywords: nanoencapsulation, plant extracts, poultry, coccidiosis, alternative therapy



1. INTRODUCTION

Coccidiosis is widely acknowledged as one of the protozoan illnesses that causes the greatest damage and incurs the highest costs in the chicken business all over the globe [1, 2]. Coccidiosis is brought on by parasite protozoa belonging to the genus *Eimeria* [3]. These protozoa infiltrate the epithelial cells of the digestive tract, causing severe tissue destruction, nutritional malabsorption, bloody diarrhea, and finally a reduction in growth, a decrease in egg production, and a high death rate [4]. The yearly economic losses resulting from this illness amount to billions of dollars [5]. These losses include expenditures associated with treatment and prevention, decreased performance, and higher death rates in flocks. Efficiently controlling coccidiosis is crucial to guarantee the well-being of animals and the financial viability of the poultry business [6].

Vaccination and the extensive and preventative use of chemical anticoccidials have been the primary means by which coccidiosis has been managed for many decades [7, 8]. Vaccination has also played a supplementary role. Even though these chemical medications were originally quite successful, their persistent and often indiscriminate use has resulted in the development and fast spread of parasite strains that are resistant to the most prevalent drugs. As a result of drug resistance, which has produced a progressive reduction in the efficiency of these drugs and, as a consequence, raised worries over the return of large losses caused by the coccidiosis, a significant challenge has been created [9]. At the same time, there is a growing concern over the presence of drug residues in chicken products (meat and eggs), as well as the potential health risks these residues pose to consumers and the environmental contamination they may cause [10].

Researchers in the sector have been motivated to seek alternatives that are not only safe but also sustainable and effective, given the significant constraints associated with chemical medications. In the meantime, the use of plant chemicals and natural products has garnered a lot of interest as a potentially valuable option. Numerous medicinal plants include a wide variety of bioactive substances, such as alkaloids, flavonoids, terpenoids, and tannins [11-13]. These compounds have been shown to possess anti-inflammatory, antioxidant, immunomodulatory, and anticoccidial properties, in particular [14-17]. It is common for these naturally occurring chemicals to possess numerous modes of action, which may considerably lessen the possibility of parasite resistance.

The practical and broad use of plant extracts is significantly hindered by severe technological difficulties, despite their great potential. A significant number of these active chemicals are plagued by several important issues, including their very low solubility in water, their low chemical stability to environmental conditions (such as light, temperature, and pH), their poor absorption from the gastrointestinal system, and their insufficient bioavailability [18]. Because of these constraints, it is sometimes necessary to provide greater dosages to obtain the intended therapeutic effect. This would not be feasible from a financial standpoint and might occasionally result in unfavorable side effects.

Significant advancements in nanotechnology have been made in recent years [19], which have resulted in the development of innovative new solutions to tackle these issues [20-22]. The process of encapsulating active substances inside nanoscale carriers, such as lipid nanoparticles, polymer nanoparticles, nanoemulsions, and liposomes, is referred to as nanoencapsulation technology [23] (Figure 1).

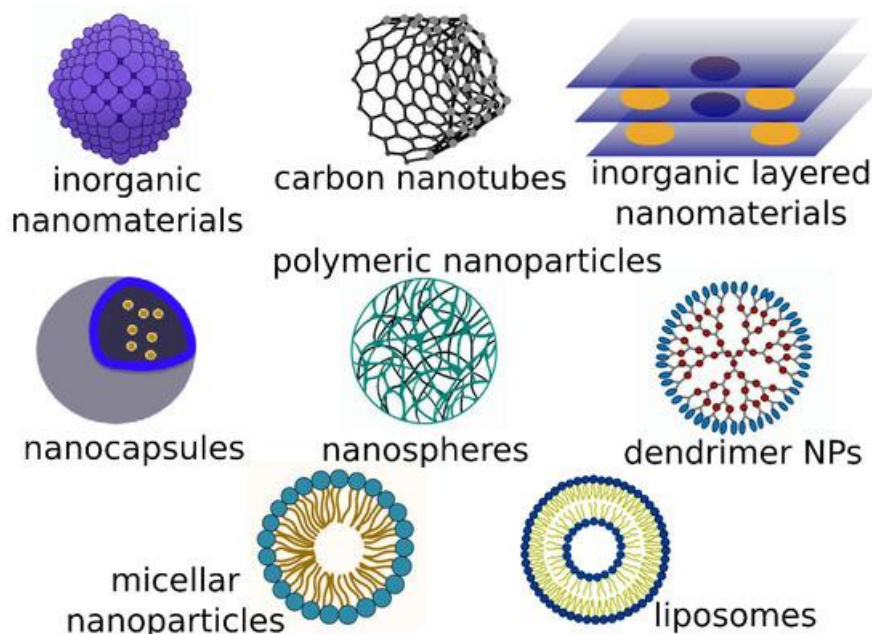


Figure 1. Types of nanoparticles used in veterinary medicine and livestock husbandry [24].

These nanoscale carriers have the potential to significantly improve the solubility and stability of herbal compounds, shield them from degradation in the gastrointestinal tract, and enable controlled and targeted release [25-27]. This could ultimately result in significant enhancements to the absorption, bioavailability, and therapeutic efficacy of these compounds (Figure 2).

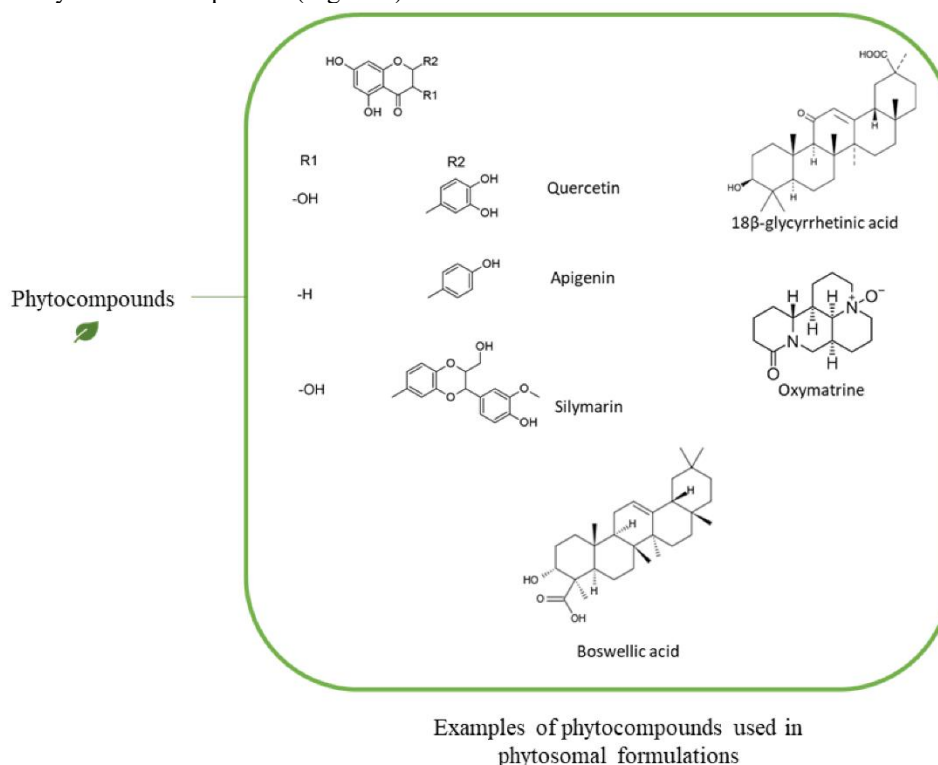


Figure 2. Scheme demonstrating examples of phytochemicals incorporated into a phytosomal delivery system [28].



The primary purpose of this systematic review is to gather, evaluate, and critically synthesize the existing scientific information on the effectiveness of nanoencapsulated formulations of herbal extracts in the treatment and management of chicken coccidiosis. This review will be conducted to accomplish this objective. The purpose of this research is to particularly investigate the benefits of these nanoformulations in comparison to conventional and unformulated versions of the same extracts. These advantages are examined in terms of efficacy metrics, safety, and probable mechanisms of effectiveness. In conclusion, this study will present a summary of the most recent discoveries, highlight any gaps in knowledge, and provide future views for the development of effective treatments based on nanotechnology and natural elements that are effective against coccidiosis.

2. METHODS AND MATERIALS

This study was conducted as a systematic review and based on the Preferred Reporting Items for Reporting Systematic Reviews and Meta-Analyses (PRISMA) protocol. This method aimed to comprehensively identify, transparently select, and critically appraise all relevant studies available within a specified time period to reach a valid and objective conclusion on the effectiveness of nanoformulated plant extracts in the treatment of poultry coccidiosis. The search period was set from January 2018 to December 2024 to take advantage of the latest scientific findings and new developments in the field of nanotechnology, so that studies that are about to be published could be covered as well.

To identify relevant studies, a systematic electronic search was conducted in international scientific databases, including Scopus, Web of Science Core Collection, PubMed/MEDLINE, Google Scholar, as well as specialized databases CAB Abstracts and ScienceDirect. The search strategy was designed using a combination of primary keywords and Medical Subject Headings (MeSH) terms and Boolean operators (AND, OR, NOT). The key keywords used included the following: ("poultry" OR "chicken" OR "broiler") AND ("coccidiosis" OR "Eimeria") AND ("herbal extract" OR "phytogenic" OR "medicinal plant") AND ("nano" OR "nanoencapsulation" OR "nanoparticle" OR "nanoemulsion") AND ("efficacy" OR "treatment" OR "antioxidant" OR "oocyst shedding"). The search was initially conducted without language restrictions, but ultimately, only studies in English published in peer-reviewed journals were reviewed.

After retrieving the studies, all records were transferred to EndNote software, and duplicates were removed. The screening process was performed in two stages: title-abstract and then full text by two reviewers independently based on predefined criteria (PICOS). Inclusion criteria included: (1) in vivo or in vitro studies on poultry; (2) investigating the effect of nanoformulation of one or more plant extracts; (3) measuring at least one indicator related to coccidiosis (e.g., oocyst count, feed conversion ratio, intestinal waste); and (4) publication in the between January 2018 and December 2024. The methodological quality of eligible studies was assessed using standard risk of bias assessment tools (e.g., SYRCLE tool for animal studies). Finally, data on study characteristics, interventions, and outcomes were extracted in a structured manner and analyzed using narrative synthesis.

3. RESULTS

From a total of 557 initial studies identified through database searches, and after removing duplicate articles and applying screening criteria based on title and abstract, 18 studies that fully met the inclusion criteria for this systematic review were selected [29-46]. These studies were conducted as in vitro or in vivo trials on poultry using experimental coccidiosis induction models by different *Eimeria* species. The primary focus of all these studies was to compare the effects of nanoformulated plant extracts (in the form of polymer nanoparticles, lipid nanoparticles, nanoemulsions, and cellulose nanoparticles) with control groups (including untreated infected groups, groups receiving conventional plant extracts, and groups receiving chemical anticoccidial drugs).

One of the most striking and consistent findings of this review was the significant superiority of nanoformulations in reducing the number of excreted oocysts (OPG) compared to traditional forms of extracts. Treatment groups receiving nanoformulated extracts showed a statistically significant ($p < 0.05$) reduction in fecal oocyst counts, which in many cases was comparable to or even superior to the efficacy of conventional chemical drugs. Proposed mechanisms for this stronger efficacy include protection of the active plant



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compounds from degradation in the acidic environment of the stomach, increased permeability through the intestinal wall due to their nanometric size, thereby increasing bioavailability, and the creation of a controlled and gradual release of the drug at the site of infection (the intestine), leading to a more prolonged and more effective exposure of the parasite to therapeutic concentrations of the active compound.

In addition to the oocyst reduction index, the significant positive effect of plant nanoformulations on improving performance and growth indices of infected poultry was another key result of this analysis. Chickens treated with nanoextracts showed significantly higher body weight gain (BWG) and lower feed conversion ratio (FCR) compared to the groups receiving conventional extract and the untreated infected group. This performance improvement was directly related to the reduction in the severity of the infection and, consequently, the maintenance of intestinal tissue integrity, better nutrient absorption, and allocation of metabolic resources instead of fighting the disease. Interestingly, in several studies, these performance indices in the groups treated with nanoformulations also came very close to the levels of the healthy uninfected groups (negative control).

In addition, the assessment of intestinal lesions as a key pathological indicator clearly confirmed the superiority of the nanotreated groups. The intestinal lesion scoring system (from 0 to 4) showed that the mean lesion score in the groups receiving nanoextracts was significantly lower than in the conventional extract groups. Histological (histopathological) examinations also showed better repair of intestinal villi, reduced infiltration of inflammatory cells, and preservation of the normal structure of the epithelium in these groups. These findings suggest that nanoformulation not only increases direct antiparasitic efficacy but also indirectly leads to reduced tissue damage and accelerated intestinal repair by reducing the parasite load.

Finally, the results regarding the enhancement of humoral and cellular immunity indices were also very promising. Higher levels of specific antibodies against *Eimeria*, as well as increased T-cell and macrophage activity, were reported in the groups treated with nanoformulations. This suggests that increasing the bioavailability of plant compounds can enhance host immune responses and provide synergistic protection against coccidiosis challenges in addition to direct antiparasitic effects (Table 1).

Table 1. The current study's most important findings are summarized in Table 1.

Outcome Measure	Result with Nanoformulations vs. Conventional Extracts
Oocyst Reduction (OPG)	Significantly greater reduction ($p < 0.05$), comparable to or superior to chemical drugs.
Body Weight Gain (BWG)	Significantly higher.
Feed Conversion Ratio (FCR)	Significantly lower.
Intestinal Lesion Score	Significantly lower (0-4 scale).
Gut Histopathology	Improved villi repair, reduced inflammation, and enhanced epithelium.
Immune Response	Higher antibody levels & increased cellular immunity.

4. DISCUSSION

The results of this comprehensive research make it abundantly evident that the nanoformulation of plant extracts is a transformational method for the control of coccidiosis in chickens. The superiority of nanoformulations in improving therapeutic parameters, such as the significant reduction of oocyst excretion and the improvement of growth indices, as well as the repair of intestinal lesions, indicates that this technology has been successful in overcoming the inherent limitations of crude extracts, which include poor solubility, insufficient stability, and low bioavailability. Nanocarriers are primarily responsible for these enhancements because of their capacity to shield the active compounds from degradation by the digestive system, to increase the permeability of the intestinal mucosa, and to permit regulated and targeted medication release at the site of infection [47]. In addition, the findings indicate that nanoformulation not only increases the direct antiparasitic action but also indirectly maintains the integrity of the digestive tract, boosts the absorption of nutrients, and strengthens the immune system of the host by lowering the parasite load. The combination of so many different actions results in a powerful synergistic response, which eventually results in a large improvement in the therapeutic effectiveness [48].



Although further research is required to fully understand the processes that underlie the effectiveness of nanoformulations, the data that is now available show that nanoparticles may exert their effects by directly interacting with the parasite, so interrupting its life cycle and increasing the innate and adaptive immune responses of the host [49, 50]. Nanoparticles, for instance, can pass through the membranes of *Eimeria* cells, hence causing mitochondrial activity to be disrupted or causing oxidative stress in the parasite [51, 52]. On the other hand, the slow release of active plant chemicals in the stomach might make it possible for the parasite to be exposed to therapeutic concentrations for a more extended period of time and with greater effectiveness [53]. This would reduce the likelihood of the parasite developing resistance to the medicine, in contrast to the standard chemical drugs. Furthermore, some nanocarriers are adjuvants in and of themselves, and they can boost cellular and humoral immune responses, which in turn assist the host in mounting a more robust protective response.

Furthermore, although the findings of this analysis are very encouraging, several obstacles must be overcome before this technology can be commercialized and used on a broader scale. To begin, the cost of generating nanoformulations on a laboratory scale is far greater than the cost of making traditional extracts or chemical medications [54]. Furthermore, to make the production method economically feasible for the poultry industry, further investment and innovation are required. Secondly, even though the studies that are now available have not indicated any substantial acute toxicity, it is still essential to conduct a comprehensive evaluation of the possible chronic toxicity and environmental impacts [55-59]. Several problems require thorough addressing, including the fate of nanoparticles in the bird, their accumulation in tissues, and the potential impact they may have on the microbiota of the brain and digestive tract. Additionally, the formulation of clear standards for the certification of nanoproducts in feed additives, the standardization of manufacturing procedures, and the guarantee of particle stability and consistency between batches are all additional challenges [60].

Although there are obstacles to overcome, it seems that the future of study in this field is quite promising. The creation of intelligent and sensitive nanocarriers should be a priority for the future. These nanocarriers should be able to release medications in response to particular stimuli, such as the pH of the digestive tract or the enzymes produced by parasites [61]. This would further boost the effectiveness of the treatment while simultaneously reducing the necessary amount. In addition, investigating novel herbal compounds with higher potential for anticoccidial activity and greater compatibility with nanotechnology may offer new avenues of opportunity. In addition, more studies should focus on analyzing the synergistic benefits of combining different herbal extracts in a single nanoformulation (also known as cocktail nanoformulations) to generate more comprehensive and multitargeted results [62]. In addition, in-depth pharmacokinetic studies are important for comprehending the behavior of nanoparticles inside the body of the bird, and ecotoxicological research is necessary for determining the influence that the excretion of nanoparticles has on the environment.

5. CONCLUSION

In conclusion, this systematic review confirms that nanoformulation of plant extracts has great potential to revolutionize the management of coccidiosis. This technology can not only reduce the dependence on chemical drugs and solve the problem of drug resistance, but also contribute significantly to flock health, food safety, and consumer health by providing a natural and sustainable solution. However, the transition from laboratory research to industrial practice requires close collaboration between researchers, pharmaceutical companies, feed manufacturers, and regulatory bodies. By focusing on overcoming technical, economic, and safety challenges, plant nano-extracts can become a powerful and common tool in the arsenal of coccidiosis control.

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Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for writing a review paper were followed.

Author contribution

Conceptualization: [Negar Ababaf Shoushtari], ...; Methodology: [Negar Ababaf Shoushtari], ...; Formal analysis and investigation: [Negar Ababaf Shoushtari], ...; Writing - original draft preparation: [Negar Ababaf Shoushtari]; Writing - review and editing: [Negar Ababaf Shoushtari], ...; Funding acquisition: [Self-funding], ...; Supervision: [Negar Ababaf Shoushtari].

Consent to participate

Not applicable

Consent for publication

Not applicable

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Declaration of the use of generative AI

This paper was composed without the use of any artificial intelligence tools for any aspect of its creation. All tasks, including research, ideation, drafting, writing, citation, and editing, were performed solely by the author using traditional academic methods and critical thinking.

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