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Review Article

A Review of the Control of Coccidiosis in Poultry Using Natural Additives, Focusing on Gut Health and Immunity

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Coccidiosis is one of the most common diseases in the poultry industry worldwide (especially in broilers aged 3–6 weeks), causing significant economic losses to poultry farmers and governments every year. Conventional methods (anticoccidial chemical compounds) for the coccidiosis debarment and control always present challenges and disadvantages, such as anticoccidial drug resistance. Herbal secondary metabolites and herbal essential oils, also known as phytogenics, are biologically active ingredients that have recently received attention as feed additives in poultry production. Plant compounds are able to stimulate the production of digestive enzymes, leading to more efficient breakdown and absorption of nutrients from the feed. In addition, they reduce the pathogen burden in poultry due to their antimicrobial and antiviral properties. Various researchers have studied the effect of herbal additives on the gastrointestinal performance and health, and their consequences on systemic health and welfare of birds, flock production efficiency, food safety, and environmental effects. A review of published studies on plant additive supplementation shows conflicting results regarding their efficacy in poultry. It can be concluded that further efforts are still needed to determine the appropriate composition and fully explain their action mechanism. The aim of this review is to investigate the control and management of coccidiosis in flocks and the effects of natural compounds on the gastrointestinal function and immunity of birds.

Keywords: broilers; coccidiosis; gut health; herbal compounds; immunity

1. Introduction

The poultry industry is under great stress from parasitic disorders known as "hidden enemies," as these agents gently lead to chronic mortality without external symptoms. It has been reported that the poultry industry spends an estimated £7.7–£13.0 billion annually in seven countries alone on the prevention, treatment, and losses caused by avian coccidiosis [1]. *Eimeria* species caused coccidiosis, a usual illness in the livestock industry that affects a large number of animals, especially poultry [2]. Coccidiosis is considered an intestinal infection created by an intracellular parasitic protozoan of the genus *Eimeria*. Gastrointestinal inflammation caused by coccidia leads to significant economic losses in poultry flocks; as a result, finding ways to reduce its prevalence is essential for researchers and breeders [3]. Poultry are affected by a variety of parasitic diseases that can cause potential chronic losses in the flock without causing overt clinical signs [1]. For instance, in the United States and China, annual costs related to coccidiosis control have been reported to exceed 127 and 73 million dollars, respectively [4]. Overall, coccidiosis alone accounts for 30% of total costs related to the pharmacological control of poultry diseases [5]. Prevention of coccidiosis is essential to boost significant growth in the poultry industry and to support the pools of financial benefit [6]. In Europe, it would not be possible to retain current levels of poultry products without an extensive anticoccidial handling program. Thus, approximately all poultry farms use antiparasitic drugs as feed additives for pullets and broiler breeders for 12–16 weeks, and for broilers for almost their entire life. This method

Table 1: The grade of pathogenicity and immunization *Eimeria* species in birds [19].

Species	Localization in the gut	Pathogenicity	Immunization	Number of life cycles to gain immunity
E. acervulina	Duodenum and jejunum	**	**	2–3
E. maxima	Duodenum, jejunum, and ileum	**	***	1
E. brunetti	Ileum and rectum	***	***	1–2
E. tenella	Cecum	****	*	3–4
E. necatrix	Jejunum and cecum	****	*	4–5
E. praecox	Duodenum and jejunum	*	***	1
E. mitis	Duodenum and jejunum	*	**	2–3

Note: *low; **moderate; ***moderate to high; ****high (pathogenic or immunogenic).

significantly comforts the preservation of the great standards of poultry health and well-being (determined by the European Union) [7].

Nowadays, due to the prevalence of intensive farming systems, it has become difficult to control coccidiosis in poultry farms. With the release and spread of infectious oocysts, the prevalence of coccidiosis in the flock increases and ultimately results in significant economic losses [8]. For this reason, researchers and breeders are always looking for new and effective methods and materials to control coccidiosis. Coccidiosis can be controlled by using anticoccidial drugs or vaccination with live vaccines. Despite the fact that these drugs have a spectrum of activity across species and are highly efficient, the number of them is limited, and antimicrobial persistence and medicine residues in eggs and meat are a significant and serious issue [9]. Moreover, the widespread use of anticoccidials also leads to environmental contamination, with residues found in environmental samples such as feces and water from poultry farms [10]. Vaccination uses live coccidia to induce immunological protection. A strong and lasting immune response is induced in all vaccinated *Eimeria* strains. However, to induce sufficient protective immunity, the coccidia must be repeatedly propagated. This method can lead to gut damage and negatively affect the performance of broilers [9]. As a result, researchers are always looking to evaluate the effectiveness of various alternatives such as probiotics, prebiotics, and herbal compounds [11]. Recently, many studies have been conducted on the effects of various forms of medicinal plants on the control of coccidiosis in birds, and interesting results have been obtained [12–14]. Thus, understanding how they work and how to use them correctly is crucial for their continued use. Noruzi et al. [12] reported that the use of different levels of aqueous extract of green pistachio hulls in the diet of broiler improved the birds' performance and antioxidant capacity without any negative effects on the morphology of the digestive tract. They also stated that the aqueous extract of green pistachio hull was more effective in the face of *Eimeria* challenge. The results of various studies showed that tannins present in plants penetrate the wall of coccidia oocysts, demolish their cytoplasm, and maybe disable the endogenous enzymes involved in the sporulation cycle in birds. Finally, the number of oocysts will reduce [15, 16]. Schizogony, gametogony, and sporogeny are the three stages of the life cycle of *Eimeria*. While sporogeny is considered an exogenous reproductive procedure, schizogony and gametogony are endogenous reproductive procedures. When the bird accidentally consumes infected oocysts, these oocysts first enter the gizzard (where the primary distribution of sporozoites occurs). The oocyst wall is broken due to the conditions in the gizzard (enzymatic digestion and mechanical crushing), resulting in the release of sporocysts. Notably, the site of sporocysts release is mostly in the gut, which is carried out under the influence of the enzyme trypsin. More sporozoites are then transported to the parasitic spot of each species, where they invade the cells of the digestive tract, as occurs in the development of *Eimeria necatrix* [17].

Due to the economic importance of coccidiosis and the effort to find suitable alternatives to synthetic drugs, the authors of this review have attempted to conduct a comprehensive review of the potential effects of medicinal plants on the gut health and immune status of birds affected by coccidiosis. After presenting information about the management and control of coccidiosis and subsequently the various natural compounds that help in this regard, we assessed the effects of this disease on the health of the gut and immunity of broilers, and finally, an outlook for the future use of herbal ingredients in poultry diets has been presented.

2. Types of *Eimeria* Species

Parasites of the genus *Eimeria* cause coccidiosis, a protozoan disease. Seven *Eimeria* species have been identified in poultry, 11 in sheep, 12 in cattle, and 9 in goats. The pathogenic species *E. brunetti*, *E. necatrix*, and *E. tenella* cause hemorrhagic disease, and *E. acervulina*, *E. mitis*, *E. maxima*, and *E. praecox* cause malabsorption [18]. The infectious procedure is fast (4–7 days) and is distinguished by parasite proliferation in host cells and vast injury to the gut mucosa. Each species has a particular growth location in the gut (upper, middle, lower of small intestine, rectum, and cecum). Table 1 shows the grade of pathogenicity and immunization *Eimeria* species in birds [20]. Poultry coccidia have a great ability for reproduction in the host. This results in a quick enhancement in parasite population in sensitive hosts and ultimately environment contamination [18].

3. Mode of Infection and Transmission

Coccidiosis is widely distributed among poultry farms worldwide. Intensive rearing methods have led to the production of *Eimeria* and the establishment of a favorable host–parasite relationship [21]. Three factors, including environmental and management risk elements, pathogen virulence, and host risk elements, influence the epidemiology of coccidiosis in poultry [19]. These factors are adjusted by environmental alterations that are able to significantly influence their dynamics and thus alter the disease transmission template. Birds raised on litter are at greater risk [22]. The incidence of poultry coccidiosis also depends on the *Eimeria* species and the dose of infecting oocysts. Oocytes may remain in houses from previous flocks and be transported by mechanical instruments, such as equipment, clothing, insects, and other animals, resulting in birds entering an infected house becoming rapidly infected [23]. Poor staff hygiene and contaminated feeding and drinking are important for the presence of *Eimeria* species and other illnesses in the house [23]. Parasite populations need time to reach perilous levels, so outbreaks normally occur when birds are between 3 and 8 weeks of age [19]. Young chicks are most susceptible to the infection because they have not had enough time to develop natural immunity. Nonetheless, adult chicks can also be contaminated and transmit the disease to other members of the flock through their feces [24]. The peak incidence of coccidiosis in chickens has been reported during the 41–50 days of age [25]. Transmission of the infection occurs via the fecal–oral route. In consequence, it is essential to control the moisture level of the litter and bedding. Moist litter may have a powerful ammonia odor that can cause parasites' overgrowth and flock management issues [26].

4. Clinical Symptoms

Symptoms such as diarrhea, fever, anorexia, weight loss, emaciation, and, in severe cases, death have been observed in birds infected with coccidiosis. During infection, birds become depressed, and their feathers become ruffled. Wings droop, diarrhea spreads through the flock, and birds tend to huddle together [25]. Feed and water intake are generally reduced, and birds may become emaciated and dehydrated. In laying hens, reduced egg production due to coccidiosis has been reported. It has been stated that cecal coccidiosis may cause bloody feces, and clinical symptoms are linked with tissue demolition caused by the release of mature merozoites and oocysts from the mucosal area throughout the last generations of merogony and during gametogony [20].

5. Methods of Infection Recognition

The recognition of coccidiosis is normally based on postmortem ulcers and assessment of feces for oocysts, when injury has already happened [27]. Important factors influencing the diagnosis of the disease include the seriousness of the lesions, as well as knowledge of the flock's look, incidence, daily fatality, feed consumption, growth performance, and egg production [28]. The position of the parasite in the host gut, the lesions shape and form, and the oocysts size are important factors in determining the species [29]. Some of the signs of coccidiosis require differential diagnosis, for example, when gut coccidiosis may be confused with necrotic enteritis, hemorrhagic enteritis, or other intestinal illness, or when cecum coccidiosis may be confused with histomoniasis and salmonellosis due to analogous ulcers. Contamination with *Salmonella pleuropneum* usually creates great mortality in young chickens and turkeys in the first 14–21 days of life. Chicks may perish in the hatchery directly following hatching. Contaminated birds gathered near a warm source, seem feeble, and have whitish diarrhea around the anus [18]. Postmortem assessments showed inflammation of the frontal part of the small intestine, which can be mistaken for coccidiosis. In addition, cannibalism makes the recognition of poultry coccidiosis more difficult due to the presence of blood on the cloaca. Recognition of various species based on oocyst morphology is tough and needs experience. Poultry coccidiosis is also identified by various ways, such as carpological evaluations, postmortem assessments, and molecular studies [18].

6. Prevention, Control, and Management of Coccidiosis

Among the three stages of the *Eimeria* life cycle, sporulation is critical for effective illness prohibition and control. From the time, *Eimeria* oocysts enter the digestive tract of the birds until they are excreted and reinfection occurs, sporulation is the most serious stage. Breaking the spore production flow or destroying nonsporulating oocysts before they become infected is able to decrease the coccidiosis outbreak [17]. Several factors, such as poor ventilation, high flock density, litter moisture, ineffective vaccination, antibiotic withdrawal, and a weak immune system, exacerbate the effects of *Eimeria* in birds [30]. Prevention of coccidiosis is essential for infection control. Methods used for prevention include biosecurity, flock management and monitoring, vaccination, and the use of anticoccidials in the feed [31]. The *Eimeria* oocyst walls are persistent, thus making protozoan insistent to numerous common antiseptics and permitting them to persist in the environment for long periods of time [32]. Even when using a hypochlorite solution (at a concentration of 5%–6%), which harms the outermost covering of *Eimeria*, the protozoa may survive and be able to cause infection; this abidance to environmental elements makes it hard to control and manage oocyst numbers on a commercial scale [32]. The following section briefly describes methods for controlling coccidiosis.

6.1. Vaccination. One method of preventing coccidiosis is vaccination, but it always presents challenges. For instance, it is difficult to achieve uniform dosing of flocks, and the antigenic diversity of *Eimeria* is considered a negative factor [33]. Vaccination methods included administering them via drinking water, and were then changed via spraying the vaccine onto the diet, which allowed for a more even distribution of the oocytes. It was also common to spray the vaccine into the eyes of poultry presently after hatching (before administrating the vaccination into the eggs for Marek disease). On the other hand, spores, including consumable gels that are painted to attract the poultry's attention, are a further vaccination strategy that is most common in the vaccination of breeder flocks. Recently, there have been successes in immunizing eggs and embryos by injecting *Eimeria* vaccine into the amniotic cavity of 18-day-old chick embryos [3]. The first group of vaccines used in the flock was derived from live wild-type spores in adjusted concentrations [34]. Recombinant vaccines have been studied for decades because they are very advantageous in producing vaccines without using live parasites. These vaccines are still not widely used, but recent endeavors indicate promise for futurity development [35]. The live wild-type oocysts' generative phases and virulence are unchanged, although live vaccines using early oocysts are also available [36]. Hasty vaccines are produced via choosing *Eimeria* spores that have smaller internal generative phases or have minor generative figures. Since these chosen oocysts have less fertility and smaller generative rounds, they create slighter injury to the host within contamination, allowing the immune response to improve [37]. However, vaccine production is a challenging process because it depends on the development of early *Eimeria* oocysts (a costly process) [35].

6.2. Anticoccidial Drugs. Anticoccidial drugs are the main compounds in the control of coccidiosis, including Amprolium, Clopidogrel, and Halofuginone, which straitly disrupt the metabolism of parasites, especially coccidian species [38]. Another class of anticoccidial medications is ionophores (Salinomycin, Maduramycin, and Sulfanilamide) that block ion transport channels and disrupt the osmotic equivalence of the parasite [38]. Nevertheless, ample use of anticoccidial drugs leads to the development of resistant strains of *Eimeria* strains [39]. Another possibility for resistance development is that inadequate doses of anticoccidial drugs used in feed can lead to resistance in birds [40]. In addition, the continuous use of such substances has resulted in toxic impacts on birds [41] and food residues that have harmful effects on human safety [42]. Factors influencing resistance to anticoccidial drugs include genetic, biological, and operational factors. For genetic factors, we can mention the diversity of populations based on their genetic structure, number of genes, and persistence alleles [38]. Biological factors are the host-parasite relationships, and operational factors include the quality of the drugs, their composition, dosage, frequency, and method of use, and the condition of the litter (which remains moist in some places and creates a substrate of sporulated oocysts for constant reinfection of animals) [43]. Approaches to decrease resistance to anticoccidial medications are of great importance. Reducing persistent reinfections by amending the husbandry status of poultry receiving anticoccidial prophylaxis or treatment will reduce the drug resistance of *Eimeria* species. Most farmers may use rotation, a mixture of anticoccidial medications, or even a rolling schedule of switching from one chemical to another within the same season to reduce resistance [38]. Over the past two decades, much effort has been made to develop new and effective strategies to the prevention and remedy of coccidiosis that are economically viable and can prevent the development of resistance.

6.3. Considering Gut Health. The reduction in flock performance and production caused by *Eimeria* is worrying, and it is capable of causing enteric diseases in susceptible birds. The most important and concerning illness related to coccidiosis is necrotic enteritis, created by *Clostridium perfringens* [44]. These bacteria are usually discovered in poultry houses, feed, and water, and are also normally present in their gut [45]. When *Eimeria* damages enterocytes, opportunistic *C. perfringens* proliferates, and necrotic enteritis develops [44]. Tissue disruption leads to serum leakage into the lumen and increased the production of mucus. This supplies more nutrients for *C. perfringens* to proliferate and exacerbate the disease [44]. Necrotic enteritis is a sample of how various agents are able to disrupt birds' health because of tension from present and peripheral infections. However, irrespective of toxic bacteria, when intestinal health conditions are poor in a herd, a decline in animal performance and enhanced stress can be expected [46].

6.4. Litter Monitoring and Management. Since all commercial birds will presumably be exposed to oocysts during their life, it is not practical to raise coccidia-free poultry. Only careful house handling and bio-safety can reduce the intensity of *Eimeria* contamination. However, this is not sufficient for complete control or prevention [34]. Additional strategies, like feed additives and vaccination, are applied to reduce coccidiosis. However, the significance of good housing handling is crucial in reducing the *Eimeria* challenge in the flock. After completing the internal stages of the life cycle, premature spores are shed in the feces and settle in the litter. High density in the flock centralizes the number of spores shed in the litter to a level that is able to overwhelm a flock, although *Eimeria* has a self-limiting life span that prevents it from destroying its host. Attentive litter management and appropriate ventilation are able to decrease moisture amounts and thus *Eimeria* spores and cycling, which in turn decreases the number of spores that the birds are exposed to in their surroundings. Great temperatures and ammonia concentrations, and reduced oxygen are the enemies of spores during the litter composting [30]. The type of litter substance, including hay, straw, wood shavings, sawdust, and rice hull, can affect microbial colonization and birds' growth and performance [47]. An unsuitable litter can allow the growth of many viruses (diseases such as avian influenza, gumboro, reovirus, laryngotracheitis, and bronchitis), bacteria (diseases such as colibacillosis and salmonellosis), fungi (diseases such as aspergillosis and mycoses), and parasites (diseases such as coccidiosis) that require a moist environment for growth and sporulation [48]. It has been found that increasing the temperature of the litter can significantly reduce its microbial load [49]. Stringfellow et al. [50] also reported that heating increased the pH of the litter, which resulted in a significant reduction in colonization of *S. typhimurium*. Chemical litter improvers have many benefits, such as reducing litter pH, preventing the conversion of nitrogen to ammonia, reducing moisture content, absorbing odors, improving the chemical composition of the litter, and inhibiting enzyme production and microbial growth [51]. Chemical and biological litter modifiers have established themselves in the poultry industry in various forms, including acidifying agents that lower the litter pH, clay-based products that absorb smells, specifically ammonia, and microbial suppressors that prevent enzyme synthesis, microbial growth, and proliferation [51]. The use of chemical litter modifiers has been more successful than other forms of modifiers, as they effectively reduce the pH and humidity content of the litter, creating undesirable situations for the survival of bacteria and viruses, as well as for the sporulation and maturation of coccidia [52]. The results of Soliman et al. [51] showed that litter modifiers had a high ability to eliminate *E. tenella* oocysts directly from the first week in litter treated with superphosphate. In addition, they reduced the number of *E. tenella* spores by stopping sporulation and reaching zero numbers in litter treated with metabisulfite. Moreover, they decreased the number of *E. tenella* oocysts without stopping sporulation and reaching zero numbers in litter treated with charcoal. The chemical improvers (superphosphate, metabisulfite, and charcoal) were able to change the abiotic status of the litter (pH and moisture) and create tough situations for *Eimeria* oocysts to complete their growth and sporulation in poultry litter. Fetterer et al. [53] reported that the use of aqueous concentrations of 300 μg/mL sodium N-methyldithiocarbamate for 24 h was able to inhibit sporulation and significantly reduce the viability of *E. tenella*, *E. acervulina*, and *E. maxima* oocysts in poultry litter. Sahoo et al. [54] also observed that treatment of litter with sodium bisulfate slightly reduced the number of *Eimeria* oocysts compared to the control group. However, these materials cannot provide solutions for inadequate ventilation, low air intake, and high bird density. Therefore, a careful management system should be established in poultry houses before using these modifiers [51].

6.5. Probiotics. One way to reduce the presence of toxic bacteria in the gut is to create a healthy intestinal microbiota by adding live microorganisms (probiotics) to the feed [55]. The application of probiotics in birds' diets is a relatively new approach, with various studies reporting improved gut health and stimulating the growth of useful microorganisms in the poultry gut [56]. Probiotics have diverse mechanisms of function to ameliorate intestinal health. One of these mechanisms is the elimination of harmful bacteria via competitive deletion [57]. In general, studies have shown that probiotics could reduce oocyst shedding (*Lactobacillusplantarum*) [58] and the severity of coccidial lesions (*Lactobacillus acidophilus*, *L. fermentum*, *L. plantarum*, and *Enterococcus faecium*) [59], as well as improved cellular and humoral immunities [59, 60] (*Pediococcus*- and *Saccharomyces*-based probiotic) and bird performance (*Lactobacillus plantarum*) [61]. It has been stated that probiotics (*Bacillus*-based direct-fed microbials) reduced clinical signs and improved immunity of broilers challenged with *E. maxima* [62]. This improvement was attributed to splenocyte generation and alterations in nitric oxide concentration of serum with the use of *Bacillus*-based probiotics. Another study showed that broiler chickens infected with *Eimeria* indicated increases in CD3+, CD4+, and CD8+ (CD: cluster of differentiation) lymphocyte numbers, body weight, and feed consumption when supplemented with *Saccharomyces cerevisiae* [63]. The study of Chalalai et al. [64] examined the individual and combined effects of probiotics (*Lactobacillus*, *Bifidobacteria*, *Enterococcus*, and *Streptococcus*) and amprolium against *Eimeria* challenge, and their results showed that the use of amprolium and probiotics is the most effective team to prevent oocyst spores. They suggested that since *Eimeria* and *Lactobacillus* share common intestinal sites, it is possible that *Lactobacillus* prevents or decreases *Eimeria* contamination via competitive exclusion and modification of the intestinal microbiota [65]. Probiotics (*Lactobacillus* and *Bifidobacterium*, *Lactobacillus casei*, *Lactobacillus paracasei*, L.*acidophilus*, *Lactobacillus salivarius*, *L. plantarum*, *Lactobacillus bulgaricus*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, and *Bifidobacterium breve*) and garlic powder protected the gut epithelium from the negative effects of coccidia [66]. In fact, the presence of a mixture of bacteria increases the diversity of the intestinal microbiota, which can produce a wide range of beneficial molecules essential for the optimal functioning of the intestinal wall [67]. Diets containing garlic and probiotics have been shown to improve intestinal parameters (such as villus height) in broiler chickens infected with coccidia [61]. Another study also showed that the use of probiotics together with phytobiotics (*B. subtilis* and *Artemisia annua Linn*. leaves, *Dichroa febrifuga Lour*. or *Punica granatum L*. bark) during *Eimeria* infection of chickens considerably decreased oocyst excretion compared to the group receiving only the plant [68].

6.6. Prebiotics. Prebiotics are usually carbohydrate-based feed additives that are indigestible and help the growth of useful microorganisms in the digestive tract and influence competitive exclusion among pathogenic bacteria [55]. In a study [69], prebiotics (trans-galactooligosaccharides) injected into birds' embryos on day 12 of incubation reduced the intensity of *Eimeria* infection. They reported that the prebiotic used reduced intestinal lesions and oocyst output. It has been reported that lactoferrin, as a prebiotic, had potent anticoccidial and anti-inflammatory activities and reduced the severity of lesions and oocyst shedding [70]. Lactoferrin was considered a potential natural anticoccidial in broilers to combat the side effects of common anticoccidial agents. Since lactoferrin had beneficial effects on the growth performance of chickens, it can be considered a natural growth promoter for them [70]. Nahed et al. [20] reported that birds fed with probiotics (*Lactobacillus acidophilus*, *L. plantarum*, *Pediococcus pentosaceus*, *Saccharomyces cerevisiae*, *Bacillus subtilis*, *B. licheniformis*) and prebiotics (beta fructan) showed reduced oocyst excretion. However, McCann et al. [71] reported that the severity of broilers contamination with a combination of *Eimeria* was not decreased when prebiotics (yeast cell wall) were administered. In addition, it has been reported that probiotics (*Lactobacillus* sp.) and prebiotics (commercially accessible fermentation product of *Aspergillus orizae*) are not effective in reducing coccidiosis and its associated outcomes compared with salinomycin and vaccination [72]. Factors such as differences in the cellular and functional components of the probiotic or prebiotic, doses, administration methods and duration of use, and inoculation doses of *Eimeria* species may explain the discrepancy between studies. In addition, bird age, feed, and farm housing and hygiene conditions should also be considered. On the other hand, probiotics and prebiotics are able to change the intestinal bacteriological pattern [20]. This change was more significant in the cecum, as these additives increased the number of lactic acid bacteria and decreased the number of coliforms and anaerobes. Several studies have shown the competitive exclusion effect of probiotics (*Bacillus subtilis*; *Lactobacillus plantarum*) [61, 73] and prebiotics (soybean oligosaccharides and soluble soybean polysaccharides) [74] in changing the intestinal microbiota of chickens contaminated with coccidia. Development of the immune system, reduction of adhesion of intestinal pathogens, stimulation of intestinal epithelial growth, and absorption of nutrients and feed energy are all influenced by the intestinal microbiota [75]. Therefore, rapid repair of the intestinal mucosa after infection would be possible through microbial recovery and maintenance of intestinal homeostasis [76].

6.7. Synbiotic. Synbiotics are synergetic compounds of probiotics and prebiotics and act as nondigestible feed substances that have a positive effect on the host by selectively stimulating intestinal bacteria. Like probiotics, synbiotics have inhibitory effects against *Eimeria* infection and are being developed as a new method for controlling coccidiosis [77]. Parveen et al. [78] stated that coccidiosis had an adverse effect on the health of broiler chickens by reducing growth performance and negatively changing blood parameters. Their study showed that coccidia-infected birds showed significant improvement in growth performance and blood parameters after synbiotic (diclacox and protexin) supplementation. They concluded that synbiotics reduced the negative effects of coccidiosis. Fructo-oligosaccharide and synbiotics (*Lactobacillus reuteri*, *Enterococcus faecium*, *Bifidobacterium animalis*, *Pediococcus acidilactici*, and a fructo-oligosaccharide prebiotic) improved body weight and feed intake in birds exposed to *Eimeria* infection [79]. It has been stated that synbiotics positively altered the intestinal environment and improved the digestion and absorption of nutrients. They also reduced parasitic infestations and increased the bioavailability of vital minerals [80]. Ogweii et al. [81] reported that the use of probiotics (*Saccharomyces cerevisiae*), prebiotics (sugar cane molasses), and synbiotics (dextrose, maltodextrin, inulin, oligofructose, fructo-oligosaccharides, *Enterococcus faecium*, *Lactobacillus casei*, *L. plantarum*, *Pedicoccus acidilactici*) in the diet of broiler chickens increased the activities of antioxidant enzymes such as glutathione peroxidase and catalase and reduced serum malondialdehyde concentrations. They suggested that these changes were indicative of the antioxidant properties of the supplements used in the diet. In the study by Ghasemi et al. [82], all groups fed synbiotic (Biomin IMBO: containing *Enterococcus faecium* and inulin) diets and infected with *Eimeria* shed significantly fewer oocysts. The synbiotic-containing groups (especially at the 1.5% diet level) showed lower lesion scores compared to the unsupplemented infected group. These results suggest that synbiotics can increase the resistance of birds to coccidiosis. Several possible mechanisms are involved. First, inulin-based probiotics are said to stimulate the growth of cecal lactic acid bacteria. Also, other intestinal lactic acid bacteria may be stimulated by inulin. These bacteria occupy the intestinal mucosal surfaces and may prevent the parasite from binding to the mucus and from penetrating the epithelial layer. Second, with the use of inulin, a large amount of undigested carbohydrates reaches the end of the digestive tract. Free fatty acids produced at the end of the digestive tract due to the action of microorganisms on these carbohydrates reduce the acidity of the cecum environment. This reduction in acidity probably reduces the growth of pathogens. Third, synbiotics can enhance the immune system in the bird by activating macrophages and lymphocytes [83–85].

6.8. Postbiotics. Postbiotics, which, like probiotics and prebiotics, are potent modulators of the intestinal microbiota, have an assistant role to anticoccidial drugs in the prevention and treatment of *Eimeria* infections [86]. Postbiotic is determined as the provision of inanimate microorganisms or their ingredients that are beneficial to the health of the host [87]. Dead microorganisms, postlysis microbial compounds, and microbial metabolites such as organic acids, tryptophan, and bacteriocins can be referred to as postbiotics [2]. Microorganism metabolites are essential for host physiological functionalities, including the arrangement of nutrients uptake, cell reproduction and differentiation, apoptosis, and immunity [88]. They are mostly derived from the bacterial species *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Faecalibacterium* [89] and have a clear chemical structure, lengthful shelf life, and benign dosage. Postbiotics have antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, cholesterol-lowering, antiproliferative, and hepatoprotective effects as well as growth-promoting, leading to improved host health [90]. It has been reported that in broilers infected with *Eimeria*, the use of a yeast product as a postbiotic enhanced nutrient utilization and expression intestinal occludin gene, while reducing intestinal interleukin-1β (IL-1β) gene expression and oocyst shedding [91]. Park et al. [86] found that in broiler chickens contaminated with *E. maxima*, indole-3-carboxylate, a yield of tryptophan metabolism, affected mucosal integrity and immune response via activation of aryl hydrocarbon receptors and nutrient transport proteins [92]. Carnosine derived from gut microbiota also improved intestinal immune responses and intestinal barrier action in broilers infected with *Eimeria*. In addition, maltol, as a candidate postbiotic growth promoter, showed direct cytotoxicity against *Eimeria* sporangia as well as positive impacts on the intestinal health, coccidiosis persistence, and growth proficiency [93]. Abd El-Ghany et al. [94] reported that the use of postbiotics (a nonviable *Lactobacillus acidophilus* species fermentation product) or probiotics (*Bacillus subtilis* and *Bacillus lischeniformis*), along with antibiotics (Amoxicillin), as well as postbiotics, significantly reduced clinical disease (necrotic enteritis), mortality, and intestinal lesion scores compared with control. It has been stated that postbiotics exert their positive effects on the performance of broiler chickens by improving immune status, growth gene expression, improving intestinal villi, reducing the limited population of *Enterobacteriaceae* and fecal pH, and increasing the population of lactic acid bacteria [95]. Humam et al. [96] found that postbiotics produced from *L. plantarum* improved performance and increased intestinal villi height, immune response, expression of some intestinal mRNA genes, and the population of beneficial bacteria in the cecum, but reduced the population of *Enterococcus* and *Escherichia coli* in broiler chickens under heat stress. Several studies have shown that postbiotics generated by *Lactobacillus* species have multiple health effects and inhibitory impacts on various intestinal pathogens such as *E. coli*, *Salmonella typhimurium*, and *Listeria monocytogenes*, and they have advised the use of postbiotics as possible substitutes to antibiotics [97–102].

6.9. Nanobiotics. Nanoparticles, which are part of the nanobiotics group, have recently been widely used in poultry diets [103, 104]. Nanoparticles have properties such as antiviral, antibacterial, antiprotozoal, antifungal, and antioxidant. It has been stated that zinc, silver, gold, and copper nanoparticles can promote animal health and growth as alternatives to antibiotics [105]. Combining metal nanoparticles with conventional drugs is a promising method to reduce pathogenicity. This approach exploits the synergistic impacts of the combined agents to improve treatment outcomes. When diverse mechanisms are applied simultaneously to eliminate parasites, the likelihood of resistance is reduced. Utilizing metal nanoparticles in combination with traditional antiparasitic medications or natural compounds are able to enhance the overall antiparasitic impact. With nanoparticles, parasite membranes or major processes are destroyed, while the added substances can be directed to specific pathways to induce resistance via an impassable barrier [105]. For example, silver nanoparticles have been used as an antibacterial additive in poultry diets and have been reported to be able to kill about 650 types of pathogens [106, 107]. In broilers, selenium nanoparticles are also highly bioavailable and harmless superseded, which enhances the absorption and distribution of substances into organs and tissues and antioxidant capability [108]. Various studies have reported the positive effects of using nanobiotics in poultry diets [109–111]. Zhang et al. [112] reported that the use of chitosan micelles conjugated with phenylboronic acid reduced intestinal damage in birds challenged with coccidiosis. Yang et al. [113] also observed a reduction in the incidence and severity of coccidiosis with the use of encapsulated cinnamaldehyde and citral. Copper nanoparticles are effective against poultry parasites such as *Ascaridia galli*. They inhibit the parasite's ability to move and absorb nutrients by interfering with the cuticle and internal tissues of the parasite. It has been found that copper and zinc have significant antimicrobial and antiparasitic activities against coccidia [114, 115]. A study by Daiba et al. [116] showed that chitosan nanoencapsulated bromelain significantly reduced the number of oocysts excreted by the animal compared to the commercial drug (diclazuril).

6.10. Antioxdants. One of the natural responses to *Eimeria* contamination is the generation of free radicals and oxidative species throughout the host's cellular immunity [117]. Despite their important role during parasitic infections, their excessive production is detrimental to the host, leading to cytotoxicity and increased tissue damage [118]. Enzymatic changes indicate the damaged antioxidant condition of birds within the *Eimeria* contamination and the development of oxidative tension after challenge. The antioxidant conditions of broilers challenged with *Eimeria* showed enhanced plasma malondialdehyde and catalase, and reduced superoxide dismutase compared with unchallenged chickens [118]. It has been shown that coccidiosis considerably reduced bird growth performance and enhanced nitric oxide concentrations [119]. Antioxidant substances have a cellular protecting function against oxidative stress. They improved the level of gut lipid peroxidation and decreased the intensity of *Eimeria* infections [120].

6.11. Organic Acids. Organic acids are normally present in livestock and plant tissues, as well as in the animal's gut, because of bacterial fermentation. These acids have the ability to inhibit bacterial growth and provide protective immunity against *Eimeria* [121]. It has been said that the use of organic acids can be considered as suitable substitutes to antibiotics, because organic acids have the ability to improve poultry performance via changing the pH of the digestive tract and its composition of the microbiome. In addition, organic acids, through changing the gut microbiome composition, protected birds from pH-sensitive pathogens and improved gut morphology and physiology, and amended the immune system [122]. Compounds such as butyric acid, acetic acid, and propionic acid are crops of microbial fermentation of undigested carbohydrates in the gut. Acetic acid also showed antimicrobial characteristics, and its positive effects on the performance and reduction of oocyte numbers in chickens infected with *E. tenella* were observed, and it was stated that its effects were comparable to amprolium, a commercial reference drug [123]. Organic acids have bacteriostatic or bactericidal impacts. This property has been attributed to the reduction of intracellular pH via the entrance of undissociated acids into the bacterial cell and the resulting degradation in the cytoplasm. Among the organic acids, butyric acid has shown a higher expression of intestinal tight junctions, thus further reducing intestinal permeability. Moreover, lactic acid bacteria (*E. coli*, *Salmonella typhimurium*, and *C. perfringens*) ferment carbohydrates and generate lactic acid, which reduces the pH of the digestive tract and the growth of pathogenic microorganisms [44]. Khukhodziinai et al. [124] observed that diets containing organic acids (benzoic acid) and oregano essential oil prevented coccidiosis by reducing oocyst shedding, increasing *Eimeria*-specific immunoglobulin Y (IgY) generation, and ameliorating immune respond and feed conversion ratio.

It has been reported that the use of organic acids significantly reduced the oocyst production rate per gram of feces and the cecal lesion score in broiler chickens of different ages, indicating that the administration of these compounds could play an important role in the control of avian coccidiosis on a large scale in poultry farms [125]. In one study [123], the use of acetic acid in drinking water resulted in protective effects against *E. tenella* by reducing the pH of the cecum and eliminating oocysts in the chickens. Acetic acid has been shown to have anticoccidial properties against *E. tenella* in broiler chickens. By reducing the pH of the cecum, oocysts are negatively affected and consequently show less severe lesions. The use of acetic and benzoic acids in the diet of broiler chickens exposed to different *Eimeria* species has been shown to reduce the severity of lesions [126]. It has been stated that acetic acid has anticoccidial properties against *E. tenella* through a decrease in cecal pH and a negative effect on oocysts, which leads to a decrease in lesion scores in broiler chickens [123]. Gao et al. [127] reported that organic acid supplementation significantly reduced lesion scores compared to the infected group without supplementation. It has been observed that organic acids inhibited nitric oxide production and reduced the expression of cytokines, including IL-6, IL-10, interferon gamma, and IL-1β, which control inflammation and maintain immune homeostasis. Organic acids regulated macrophage activity in the intestine, and macrophages activated the function of T cells and dendritic cells (which play a role in host immunity) in the intestine. T-cell-mediated immune responses reduced oocyst shedding in *Eimeria*-infected animals and mainly involved CD4+ and CD8+ lymphocytes [128]. Therefore, it can be said that organic acids exert their immunomodulatory properties through the production of host defense peptides and have no effect on inducing inflammation [129].

6.12. Herbal Compounds. The most prevalent method to rein coccidiosis in poultry is the use of chemical substances, such as ionophores and antiparasitic drugs like metronidazole. Nonetheless, the excessive use of antibiotics in animal production has been associated with the evolution of antibiotic-resistant bacteria, which can be a menace to public safety. Furthermore, antibiotic debris in poultry products has created worries across the world, leading to increased encouragement by farmers to use natural and organic substances in poultry production [130]. Plant parts and several chemicals obtained from them have been used for a long time to improve the health of humans and animals. Humans have expanded various methods and techniques to understand the characteristics of chemicals extracted from herbs, which play an important role in controlling parasites [131]. Herbs, especially pharmaceutical herbs, have been investigated as natural additives in various studies because of their antioxidant, anti-inflammatory, and immunomodulatory characteristics [132–135]. Medicinal plants are generally composed of herb derivatives such as essential oils, spices, oleoresins, and flavonoids, and other compounds that are used to amend poultry intestinal health and ultimately performance [46, 56]. More than 1200 medicinal plants have been stated to have antiprotozoal activity, some of which are used in poultry diets due to their growth-stimulating and natural immune-inducing effects [12]. Hailat et al. [136] conducted an experiment to compare the effectiveness of conventional anticoccidials and herbal additives (they used three commercial products: the first product contained saponins, flavonoids, phenolics, terpenes, carotenoids, and alkaloids. The second product contained dried herbs, plant extracts, pigment, esterified fatty acids [butyric, lauric, sorbic acid], medium chain fatty acids [capric, caprylic], calcium propionate, and essential oils, and the third product contained *Holarrhena antidysenterica* and *Allium sativum*). Their results showed that all types of additives used effectively controlled coccidiosis and could be considered as suitable alternatives to chemical anticoccidial drugs. Upadhaya et al. [137] declared that the *Eimeria*-infected birds fed with essential oils showed better performance compared to unchallenged birds. Studies showed that a mixture of essential oils (thymol, carvacrol, cinnolene, and camphor) or a mixture of eucalyptus and peppermint significantly reduced oocyst shedding and the severity of intestinal lesions [138, 139]. A study by Ghaniei et al. [140] showed that the efficacy of herbal mixtures (*Artemisia Annua*, *Quercus infectoria*, and *Allium sativum*) in decreasing oocyst excretion and lesion scores was comparable to monensin (a common coccidiosis medication). They reported that the herbal composition decreased oocyst excretion in the feces compared to the control. Tchodo et al. [141] stated that various factors, such as age, management, strain, and frequency of disease prohibition are the main factors influencing the incidence of coccidiosis. Young chicks (<32 days of age) were more sensitive to contamination compared to adults, and tangled species infection with multiplex *Eimeria* types was usual. In addition, their results showed that *Sarcocephalus latifolius* root extract reduced clinical signs, cecum lesions, and oocyst shedding. Despite the widespread use of herbal compounds in the prevention of coccidiosis, the role of other natural compounds cannot be ignored. For this reason, a brief explanation of each compound was given in the previous sections. Given the economic importance of coccidiosis in the poultry farms, the low price of herbal compounds, and their convenient availability, the authors focused on the effects of herbal compounds. Since the issues of immunity and digestive health of birds are closely related, and during coccidiosis, the immune and digestive status of birds are disturbed, we decided to investigate the role of herbal compounds on these two issues in this review and create a centralized resource for researchers who intend to conduct new studies.

7. Herbal Compounds and Gut Health During *Eimeria* Infection

A functioning and structurally normal gut is the basis for impressive digestion and absorption of nutrients and, eventually, animal growth. Villi height, crypt depth, and the ratio of villus height to crypt depth are critical factors in evaluating gut digestion and absorption in birds. It has been suggested that longer villi indicate improved gut health, which, in addition to a greater valence for nutrient absorption, generates a uniform and unified mucosa [142]. The intestine is the primitive spot where birds decompose macromolecules like carbohydrates, proteins, and fats from feed into absorbable nutrients. The existence of villi structures in the small intestine enhances the intestinal surface zone to comfort rapid absorbency of nutrients from the lumen within digestion [143]. Moreover, the physical barrier of the digestive tract, which is composed of gut epithelial cells and intercellular junctional complexes, prevents the entry of harmful materials and pathogens into the internal environment [144]. Nonetheless, the intestinal epithelium is a location of evolution and multiplication of *Eimeria* species.

In addition, birds infected with *Eimeria* indicated intestinal epithelial cells shedding, postponed villous growth, and crypts demolition [145]. The incidence of this phenomenon is closely associated with the arrangement of host cell apoptosis by *Eimeria* species. It has been shown that *Eimeria* species prevent apoptosis of intestinal epithelial cells at the primary steps to elude host immunity and, as a result, keep growing and proliferating in the cells [146]. Nonetheless, *Eimeria* species are discharged at intermediate and late phases of evolution via promoting epithelial cell apoptosis, which, in turn, forays new epithelial cells, thereby causing acute harm to the intestine [147].

A main part of the intestinal epithelium is the goblet cells. The mucins produced by these cells create a great netted polymer that coats the surface of intestinal epithelial cells and protects the mucosa from incursion by intestinal microorganisms and exogenous pathogens [148]. Nevertheless, it has been shown that in poultry infected with *Eimeria*, goblet cells and mucin production are reduced [149]. It has been reported that the use of *Radix Sophorae Flavescentis* in the diet of laying hens enhanced the number of goblet cells and mucin amount in the cecum and increased the cecal villi height to crypt depth ratio in birds infected with *Eimeria* [150]. According to the studies conducted, it can be concluded that herbal compounds can alleviate systematic and morphological intestinal harm and mitigate dysfunction caused by *Eimeria* species.

Excessive production of reactive oxygen species (ROS) disrupts the intracellular antioxidant system to eliminate free radicals and causes oxidative harm to biomolecules such as proteins or nucleic acids, ultimately causing disruption of cell function and health [151]. Antioxidants are able to mitigate damage to birds' intestinal tissues during parasite infection by decreasing the cytotoxic effects of ROS [152].

Some polyphenolic compounds, such as grape, green tea, and cinnamon, have antioxidant characteristics that help reduce oxidative damage to the gut in poultry challenged with *Eimeria* [153–155]. Therefore, it can be concluded that plants are able to reduce oxidative stress caused by *Eimeria* species in poultry via adjusting the host's antioxidant levels. In addition, some researches showed that medicinal plants, due to their antimicrobial properties, could improve the microbial population and gut health of birds by reducing the colonization of pathogenic bacteria [156].

Various studies have investigated the effects of different forms of medicinal plants on the digestive function of birds affected by coccidiosis, the most recent of which, along with the results obtained, are presented in Table 2. We tried to provide an overview of articles published since 2020.

8. Herbal Compounds and Immunity Response During *Eimeria* Infection

The immune system protects the animals from the pathogenic microorganisms by identifying antigens (such as bacteria, viruses, and parasites) in the gut and inducing humoral and cellular immunity [172]. Foreign agents contain a large number of antigens. The immune system of the gut identified these antigens during their attack on epithelial cells of the gut, ultimately triggering a series of immune responds in the host [135]. In birds challenged with *Eimeria*, the humoral immune system is activated to generate various antibodies immunoglobulins [173]. Nonetheless, since *Eimeria* species are classified as intracellular parasites, there is little possibility of them coming into direct contact with antibodies. As a result, cellular immunity is considered the main method for controlling this illness [150].

Cytokines such as interferons and ILs stimulated T helper 1 and 2 cells. In order to prevent the *Eimeria* species multiplication in gut epithelial cells, T helper 1 cells specialized in dealing with intracellular parasites and generated interferon IFN-γ [174].

Furthermore, in response to *Eimeria* infection, cytokines such as IL-1β, IL-6, IL-12, IL-15, and IL-17 are produced by T helper 1 cells [150]. In contrast, T helper 2 cells are specialized to produce cytokines such as IL-4, IL-5, and IL-13 to mount an immune response against extracellular pathogens [173]. These immune cells and the production of these immune substances play an important role in combating coccidiosis in poultry [175]. Consequently, one of the most essential strategies for the treatment and prevention of coccidiosis is to enhance the host's immune response to *Eimeria* species.

It has been stated that some herbal compounds have the ability to boost the bird's immune system and can act as natural alternatives to ameliorate the immune respond to coccidiosis [135]. Among the diverse bioactive compounds, active substances including glycoproteins, tannins, flavonoids, and polysaccharides have a special place in strengthening the host immune system [152, 153, 176]. It has been declared that herbal compounds and their bioactive substances took part in the combat against *Eimeria* in poultry via stimulating the multiplication of immune cells (natural killer cells, macrophages, CD4+ and CD8+ T cells) [177]. In addition, medicinal plants stimulated the immune cells activation (mainly T helper1 cells) to produce disparate immune cytokines to engage in the conflict with *Eimeria* [61]. For instance, oxymatrine, the effective substance of *Radix Sophorae Flavescentis*, reduced and increased the levels of T helper1 (IFN-β, TNF-α, and IL-1β) and T helper2 cytokines (IL-4 and IL-10), respectively [178].

A study by Chang et al. [179] showed that the use of garlic essential oil ameliorated the immune response of laying hens during coccidiosis by enhancing serum immunoglobulins (IgA, IgG, IgM) levels, and its effect was reported to be similar to the anticoccidial impact of diclazuril. It has also been reported that *Magnolia officinalis*, *Emblica officinalis*, arabinoxylans derived from wheat bran (*Triticum aestivum*), and *Scrophularia striata* significantly enhanced the amount of antibodies in the serum of poultry when challenged with *Eimeria* [180–183].

The study by Abbasi et al. [155] revealed improvement of broiler chickens' resistance to *Eimeria* due to the use of *Radix Sophorae Flavescentis*. They acknowledged that *Radix Sophorae Flavescentis* exerts this effect via enhancing mucin production in cecum tissue, decreasing the pro-inflammatory agents' gene expression, and increasing gene levels of the anti-inflammatory factor IL-10. A large number of plants, such as *Radix Sophorae Flavescentis*, have been found to play an important role in regulating IL-17A gene expression in the gut of poultry challenged with *Eimeria* species [184]. It has

Table 2: Effects of different herbal compounds on the gut health and status of poultry during *Eimeria* challenge.

Plants	Bioactive substances	Results	Reference
(1) *Bidens pilosa*	Polyyne and cytopiloyne	Decrease: • Generation of sporozoite • Sporozoite incursion of host cells, • Number of oocyte per gram • Expression of proinflammatory factors IL-6 and IFN-γ gene Increase: • Cecal villus height to crypt depth ratio • Expression of antioxidant enzymes (catalase and superoxide dismutase) • Expression of tight junction protein ZO-1 gene	[157]
(2) *Dichroa febrifuga*	α-Dichroine and β-dichroine	Decrease: • Number of oocyte per gram • Cecal lesions • Diarrhea	[158]
(3) *Allium sativum* (garlic)	Organosulfur compositions	Decrease: • Sporulation of oocyst • Number of oocyte per gram • Gut inflammation Increase: • Cecal mucous epithelium regeneration • Antioxidant capacity	[159]
(4) *Camellia sinensis* (green tea)	Polyphenolic compounds	Decrease: • Population of enteropathogenic strains of *coliforms* and *Clostridium perfringens* Increase: • Intestinal morphology parameters • Beneficial microflora population (lactobacilli)	[154]
(5) *Radix Sophorae Flavescentis*	Oxymatrine, matrine, and flavonoids	Decrease: • Number of oocyte per gram • Inflammation of cecal tissue Increase: • Villus height and villus height to crypt depth ratio • Mucin secretion	[150]
(6) A commercial product	Myricetin	Decrease: • Sporulation of oocyst • Number of oocyte per gram Increase: • Antioxidant and anti-inflammatory abilities in jejunum	[152]
(7) A commercial product	Thymol and carvacrol	Decrease: • Pathological scores in jejunum Increase: • Crypt depth in jejunum • Abundance of *Bacteroides caecigallinarum* in cecum	[160]
(8) *Salvadora persica*, *Zingiber officinale*, *Curcuma longa*	Polyphenolic compound	Decrease: • Oocyst production • Cecum lesion score Increase: • Cecum histopathology	[161]
(9) *Phyllanthus emblica*	Phenolic compounds, alkaloids, phytosterols, terpenoids, organic acids, amino acids, and vitamins	Decrease: • Oocyst sporulation • Oocyst infectivity, pathogenicity, and fecal excretion	[15]

Table 2: Continued.

Plants	Bioactive substances	Results	Reference
(10) Rosemary	Polyphenols	Increase: • Oocyst lysis (in vitro) Decrease: • Fecal oocyst output • Cecum coccidia oocysts • Intestinal damage • Cecum inflammation Increase: • Integrity of intestinal epithelium • Antioxidant capacity	[162]
(11) *Aloe Vera*	Vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids	Decrease: • Cecum lesion score • Oocyte shedding • Number of *Eimeria* developmental phases in the tissues • Histopathological changes Increase: • Epithelial goblet cells (intestinal mucosal barrier maintenance)	[163]
(12) *Piper betle L.*	Eugenol, 1,2,3,5,4,4a,5,6,8a-octahydro-4a,8-dimethyl-2-(1-methylethenyl)-naphthalene, decahydro-4a-methyl-1-methylene-7-(1-methylethenyl)-naphthalene, 4-allylphenyl acetate, 3-allyl-6-methoxyphenyl acetate, 4,11,11-trimethyl-8-methylene-bicyclo [7.2.0] undec-4-ene, n-heptadecane, 4-(2-propenyl)-phenol	Decrease: • Oocyst sporulation Increase: • Rate of oocyst disintegration	[164]
(13) *Olea europaea*	Maslinic acid, polyphenolic or biophenols (cynarosid/luteolin-7-O-glucoside; tyrosololeuropein quercetinisohamnetin; neobavaisoflavone 2, 3-dihydro-amentoflavone quercetin-3 Orutinosidechlorogenic acid, isorhamnetin 3-O-(6″-O-feruloyl) -glucoside), diligustilide quercetin-o-(o-galloyl)-hexoside)	Decrease: • Lesion index, • Oocyst index Increase: • Anticoccidial index	[165]
(14) Herbal powder (Shi Yin Zi): *Cnidium monnieri* (L.) Cuss, *Taraxacum mongolicum* Hand.-Mazz., and sodium chloride	Osthole, chlorogenic acid, and caffeic acid	Decrease: • Oocyst sporulation • Histopathological changes of the cecum • Mucosa cell necrocytosis Increase: • Anti-Coccidiosis index	[166]
(15) *Camellia sinensis* (green tea)	Polyphenolic compounds	Decrease: • Villus diameter Increase: • Villus height • Villus height to crypt depth ratio	[13]
(16) *Yucca schidigera*	Steroid-like saponins, polyphenols like resveratrol, and yuccaols A–E	Decrease: • Crypt depth • Number of apoptotic cells in the jejunum mucosa • Effect of challenge on apoptotic cell count in jejunum • Malondialdehyde jejunal mucosa Increase: • Activity of trypsin, lipase in jejunum • Villus height to crypt depth ratio • Total antioxidant capacity jejunal mucosa	[167]

Table 2: Continued.

Plants	Bioactive substances	Results	Reference
		• Myeloperoxidase activity in jejunum • mRNA expression of CLDN-1, NQO1, Nrf2, and OCLN in the jejunum	
(17) *Lawsonia inermis* and *Acacia nilotica*	Mucilage, mannite, gallic acid, and tannic acid. Tannins, saponins, glycosides, and flavonoids	Decrease: • Number of oocyte per gram • Histological changes of the intestine Increase: • Restoration of most structures of cecum layers	[168]
(18) A commercial mixture	Essential oils, saponins, and tannins	Decrease: • Number of oocyte per gram • Coccidial lesion scores • Crypt depth in the duodenum, jejunum, and ileum Increase: • Anticoccidial index • Villous height in the jejunum, and ileum	[169]
(19) Oregano essential oil (*Origanum vulgare* spp.) and probiotic	Thymol and carvacrol	Decrease: • Oocyst shedding • Lesion scores • Gut *C. perfringens*, *E. coli*, and Coliforms count Increase: • Gut *Lactobacillus* count • Gene expression of MUC2 and CAT-1	[170]
(20) *Trifolium pretense* L. (red clover)	Coumarins, isoflavones, phenylpropanoids, and pterocarpans	Decrease: • Sporozoites of *E.tenella* • Lesion scores • Gut *C. perfringens*, *E. coli*, and Coliforms count Increase: • Anticoccidial index • The contents of organic acids (citric acid, fumaric acid, lactic acid, and butanoic acid) • Trans-4-hydroxy-L-proline level	[171]

been proven that IL-17A is a possible remedial goal for the control of coccidiosis, which can adjust the puberty and migration of *Eimeria* schizonts [185]. It has also been observed that B. *piloza* also inhibited the development of *Eimeria* through improving T-cell-mediated immunity [113]. In addition, the use of plant compounds that have immunostimulatory characteristics (like saponins and polysaccharides) as vaccine adjuvants has also been considered to improve the vaccine's immunomodulatory [186].

Table 3 shows some studies that have investigated the effect of medicinal plants on the immune response of poultry affected by coccidiosis since 2020.

9. Perspective

Coccidiosis is a notable menace to the poultry industry due to its prevalent effect and its capability to contaminate birds irrespective of season, age, or species. The disease is mainly spread by sporulating oocysts present in the surroundings. The use of disinfectants within the empty periods of the birds' production round to destroy spores is a tactical method to inhibit the prevalence of coccidiosis. Traditional antiseptics are usually ineffectual against coccidial oocysts. Inappropriate use of antibiotics has led to medication resistance and residual problems, resulting in the prohibiting of a large number of anticoccidial medications. Thus, there is an instant requirement for novel, efficient, and secure anticoccidial approaches.

Natural feed additives with various and promising functions have been considered as suitable alternatives to antibiotics. Despite numerous studies, the exact mechanisms of the effects of herbal compounds on digestive function, the immune system, and microbiota are still not fully understood. Investigating the synergistic effects of these compounds, especially in combination with organic acids, probiotics, prebiotics, or antioxidants, could open the way to designing more effective and cost-effective experiments [199]. One of the main challenges in the use of medicinal plants is the variability of effects in different studies. This variability is often related to

Table 3: Effects of different herbal compounds on the immune response of poultry during *Eimeria* challenge.

Plants	Bioactive substances	Results	Reference
(1) *Allium sativum* (garlic)	Organosulfur compositions	Expression of NF-κB, IL- 1β, and IFN-γ genes	[135]
(2) *Radix Sophorae Flavescentis*	Oxymatrine, matrine, and flavonoids	Expression of IL-1β, IL-2, IL-4, IL-6, IL-10, and IL-17	[150]
(3) A commercial product	Myricetin	Decrease: • C-reactive protein values • Nitric oxide level • Myeloperoxidase level • Expression of CCL4, CCL20, and CXCL13 Increase: • Immunoglobulin G level • Expression of IL-1β, IL-6, and TNF-α • Expression of anti-inflammatory cytokine IL-10, AvBD6, and AvBD612 genes	[152]
(4) Rosemary	Polyphenols	Increase: • levels of immunoglobulin A	[162]
(5) *Aloe Vera*	Vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids	Decrease: • Nitric oxide level Increase: • Number of red and white blood cells • Production of IL-5	[163]
(6) *Lawsonia inermis* and *Acacia nilotica*	Mucilage, mannite, gallic acid, and tannic acid Tannins, saponins, glycosides, and flavonoids	Decrease: • IL-4 and TNF-α Increase: • IL-10	[168]
(7) Oregano essential oil (*Origanum vulgare* spp.) and probiotic	Thymol and carvacrol	Decrease: • IL-6 Increase: • Immunoglobulins A and G and IL-10	[170]
(8) *Aloe barbadensis, Tinospora cordifolia, Bambusa arundinacea, Emblica officinalis, Ferula foetida regal, Tamarindus indica*	Polyphenolic compounds, alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoids, phenolics, aliphatic compounds, polysaccharides, carotenoids, anthocyanins, phytosterols	Increase: • Antibody titer of Newcastle disease • Antibody titer of Avian influenza • Expression of immunity-related TLRs genes	[187]
(9) A commercial product (essential oil)	Eugenol (a phenolic aromatic compound)	Decrease: • Expression of the pro-inflammatory factors IL-1β and IL-6 Increase: • Expression of the cytokines IL-4 and IFN-γ	[188]
(10) Garlic essential oil	Allicin	Increase: • Immunoglobulins M, G, and A	[179]
(11) *Scrophularia striata hydroalcoholic* extract	Phenyl propanoid glycoside, flavonoids, and cinnamic acid	Decrease: • Serum IL-6 concentration Increase: • Immunoglobulins G and M • TGF-β levels in serum	[183]
(12) Chinese herbal mixture	Flavonoids	Decrease: • TNF-α • mRNA expression of IL-2 and IL-6 • mRNA expressions of IL-17A Increase: • Immunoglobulin M • IL-10 in serum • mRNA expression of IL-10 in the liver	[184]

Table 3: Continued.

Plants	Bioactive substances	Results	Reference
(13) *Magnolia officinalis*	Magnolol	Decrease: • IL-1b, IL-6, TNF-α, and IFN-g Increase: • L-4 and IL-10 • Nitric oxide • Immunoglobulins M, G	[180]
(14) *Ficus religiosa*	Phenol, 2-propyl, oxirane-undecanoic acid, and squalene	Decrease: • IL-1b, IL-6, TNF-α, and IFN-g Increase: • Lymphoblastogenic responses • Immunoglobulins total, M, G	[189]
(15) Curcumin (essential oil)	Curcumin, carvacrol, thymol, and cinnamaldehyde	Decrease: • Total leukocyte, heterophils, and lymphocytes numbers	[190]
(16) Laminarin-rich algal extract	Fucoidan, alginate, phlorotannins, and fucoxanthins	Decrease: • TCRγ/δ+CD8$\alpha\beta$ and TCRγ/δ+CD8$\alpha\alpha$ T-cells Increase: • Total population of lymphocytes and lymphocyte subpopulations	[191]
(17) Turmeric rhizomes	Curcumin	Decrease: • mRNA levels of IL-1β, TNF-α, and IL-2	[192]
(18) Neem extract	Nimbidin, sodium nimbolide, gedunin, azadirachtin, mahmoodin, epicatechin and catechin, margalone, margolonone, and isomargolonone, cyclic trisulfides, polysaccharides GIa, GIIa, GIIIa, GIb, NB-II, and peptidoglycan	Decrease: • Lymphocytes, heterophile, eosinophile, basophile, and monocyte numbers Increase: • Nitric oxide, • Lysozyme, • Phagocytic percent and phagocytic index	[193]
(19) *Rosmarinus officinalis* ethanolic extract	Carnosic acid and carnosol	Decrease: • CD4+ and CD8+ T lymphocytes protein expression • IFN-γ, IL-1β, and IL-6 mRNA expression	[194]
(20) Garlic essential oil	Allicin	Increase: • The thymus index • Immunoglobulins M and G	[195]
(21) *Artemisia brevifolia* extract	Flavonoids, terpenoids, and artemisinin	Increase: • Cellular immune response (PHA-P) • IgG and IgM levels	[196]
(22) *Carica papaya* extract	Polyphenolic compounds	Increase: • Cellular immune response (PHA-P) • IgG and IgM levels	[197]
(23) *Illicium verum* essential oil	Alpha pinenes, beta-pinene, sabinene, phellandrene	Decrease: • Lesion scores, fecal scores, oocyst scores, and oocyst per gram of feces (OPG)	[198]

differences in plant origin, chemical composition, consumption level, or processing technology. Therefore, future research should emphasize the design of formulations with standardized, safe, and reproducible compounds [200]. To increase biochemical stability and more precise targeting in the avian intestine, technologies such as microencapsulation or nanocarrier systems can produce more effective herbal compounds with minimal adverse effects. These technologies have a bright future for better productivity and reduced consumption costs [201]. Progress in bioinformatics and its implementation in parasitology, together with the establishment of gene editing technology in *Eimeria*, suggest encouraging methods for in-depth analysis of the *Eimeria* sporogenesis regulating mechanisms. Recognizing of main managerial genes and development of vaccines based on sporogenesis-deficient strains are critical management for further coccidiosis vaccine evolution [192]. Furthermore, finding how *Eimeria* answer to outer environmental motives to commence sporogenesis could comfort the improvement of highly efficient and specific *Eimeria* sporogenesis suppressors. This science could lead to the development of new products that considerably ameliorate the control and management of coccidiosis.

10. Conclusions

Coccidiosis infection remains one of the major challenges in the poultry industry, which, in addition to reducing productivity and causing economic losses, provides a suitable environment for the occurrence of secondary infections and digestive disorders. Global restrictions on the use of antibiotics and chemical anticoccidial drugs have highlighted the need for alternative nutritional approaches. A review of the available evidence showed that plant compounds, with a wide range of bioactive metabolites such as polyphenols, flavonoids, alkaloids, saponins, and volatile essential oils, are able to exert significant protective effects against coccidiosis-induced damage through multiple mechanisms, including improving the integrity of the intestinal barrier, modulating the innate and adaptive immune response, and regulating the microbial population. These effects, whether directly on the parasite or indirectly through improving the physiological status of the host, indicate the high potential of these compounds for use in coccidiosis management programs. However, the heterogeneity of results across studies, differences in the origin and chemical composition of plants, dosage, extraction methods, and farming conditions, suggest that the successful application of these additives requires careful standardization, the use of modern processing and release technologies, and comprehensive evaluation under real-world farm conditions. Also, intelligently combining herbal compounds with other natural additives such as probiotics, prebiotics, and organic acids can lead to synergistic effects and increased stability of immune and digestive responses. Finally, given the growing global demand for antibiotic-free meat and eggs, and the need to respond to consumer concerns and international regulations, botanicals as a key part of sustainable nutritional strategies offer a bright future in controlling coccidiosis and improving the health and productivity of poultry flocks. Success in this direction will depend on continued interdisciplinary research, investment in the development of standardized products, and close collaboration between researchers, industry, and policymakers.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Disclosure

All authors approved the submitted version.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, original draft: Fatemeh Aziz-Aliabadi and Hadi Noruzi. Source collection, writing – review and editing: Fatemeh Aziz-Aliabadi, Hadi Noruzi, and Zeyad Kamal Imari. All authors collected the relevant published articles from highly indexed journals, wrote the full review manuscript.

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