

Phytochemical control of poultry coccidiosis: a review

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ABSTRACT Avian coccidiosis is a major parasitic disorder in chickens resulting from the intracellular apicomplexan protozoa *Eimeria* that target the intestinal tract leading to a devastating disease. *Eimeria* life cycle is complex and consists of intra- and extracellular stages inducing a potent inflammatory response that results in tissue damage associated with oxidative stress and lipid peroxidation, diarrheal hemorrhage, poor growth, increased susceptibility to other disease agents, and in severe cases, mortality. Various anticoccidial drugs and vaccines have been used to prevent and control this disorder; however, many drawbacks have been reported. Drug residues concerning the consumers have directed research toward natural, safe, and effective alternative compounds. Phytochemical/herbal medicine is one of these natural alternatives to anticoccidial drugs, which is considered an attractive way to combat coccidiosis in

compliance with the “anticoccidial chemical-free” regulations. The anticoccidial properties of several natural herbal products (or their extracts) have been reported. The effect of herbal additives on avian coccidiosis is based on diminishing the oocyst output through inhibition or impairment of the invasion, replication, and development of *Eimeria* species in the gut tissues of chickens; lowering oocyst counts due to the presence of phenolic compounds in herbal extracts which reacts with cytoplasmic membranes causing coccidial cell death; ameliorating the degree of intestinal lipid peroxidation; facilitating the repair of epithelial injuries; and decreasing the intestinal permeability induced by *Eimeria* species through the upregulation of epithelial turnover. This current review highlights the anticoccidial activity of several herbal products, and their other beneficial effects.

Key words: chicken, coccidiosis, control, *Eimeria*, herbs

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INTRODUCTION

The poultry industry is under tremendous pressure due to parasitic disorders named “hidden enemies” as

they gradually results in chronic losses without external symptoms. Annually, the poultry industry spends about £7.7 to £13.0 billion (at 2016 prices) in only seven countries on prophylaxis, treatment, and production losses due to avian coccidiosis (Blake et al., 2020). These losses are caused by seven *Eimeria* spp. The species grow in specific locations within the broiler digestive system (Blake et al., 2020).

Many factors facilitates the development of coccidiosis, including a direct life cycle, fecal-oral transmission,

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presence of resistant oocysts, absence of cross-protection between *Eimeria* species, high oocyst reproductive potential, high stocking density, and suitable environmental conditions for infectivity (sporulation). The most significant problem is the subclinical coccidiosis representing nearly three-quarters of the total economic costs. This is characterized by suboptimal flock performance due to increased feed intake and reduced body weight gain (BWG) (Remmal et al., 2011).

Several chemicals and ionophore anticoccidial feed additives have been used widely since 1939 to fight these parasites which are potentially dangerous for poultry (Nogueira et al., 2009). However, drug resistance has emerged (Abbas et al., 2011), and there are hazardous effects for consumers through drug residues in poultry products. Fortunately, the long-lasting and robust immunity produced by infections with *Eimeria* makes vaccination an effective alternative to anticoccidial drugs for control (Allen et al., 2005; Chapman et al., 2005). However, these vaccines can trigger severe hemorrhagic reactions or malabsorptive coccidiosis where poor management affects flocks' performance and uniformity (Chapman et al., 2002; Shirley et al., 2005).

Microbial infections negatively affect the production of poultry as they occupy the digestive system and have adverse effects on the final body weight, gut health, and meat quality of broiler (Abd El-Hack et al., 2021a; Swelum et al., 2021; Yaqoob et al., 2021). Therefore, antibiotics effectively suppressed and inhibited bacteria until the emergence of antibiotic-resistant bacteria (Alagawany et al., 2021a,b; Reda et al., 2021). The tendency to use phytochemical compounds solves this problem, such as phenolic compounds in herbal extracts (Abou-Kassem et al., 2021; El-Saadony et al., 2021a; Saad et al., 2021a,b). In addition, peptides and essential oils also act as a powerful antimicrobial agent against Gram negative and/or Gram positive bacteria (El-Saadony et al., 2020, 2021b,c; Saad et al., 2020, 2021c; El-Tarabily et al., 2021). The antimicrobial mechanism of these compounds is represented in their electrostatic interaction with specific compounds in the bacterial cell wall, which disrupted and allowed the additives' entry and changes the behavior of DNA in the bacterial cell causing cell death (Abd El-Hack et al., 2021b,c,d).

Recently there is an international interest in using herbal products as safe alternatives to control various diseases with a lower risk of resistance development (Abd El-Hack et al., 2020a,b; Abdelnour et al., 2020; Ashour et al., 2020). Over 1200 plants had been reported to have antiprotozoal activity (Willcox and Bodker, 2004; Muthamilselvan et al., 2016). Some of these herbal remedies are used in poultry diets due to their growth-promoting and natural immuno-stimulating effects.

This review discusses the etiology, factors affecting the clinical outcomes of poultry coccidiosis as well as the up-to-date known different types of herbal medicine of coccidiosis, and highlights their beneficial effects to pay much more attention for their use in the poultry industry.

ETIOLOGY OF POULTRY COCCIDIOSIS

Poultry coccidiosis affects all domestic and wild bird species and is caused by the protozoan *Eimeria* (phylum Apicomplexa). The protozoa replicates with a 4 to 6-d fecal-oral life cycle depending on species (Figure 1). Their replication includes both asexual (merogony or schizogony) and sexual (gametogenic) stages inside the host's intestinal cells, during which high numbers of oocysts are produced. The oocysts are then excreted with feces, sporulate in the environment, and become infective. Inside each oocyst are four sporocysts, each including 2 sporozoites (Shirley et al., 2005).

Seven *Eimeria* species are the most precious parasites infecting ~60 billion chickens annually worldwide; *E. acervulina*, *E. maxima*, *E. brunette*, *E. praecox*, *E. mitis*, *E. tenella*, and *E. necatrix*, each with variable pathogenicity (Shirley et al., 2005) (Table 1).

Concurrent infection with at least six species is widespread in a single flock causing independent, distinct, and recognizable diseases leading to the subclinical enteric infection to sub-acute mortality (McDougald, 2003).

FACTORS AFFECTING THE OUTCOME OF COCCIDIOSIS INFECTION

Factors affecting the outcome of coccidiosis infection are discussed below and illustrated in Figure 2.

Effect of Age on the Outcome of Infection

Many studies reported that infection prevalence increased among the younger chicks (McDougald, 2003), while older chickens were relatively resistant to infection (Lillehoj, 1998). Gardiner (1955) demonstrated that chicks at 4-wk old are more susceptible to cecal coccidiosis, while at 2-wk old, they are more resistant than at any other time during the first 6 wk, which may be due to the difference in inherent resistance of the host, or variations in the virulence of the inocula used.

Most *Eimeria* species affects birds between 3 and 18 wk age; however, higher mortality rates appeared obviously in young chicks (Razmi and Kalideri, 2000; Al-Natour et al., 2002). The incidence of caecal coccidiosis in White Leghorn chickens was found to be 69% in chickens <45-d old and 29.58% >20-wk old. Bachaya et al. (2012) showed a high infection rate among younger chicks (60%) compared to older chickens (37%). Ola-Fadunsin (2017) reported a 52.7% of young birds and 21.1% of adult (sexually mature) birds were positive for coccidiosis. Subclinical coccidiosis was more frequently found >4 to 5 wk in broilers (Razmi and Kalideri, 2000).

Genetic Background of the Host

The chickens' genetic background influences the development of the parasites, affects BWG and the severity of lesions and is potentially correlated with immunity to infection (Clare et al., 1985). For instance, the susceptibility to

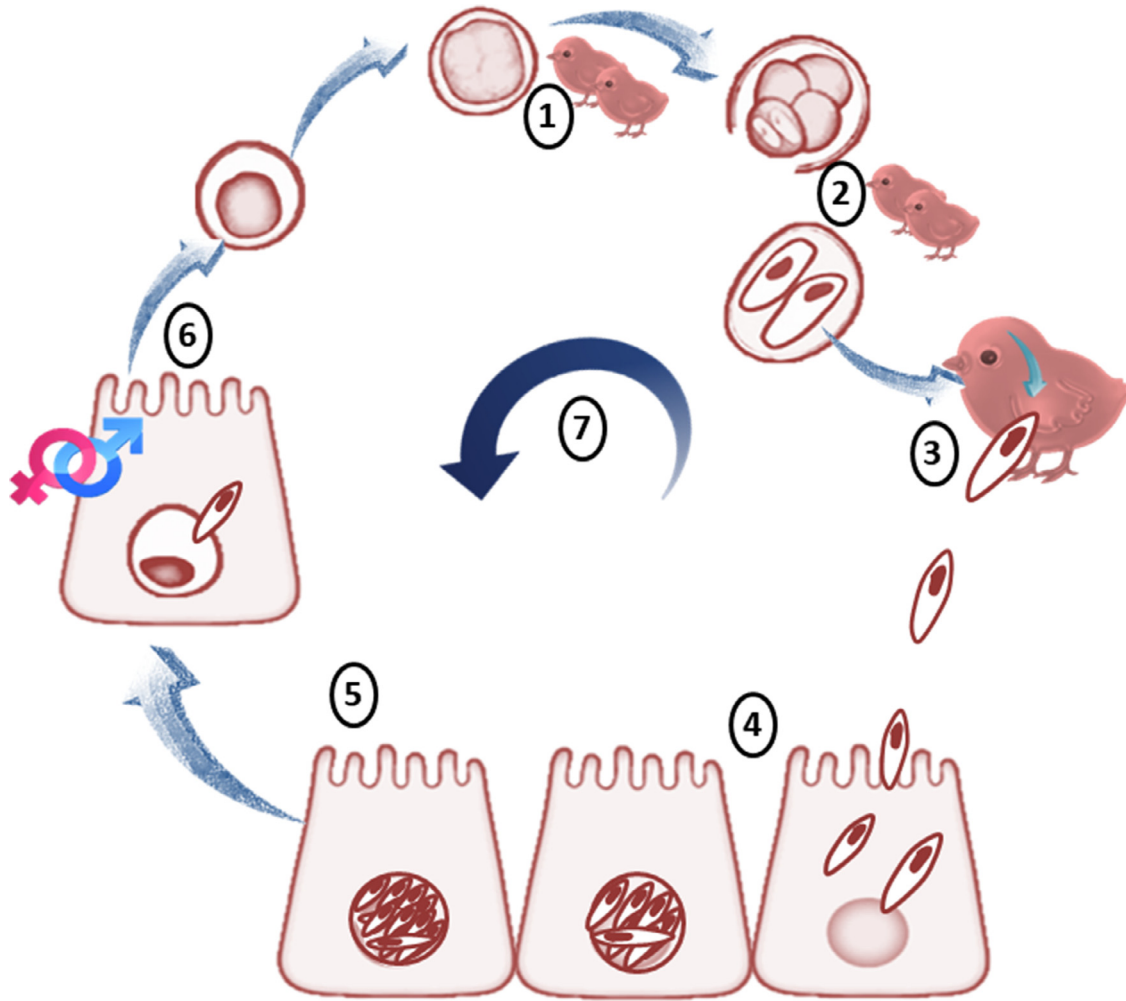


Figure 1. *Eimeria* life cycle. Birds get infected by fecal matter, and the protozoan reproduction occurs in the intestinal cells, resulting in damage to the intestinal wall.

coccidiosis was observed frequently in layers more than in broilers (Williams and Catchpole, 2000). Lillehoj et al., (1986) showed that different lines of chickens displayed a different susceptibility to the same *Eimeria* infections as shown by oocyst production, lesion score, and clinical signs.

Inbred lines of chickens (such as White Leghorn) have a high resistance to infection to specific *Eimeria* species but showed lower infection resistance with other species (Bumstead and Millard, 1992). Lee et al. (2016) compared the resistance of congenic Fayoumi lines to *E. tenella* infestation and additionally they evaluated the genetic differences regarding *Eimeria* egression. Chickens were inoculated orally with 5×10^4 *E. tenella* sporulated oocysts then challenged on the 10th d with 5×10^6

oocysts. The Fayoumi M5.1 line had higher BW gain, lower oocyst shedding, and a higher ratio of B and CD4 (+)/CD8 (+) T cells than the M15.2 chickens. These results suggest that the M5.1 line is least susceptible to *E. tenella* infection than the M15.2 line.

Additionally, the percentage of sporozoite released from peripheral blood mononuclear cells (PBMCs) in the M5.1 line was higher. This suggests that promoted resistance of Fayoumi M5.1 to *E. tenella* infestation may involve an adaptive immunity resulting in reduced intracellular progress of *Eimeria* spp. (Lee et al., 2016).

The schematic process of immune response of chickens to herbal anticoccidian compounds is presented in Figure 3.

Table 1. The degree of pathogenicity and immunization of avian *Eimeria* species.

Species	Localization in the intestine	Pathogenicity*	Immunization**	No. of exposure (life cycles) to achieve immunity
<i>E. acervulina</i>	Duodenum, jejunum	++	++	2-3
<i>E. maxima</i>	Duodenum, jejunum, ileum	++	+++	1
<i>E. brunetti</i>	Ileum, rectum	+++	+++	1-2
<i>E. tenella</i>	Caeca	++++	+	3-4
<i>E. necatrix</i>	Jejunum, caeca	++++	+	4-5
<i>E. praecox</i>	Duodenum, jejunum	+	+++	1
<i>E. mitis</i>	Duodenum, jejunum	+	++	2-3

* + low pathogenic; ++ moderately pathogenic; +++ moderately to highly pathogenic; ++++ highly pathogenic.

** + low immunogenic; ++ moderately immunogenic; +++ highly immunogenic.

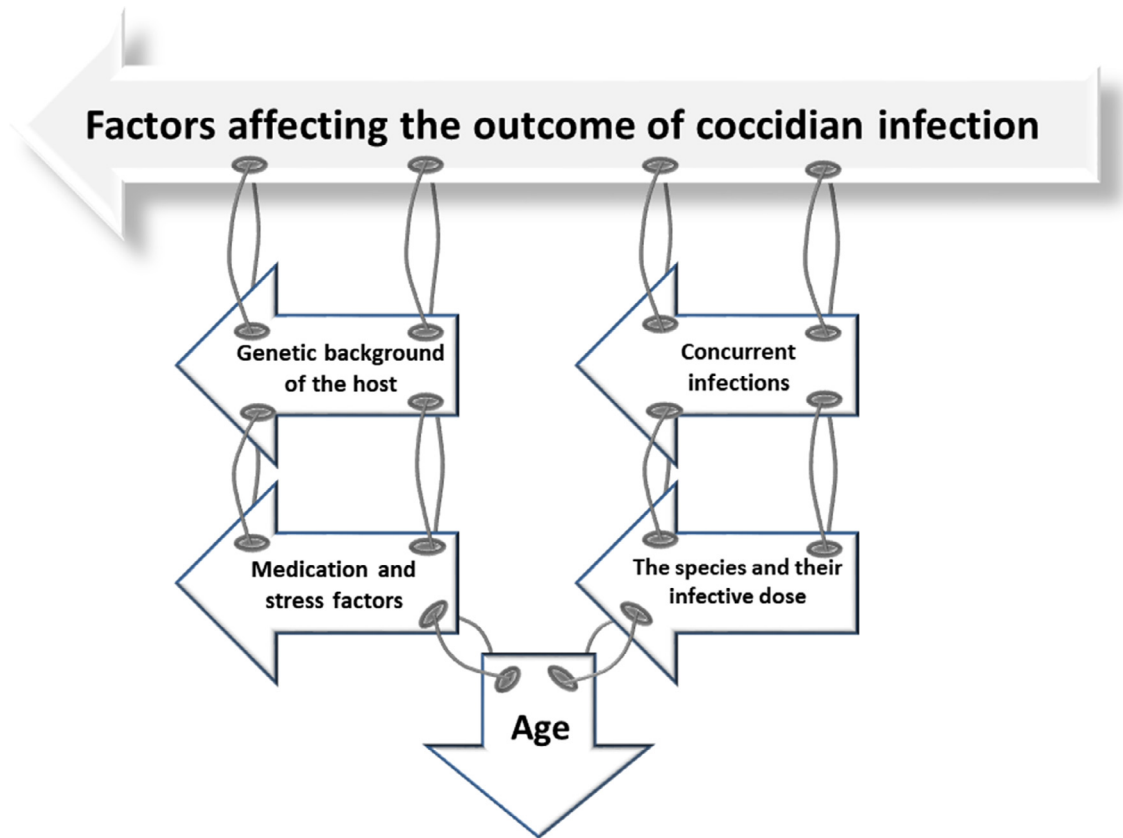


Figure 2. Factors affecting the outcome of coccidian infection.

Flock Size and Season

Large farms need more water, feed, litter, and generate higher amounts of feces so that they might act as a potential source of subclinical coccidiosis infection (Razmi and Kalideri, 2000). The prevalence of clinical or subclinical coccidiosis in broilers during spring and winter was higher than in autumn and summer (Razmi and Kalideri, 2000) due to oocysts' survival. Sporulation favors high humidity in litter and increases oocysts spread in chicken farms (Jordan, 1996). Coccidiosis had a low presence in winter (20.29%), while it was most prevalent in autumn at 45.12%, followed by summer (30.84%) and spring (23.81%) (Ahad et al., 2015).

Awais and Akhtar (2012) also recorded the incidence of disease was notably higher in autumn (60.02%) than summer (47.42%), spring (36.92%), and winter (29.89%). The rate and degree of sporulation of released oocysts are crucial factors affecting the infection rate in a flock, influencing the infection's epidemiology. Relative ambient temperature and humidity might be responsible for sporulation and affect the disease's incidence in different seasons (Awais and Akhtar, 2012).

The Species Involved and Their Infective Dose

The severity of infection caused by avian coccidiosis is directly related to the parasite species, the particular isolate or strain involved, and the number of oocysts ingested (Dakpogan et al., 2012). Using a single oocyst

isolation technique; variable virulence was obtained from 4 *E. tenella* strains (Beheira, Kafr El-Sheikh, Gharbia, and Alexandria) from a dose of 25×10^3 oocysts/chick at 2-wk old (Sedeik et al., 2019). The Alexandria strain was the most virulent (60 % mortality and showed a significant reduction in weight gain), while the Beheira strain was second (33.33 % mortality). The Kafr El-Sheikh and Gharbia strains had no mortality. The clinical manifestations of coccidiosis are related to many infective oocysts to which susceptible birds are exposed in their first month (Martins et al., 2012).

The crowding effect means that a maximum infective dose exists, after which the reproductive potency decreases (Williams, 2001). El-Shall (2015) recorded 34.48 and 60% mortality from inoculation of 2-wk old chicks with *E. tenella* Alex strain using doses of 10^4 and 25×10^3 oocysts/chick, while *E. tenella* Beheira stain resulted in 0 and 33.33% mortality using doses of 10^4 and 25×10^3 oocysts/chick. The intensive breeding system is a precious factor in propagating coccidiosis disease (Badran and Lukesova, 2006).

Medications and Other Stress Factors

Suboptimal inclusion or extensive use of anticoccidials in feed creates resistance and poor litter management. The absence of litter disposal and inadequate sterilization could provide optimal temperature (24–28°C) and relative humidity (exceeding 30%) for sporulation of oocysts (Chanie et al., 2009).

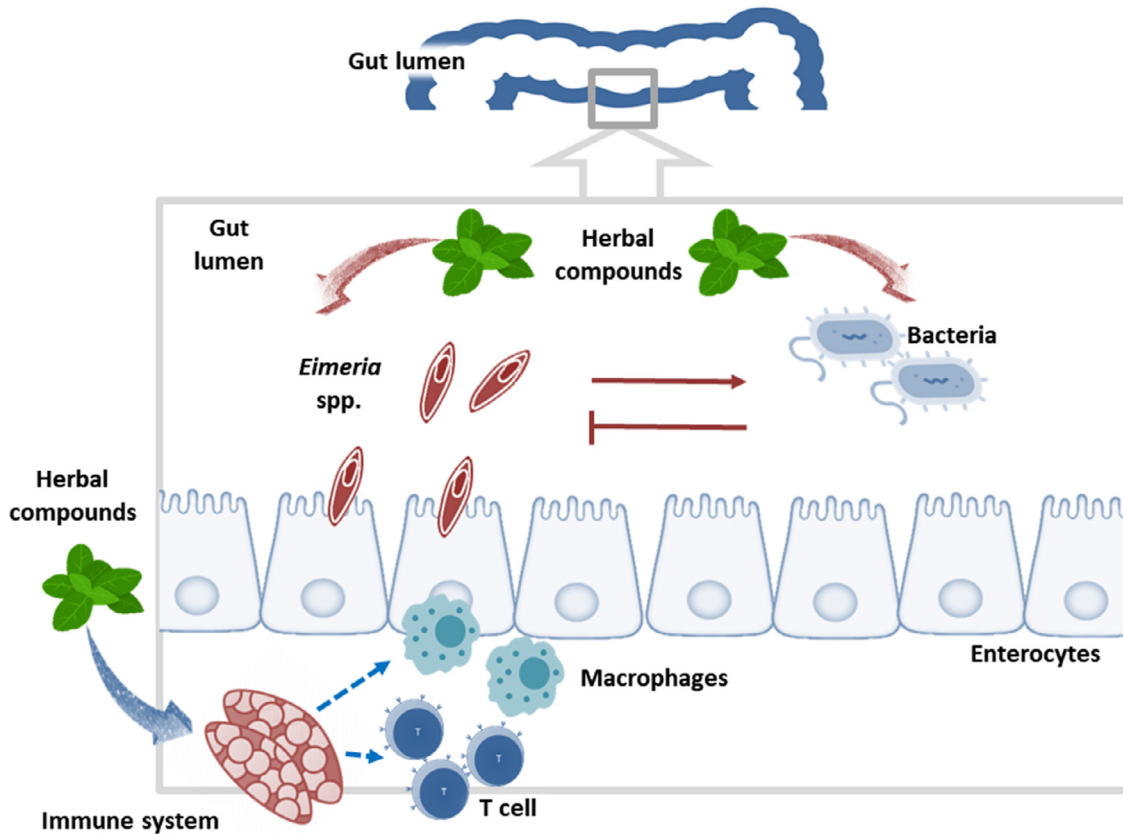


Figure 3. Gut-associated T cells, macrophages, and the schematic process of immune response of chickens to herbal anticoccidian compounds.

The key factors in the epidemiology of coccidiosis are the presence of sporulated oocysts in the environment for long period, bad ventilation, the absence of all-in all-out system, and other stressors (i.e., dietary changes, and immunosuppressive effects) are all possible risk factors associated with the outbreak of coccidiosis (Chanie et al., 2009).

Awadalla (1998) studied the effect of stressors like vaccination and crowding on the pathogenicity of *E. tenella* in broiler chickens. Each chick was inoculated with 10^4 sporulated *E. tenella* oocysts at 3-d old, followed by a challenge with a further 15×10^3 sporulated oocysts on d 28. The results revealed that overstocking chickens elevated corticosterone levels and lowered total proteins, calcium, glucose, and phosphorus levels. The crowded vaccinated group had the highest mortality, oocysts production, caecal indices, and the lowest body, spleen, bursa, and thymus weight (Awadalla, 1998).

In chickens, aflatoxins in the diet act as a precious stress factor, increasing the severity or susceptibility to caecal coccidiosis, inducing impairment of cellular and humoral immune responses resulting in lower resistance to serious infectious diseases including coccidiosis (Bakshi et al., 2000). Shakshouk et al. (1990) reported that aflatoxins at 5 ppm in the feed ration for 2 wk, followed by 2.5 ppm for a further 2 wk, increased the susceptibility of chickens to caecal coccidiosis with 20×10^3 sporulated oocysts/bird. Aflatoxins (200 ppb) in the diet of broiler chickens increased the mortality caused

by *E. tenella* infection and results in a significant loss in BW and a deteriorated food conversion ratio (FCR) in survivors (Allameh et al., 2005; Ellakany et al., 2011).

The effect of heat stress on the pathogenesis of *Eimeria maxima* in meat-type chickens was studied by Schneiders et al. (2020), who demonstrated a significant detrimental effect of heat stress on the pathogenesis of *E. maxima* infection in broilers. They reported a restrictive replication of the parasite in heat-stressed chickens evidenced by significantly reduced oocyst shedding and disruption of the intestinal blood barrier. In addition, there was downregulation of *Eimeria* species genes related to gamete fusion, oocyst shedding, mitosis, and spermiogenesis which led to the alterations in the cytokine expression that could be related to reduce parasite development *in vivo* during the exposure to heat stress (Schneiders et al., 2020).

Impact of Routine Vaccines and Concurrent Infections on Susceptibility to Coccidiosis

The clinical signs of *Eimeria* infection are enhanced by simultaneous infection with several species and interactions with other pathogens such as enteric bacteria and viruses. Coccidia-free chickens exhibit no difference in innate susceptibility to coccidiosis according to age (Pellérdy, 1974). Therefore, exogenous factors that have an immunosuppressive effects such as Marek's disease

Table 2. Different phytochemical/herbal remedies and/or their extracts; bioactive compounds; specific anticoccidial properties and their effects exerted on poultry and the studied coccidian species.

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Acacia concinna</i>	Saponins	Binds to the 4-sterol molecules on <i>Eimeria</i> cell membrane, as they disturbs the lipids in the parasite cell membrane. This affects the enzymatic activity and metabolism leading to cell death. Cell death then induces a toxic effect in mature enterocytes in the intestinal mucosa, causing sporozoite-infected cells to be released before the merozoite phase of the protozoa.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Enhances the nonspecific immunity. Improves the productive performance (daily body weight gain and reduces feed conversion ratio. Reduces the mortality rate. Decreases the fecal oocyst shedding. Reduces ammonia production.	(Wang et al., 1998; Cheeke, 2000; Alfaro et al., 2007).
<i>Allium sativum</i> (Garlic) <i>Allium tripedale</i> (<i>Nectaroscordum tripedale</i>)	Sulfur derivatives, alliin, alliin, ajoene, diallyl sulfide, dithiin, and allylcysteine	Hinder sporulation. However, the full anticoccidial mechanism of garlic and its sulfur derivatives are still ambiguous.	<i>Eimeria tenella</i>	Shows broad antimicrobial activity that reduces the deleterious effects of microbial infections.	(El-Khtam et al., 2014; Pourali et al., 2014; Alnassan et al., 2015; Habibi et al., 2016; Udo and Abba, 2018; Ali et al., 2019; Sidiropoulou et al., 2020).
	Propylthiosulfinate (PTS) and propylthiosulfinate oxide (PTSO)	-	-	Modulates the intestinal immunity through expression levels of 1227 intestinal lymphocytes. Stimulates the NF-B transcription factor, which plays a significant role in regulating the immune response upon infection. Shows antioxidant properties.	(Rose et al., 2005; Ogunlana et al., 2008; Kim et al., 2013b).
<i>Aloe vera</i> (Gavakava) <i>A. secundiflora</i> <i>A. excelsa</i> <i>A. debrana</i> <i>A. pulcherrima</i> <i>A. excels</i> <i>A. spicata</i>	Tannins Phlobatannins Saponin Flavonoids Treprenoids carbohydrates	Tannins: Penetrates the coccidia's oocyst wall and destroy the cytoplasm, as they probably inactivate the endogenous enzymes responsible for the cycle of sporulation in chickens. Saponins: as mentioned above. Flavonoids and treprenoids: inhibits the invasion and replication of different species of coccidia. Aloe polysaccharide acemannan, binds to the mannose receptor on macrophages, stimulating them to produce inflammatory cytokines such as IL-1 through IL-6 and TNF- and eventually suppress coccidiosis as shown by higher weight gain and lower fecal oocyst counts.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Improves body weight gain and reduces mortality. Shows antioxidant and immunostimulatory properties.	(Molan et al., 2004; Mwale et al., 2006; Yim et al., 2011; Akhtar et al., 2012; Narsih and Wignyanto, 2012; Kheirabadi et al., 2014; Muthamilselvan et al., 2016; Kaingu et al. 2017; Isah et al., 2019; Desalegn and Ahmed 2020).
<i>Artemisia annua</i> (<i>A. annua</i>)	Artemisinin (anticoccidial)	Reduces the sporulation rate through minimizing the sarco/endoplasmic reticulum calcium ATPase expression in macrogametes. This has a role in calcium homeostasis affecting the wall-forming bodies' secretion, a calcium-dependent mechanism leading to inhibition of the oocyst wall formation process leading to oocyst defect wall and oocyst death. Expresses the formation of reactive oxygen species through iron-implicated peroxide complex degradation and promotes oxidative stress. Reactive oxygen species inhibits sporulation directly and the formation of the cell wall in <i>Eimeria</i> species, resulting in life cycle interference. Reduces oocyst shedding in broiler chickens.	<i>Eimeria tenella</i> , <i>Eimeria maxima</i> , and <i>Eimeria acervulina</i>	Improves feed conversion ratio and body weight gain.	(Del Cacho et al., 2010; Drăgan et al., 2010, 2014; de Almeida et al., 2014; Kaboutari et al., 2014; Jiao et al., 2018)

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Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Artemisia annua</i> (<i>A. annua</i>)	Leaf powder of <i>A. annua</i>	Protects chickens from pathological symptoms and mortality associated with <i>Eimeria tenella</i> infection and reduces the lesion score, and fecal oocyst output. The leaf powder was more efficient than the essential oil, which could be due to a lack of artemisinin in the oil, and to the greater antioxidant ability of <i>A. annua</i> leaves than the oils.	<i>Eimeria tenella</i>		(Ferreira et al., 2010)
	Ethanollic extract of <i>A. annua</i> (AE)	Preventive role is better than treatment. The leaf extract was the most effective treatment to decrease the oocysts in chicken feces. Reduces the caecal lesion value.	<i>Eimeria acervulina</i> , <i>Eimeria necatrix</i> and <i>Eimeria tenella</i>	Improves body weight gain.	(Fatemi et al., 2017)
	Phenolic compounds, flavonoids, and phytochemicals of <i>A. annua</i>	Flavonoids have antioxidant capacity due to their redox activities. Some flavonoids work on the disturbance of protozoan parasites, and others are responsible for host-parasite interactions.	<i>Eimeria tenella</i>	Keeps the packed cell volume at a regular stage. Maintains a healthy microflora and consumes large amounts of nitrogen. Commensal bacteria play an essential role in activating food digestion and nutrients absorption. Improves body weight gain and reduces feed conversion ratio. Promotes acquired and innate immune response in poultry.	(Jamshidi et al., 2014; Wiedosari and Wardhana, 2018) (Brisbin et al., 2008; Zhang et al., 2012a)
<i>Artemisia herba-alba</i>	Artemisinin; camphor; 1,8-cineole, tannins, and antioxidant compounds	Artemisinin slows down <i>Eimeria</i> reproduction. It decreases the sporulation and survival capability of the oocysts in the litter. The functional endoperoxide bridge of artemisinin induces oxidative stress by generating a cascade of free radicals (key point in the antiprotozoal activities of artemisinin and subsequently alkylation of proteins and lipid peroxidation). Artemisinin blocks the pro-inflammatory factors activated by the parasite.	<i>Eimeria tenella</i>	Protects infected broiler chickens from mortality and pathological symptoms. Reduces the cecal lesions in infected broiler chickens. Improves the hematological parameters and lowers the intensity of bloody diarrhea.	(Allen 1997; Meshnick, 2002; Del Cacho et al., 2010; Dragan et al., 2010; de Almeida et al., 2012; Zaman et al., 2012; Kaboutari et al., 2014; Kheirabadi et al., 2014; Lu et al., 2019; Zhang et al., 2020).
<i>Artemisia sieberi</i> <i>A. asiatica</i>	Artemisinin	Reduces oocyst counts in the infected broiler chickens.	Mixed suspension of <i>Eimeria acervulina</i> , <i>Eimeria tenella</i> , <i>Eimeria necatrix</i> , and <i>Eimeria maxima</i>	Enhances body weight gain and reduces feed intake.	(Kheirabadi et al., 2014).
<i>Astragalus membranaceus</i>	Polysaccharides, flavonoids tannins and saponins	Enhances anticoccidial antibodies activity via increase in the cellular and humoral immunity.	<i>Eimeria tenella</i>	Shows anti-inflammatory characteristic and improves intestinal integrity.	(Guo et al., 2004; Abdel-Tawab et al., 2020).
<i>Azadirachta indica</i> (Neem)	Salinomycin and bioactive molecules such as azadirachtin limonoids, protolimonoids, tetranortriterpenoids, pentanortriterpenoids, hexanortriterpenoids, some nonterpenoid (anticoccidial)	Shows high efficacy against protozoan parasites (such as coccidian species).	<i>Eimeria tenella</i>	Shows high efficacy against bacterial, fungal and viral pathogens. Shows antitumor and anti-inflammatory properties.	(Donli and Buahin, 1998; Etuk et al., 2004; Abbas et al., 2006; Koul et al., 2006; Tipu et al., 2006).

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Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Berberis lycium</i> extracts <i>Ageratum conyzoides</i> <i>Linum usitatissimum</i> <i>Vernonia amygdalina</i> <i>Beta vulgaris</i> (Sugar beet)	Berberine N-3 fatty acids, flavonoids, and vernoside Betaine	Inhibits the <i>Eimeria tenella</i> sporozoites invasion into intestinal epithelial cells in poultry via oxidative stress induction (Reactive nitrogen species and reactive oxygen species production). Oxidative stress is known to induce imbalance in the host of oxidant or antioxidant cells. Suppresses <i>Eimeria</i> developmental life cycle in the chicken's intestinal cells before oocysts are released in feces. Decreases <i>Eimeria</i> oocyst excretion and the severity of infection or indirectly by interaction with intestinal microflora blocking proinflammatory factors activated by the parasite. This enhances immunity and the resistance to infection. Decreases the risk of secondary bacterial infections. Reduces the severity of <i>Eimeria</i> infections by ameliorating the degree of intestinal lipid peroxidation. Stabilizes and assists the defense of the epithelial cells in which <i>Eimeria</i> multiply. Acts as osmolyte (maintains the water inside the epithelial cells decreasing diarrhea in coccidial infection).	<i>Eimeria tenella</i> <i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Improves the growth of chicken without any toxicity. Shows antimicrobial activity. Improves gut health, integrity of cell membrane and increases digestibility. Improves the productive performance (daily body weight gain). Shows anticoccidial potential in dose dependent manner in terms of better feed conversion ratio, reduction in oocysts per gram of feces and lesion scores.	(Allen, 1997; Danforth et al., 1997; Allen et al., 1998; Al-Fifi, 2007; Nweze and Obiwulu, 2009; Oyagbemi and Adejinmi, 2012; Malik et al., 2014). (Allen et al., 1998; Molan et al., 2009; Abbas et al., 2017).
<i>Bidens pilosa</i>	Unknown, as this plant is a rich source of phytochemicals, including 70 aliphatics, 60 flavonoids (e.g., (quercetin-3,3-dimethoxy-7-O-rhamno-glucopyranose), 25 terpenoids, 19 phenylpropanoids, 13 aromatics, 8 porphyrins, and 6 other compounds.	Suppresses oocyst sporulation, sporozoite invasion, and schizonts in the life cycle.	<i>Eimeria tenella</i>	Enhances T cell-mediated immunity. Improves body weight gain, survival rate, fecal oocyst count, gut pathology, and decreases bloody diarrhea.	(Bartolome et al., 2013; Akram et al., 2014; Yang et al., 2015; Chang et al., 2016; Yang et al., 2019)
<i>Camellia sinensis</i> (Green tea) extracts	Polyphenolic compounds and selenium	Inhibits the enzymes responsible for coccidian sporulation.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Shows antioxidant properties.	(Jang et al., 2007; Ogunlana et al., 2008; Molan and Faraj, 2015).
<i>Carica papaya</i>	Papain Vitamin A	Prevents sporozoite invasion into intestinal epithelial cells. Shows proteolytic destruction of <i>Eimeria</i> by papain. Shows improvement in the intestinal epithelial cells by vitamin A.	<i>Eimeria tenella</i>	-	(Al-Fifi, 2007; Nghonjuyi et al., 2015; Dakpogan et al., 2018; Akhter et al., 2021).
<i>Cinnamomum cassia</i>	Cinnamaldehyde	Increases the T-cells and their cytokines inducing immunomodulation against <i>Eimeria</i> .	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Enhances immunity. Improves body weight gain, survival rate, gut integrity, and decreases diarrhea.	(Lee et al., 2011; Orengo et al., 2012)
<i>Commiphora suygnertonii</i>	Phenolic compounds tannins, alkaloids, saponins, anthraquinones, cardiac glycosides, and terpenes	Tannins and saponins shows anticoccidial effect.	<i>Eimeria necatrix</i> , <i>Eimeria tenella</i> , and <i>E. mitis</i>	Reduces the mortality rate and oocysts counts.	(Hanuš et al., 2005; Max et al., 2009; Baghdadi and Al-Mathal, 2010; Bakari et al., 2012).

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Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Curcuma longa</i> (Turmeric)	Phenolic compounds (Curcumins or diferuloylmethane)	Inhibits the growth of <i>Eimeria</i> species at sporogony (destroy sporozoite) preventing sporozoite invasion into intestinal epithelial cells and merogony stages. Reduces oocyst shedding and gut lesions.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Increases body weight gain. Shows antioxidative, anti-inflammatory and immunomodulatory properties.	(Allen et al., 1998; Abbas et al., 2010, Abbas et al., 2011; Khalafalla et al., 2011; Kim et al., 2013a; Aljedaie and Al-Malki 2020).
<i>Cyamopsis tetragoloba</i> (Guar) bean	Saponins	Inhibits the growth of <i>Eimeria</i> species at sporogony (destroys sporozoite). Prevents sporozoite invasion into intestinal epithelial cells and merogony stages. Reduces oocyst shedding and gut lesions.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Enhances the nonspecific immunity. Improves the daily body weight gain and reduces feed conversion ratio. Reduces the mortality rate. Decreases the fecal oocyst shedding. Reduces ammonia production.	(Sánchez-Hernández et al., 2019).
<i>Dichroa febrifuga</i> (halofuginone)	Febrifugine is an alkaloid isolated from this plant, and its halogenated derivative, halofuginone	Shows coccidiostatic effect acting only at the early stages, about 0–72 h post inoculation, (sporozoites, schizonts and merozoites) of first and second generation of schizogony stages of <i>E. tenella</i> endogenous development. The halofuginone acts in inhibiting the adherence of the parasites and invasion of host intestinal hypothetical cells but remain unable to kill the parasites directly and thus only delay the development of <i>Eimeria</i> .	<i>Eimeria tenella</i>	Enhances immunity, especially T cell-mediated immunity. Improves body weight gain, survival rate, gut pathology, and decreases bloody diarrhea.	(Youn and Noh, 2001; Lillehoj et al., 2011; Zhang et al., 2012a,b; Yang et al., 2015; Muthamilselvan et al., 2016).
<i>Echinacea purpurea</i> <i>E. officinalis</i>	Chicoric acid and tannins (pedunculagin)	-	<i>Eimeria tenella</i>	Shows an effective humoral immune response against coccidial infection in chickens.	(Allen, 2003; Kaleem et al., 2014).
<i>Emblica officinalis</i>	Tannins, alkaloids, carbohydrates, polyphenolics, essential amino acids, and vitamins (high concentration of vitamin C), ellagitannin, gallic acid, emblicanin A, emblicanin B, ellagic acid, flavonoids and kaempferol	Shows coccidiocidal or coccidiostatic, in a concentration-dependent. Shows oocysticidal activity and inhibits sporulation. Tannins inhibits the development of the parasites life cycle.	<i>Eimeria acervulina</i> , <i>Eimeria maxima</i> , <i>Eimeria necatrix</i> , and <i>Eimeria tenella</i>	Shows higher daily body weight gain and lowers oocyst shedding. Promotes humoral and cellular immune response.	(Kaleem et al., 2014; Sharma et al., 2021).
<i>Fomitella fraxinea</i> (wood-rotting mushroom)	Fungal lectin.	Strengthens cellular and humoral immune responses of <i>Eimeria</i> species.	<i>Eimeria acervulina</i>	Shows immuno-stimulatory activity.	(Dalloul et al., 2006).
Fructus Meliae toosendan	Triterpenoids, steroids and limonoids.	Shows strong inhibitory properties against oocysts sporulation and increases the proportion of degenerated oocysts.	<i>Eimeria tenella</i>	Decreases the degree of bloody diarrhea and the output of oocysts. Enhances the relative weight gain rate and inhibits mortality. Improves the caecum intestinal microflora. Reduces the colonization of secondary bacterial infections or oocysts of <i>E. tenella</i> in the intestinal tract. Enhances the immune function of chickens.	(Wu et al. 2010; Zhang et al., 2010 ; Hu et al., 2011,2018; Yong et al., 2020).
<i>Galla rhois</i> powder	Methyl gallate; 3-galloyl-gallic acid; 4-galloyl- gallic acid isomers; 1,2,3,4,6-penta-O-galloyl- β -D-glucose; 2 inactive phenolic compounds, gallic acid methyl ester and gallic acid.	Stops oocyte shedding and decreases lesion scores.	<i>Eimeria tenella</i>	Improves body weight gain, reduces feed intake. Shows antibacterial and antiviral effect.	(Lee et al., 2012).

Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Ganoderma applanatum</i> <i>Ganoderma lucidum</i> <i>Pleurotus ostreatus</i> (wild mushrooms)	Active polysaccharides, glycoproteins, organic acids, resins, glycosides (steroid, triterpenoid and saponins)	Polysaccharides are known to block colonization of the intestine by pathogens. Suppresses oocyst sporulation.	<i>Eimeria tenella</i>	Improves carcass weight. Ameliorates bloody diarrhea.	(Ogbe et al., 2008; Ogbe et al., 2010; Ahad et al., 2016).
<i>Glycyrrhiza glabra</i> , <i>Gypsophila paniculate</i> , <i>Aesculus hippocastanum</i> .	Saponins	Saponins used in coating the <i>Eimeria</i> antigens in immunostimulation complexes during vaccine preparation.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Transports antigens and maintains their activity and stimulates IgG and IgM.	(Berezin et al., 2010).
<i>Khaya senegalensis</i> bark	Alkaloids and phenolics	Shows antioxidant properties. Ameliorates the degree of intestinal lipid peroxidation.	<i>Eimeria tenella</i>	Improves body weight gain and reduces feed conversion ratio. Reduces lesion scores and oocysts excretion	(Dakpogan et al., 2019).
<i>Lepidium sativum</i> (garden cress) seeds	Tocopherol, carotenoid, oleic acid, and α -linolenic acid. Antioxidant-rich extracts with high n-3 fatty acids (n-3 FA)	Tocopherols are lipid-soluble antioxidants. Have an effect on the intracellular development of the parasites. Reduces the invasion and development in chickens. Induces ultra-structural changes in both the asexual and sexual stages induced by n-3 fatty acids.	<i>Eimeria tenella</i>	Decreases mortality, faecal oocyst shedding and lesion score.	(Allen et al., 1996; Danforth et al., 1997; Diwakar et al. 2010; Adamu and Boonkaewwan, 2014).
<i>Morinda lucida</i> Benth (Rubiaceae), <i>Morinda cordifolia</i> , <i>M. citrifolia</i> , <i>Myrianthus arboreus</i> .	Acetone leaf extract contains alkaloids, anthraquinones, anthraquinols	Inhibits fecal oocyst, and reduces fecal oocyst score.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Improves body weight gain, and hematological parameters. Shows antioxidant properties.	(Ola-Fadunsin and Ademola, 2014; Rakhmani et al., 2014).
<i>Moringa oleifera</i>	Saponins	Inhibits fecal oocyst, and reduces fecal oocyst score.			
	Ascorbic acid, flavonoids, phenolics, carotenoid, zeatin, quercetin, β - sitosterol, caffeoylquinic acid and kaempferol. Protein, vitamins (C, A), amino acids and various phenolics.	Shows antioxidant properties. Ameliorates the degree of intestinal lipid peroxidation.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , <i>Eimeria necatrix</i> , <i>Eimeria maxima</i> and <i>Eimeria brunetti</i>	Inhibits oocyst output. Decreases fecal score, mortality and improves body weight gain.	(Ola-Fadunsin and Ademola, 2013).
<i>Musa paradisiaca</i> (banana roots)	Pectin and several flavonoids (Leucocyanidin, quercetin and its 3-O-galactoside, 3-O-glucoside, and 3-O-rhamnosyl glucoside)	Prevents coccidial developments and reduces its reproduction.	<i>Eimeria tenella</i>	Decreases the infection severity and oocyst shedding in a dose-dependent manner (1 g/kg body weight).	(Anosa and Okoro, 2011)
<i>Nauclea diderichii</i>	Ursolic and betulinic acids	Destroys the sporulated oocysts.	<i>Eimeria tenella</i>	Improves body weight gain, and hematological parameters.	(Ibrahim, 2016).

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Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Olea europaea</i> (Olive tree)	Maslinic acid, large concentrations of poly-phenolic or biophenols (cynarosid/luteolin-7-O-glucoside; tyrosol-leuropein quercetinisorhamnetin; neobavaisoflavone 2, 3-dihydro-amentoflavone quercetin-3-O-rutinosidechlorogenic acid, isorhamnetin 3-O-(6"-O-feruloyl)-glucoside), diligustilide quercetin-o-(o-galloyl)-hexoside)	Shows destructive effect on sporulated oocysts.	<i>Eimeria tenella</i> ; <i>Eimeria acervulina</i> , <i>Eimeria tenella</i> , <i>Eimeria mitis</i> , <i>Eimeria brunetti</i> and <i>Eimeria maxima</i>	Improves lesion index, the oocyst index, and the anticoccidial index.	(De Pablos et al., 2010; Debou-Iouknane et al., 2021).
<i>Origanum vulgare</i> (Oregano oil)	Phenols (thymol and carvacrol)	Phenols (thymol and carvacrol) interacts with the cytoplasmic membrane by changing its permeability for cations, (H ⁺ and K ⁺). The dissipation of ion gradients leads to impairment of essential processes in the cell. This allows leakage of cellular constituents, resulting in water unbalance, the collapse of the membrane potential and inhibition of ATP synthesis, and finally, cell death. Have a toxic effect on the upper layer of mature enterocytes of the intestinal mucosa. This is due to carvacrol's hydrophobicity, which accelerates the natural renewal process, therefor sporozoite infected cells are shed before the merozoite phase.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Increases body weight gain and reduces feed conversion ratio.	(Weber and de Bont, 1996; Ultee et al., 2002; Giannenas et al., 2003; Tsinas et al. 2011; Mohiti-Asli and Ghanaatparast-Rashti, 2015; Sidiropoulou et al., 2020).
<i>Parkia biglobosa</i> (Bark root)	Phenolic compounds (tannins, saponins and flavonoids)	Reduces the oocyte count.	<i>Eimeria tenella</i>	Improves carcass weight, stopped mortality. Reduces blood droppings.	(Mertz et al., 2001; Maikai et al., 2007; Ugwuoke and Pewan, 2020).
<i>Pimpinella anisum</i>	Anethole, methylchavicol, eugenol, anisaldehyde and estragole	Reduces the oocyte number in broiler chickens only in case of combination with <i>A. annua</i> .	<i>Eimeria tenella</i>	Enhances performance (better body weight gain and reduces feed conversion ratio).	(Drăgan et al., 2010).
<i>Pinus radiata</i> (Pine bark)	Tannins	Penetrates the coccidia's oocyst wall and destroys the cytoplasm. Inactivates the endogenous enzymes responsible for the sporulation in chickens.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Enhances performance (better body weight gain and reduces feed conversion ratio).	(Jang et al., 2007; Wang et al., 2008; Molan et al., 2009; Nweze and Obiwulu, 2009; Muthamilselvan et al., 2016).
<i>Prunus domestica</i> <i>Prunus salicina</i> (Plums fruit powder)	High levels of phenolic compounds, including flavonoids (anthocyanins)	Lowers fecal oocysts shedding.	<i>Eimeria acervulina</i>	Increases body weight gain and increases the IFN-gamma and IL-15 transcription and the proliferation of splenocytes. Improves the immune response to coccidiosis. Shows antioxidant and anti-inflammatory properties.	(Lee et al., 2008; Ogunlana et al. 2008; Jaiswal et al., 2013; Igwe and Charlton, 2016; Muthamilselvan et al., 2016).
<i>Psidium guajava</i> (guava)	Tannins, phenols, triterpenes, flavonoids, essential oils, saponins, carotenoids, lectins, vitamins (A, C and B complex), fiber and fatty acids and pectin	<i>Psidium guajava</i> extract inhibits sporulation process of <i>Eimeria</i> oocysts by inhibiting or inactivating the enzymes responsible for the sporulation. Penetrates the wall of the oocysts affecting the internal and external morphology of oocysts.	<i>Eimeria tenella</i>	Shows anti-inflammatory, antibacterial, and antioxidants properties.	(Ahmed et al., 2018).

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Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Punica granatum</i>	Casuarinin, corilagin, granatin-A, tellimagrandin-I, punicalin, punicalagin, terminalin/gallayldilacton, ellagic acid	Recuses oocyst output.	<i>Eimeria tenella</i>	Improves intestinal lesions and enhances body weight gain and reduces feed conversion ratio.	(Dkhil, 2013; Ahad et al., 2018).
<i>Saccharum officinarum</i> (sugarcane)	Phenolic compounds like flavones (luteolin, apigenin and triclin derivatives), caffeic, hydroxycinnamic and sinapic acids (laborious methanolic extraction method)	Shows <i>in vitro</i> inhibitory potential on sporulation of coccidian oocysts.	<i>Eimeria tenella</i> , <i>Eimeria necatrix</i> , <i>Eimeria mitis</i> , <i>Eimeria brunetti</i>	Shows anti-inflammatory, antioxidant, antistress, antiviral, antibacterial and immunomodulatory activities.	(Fornazier et al., 2002; Abbas et al., 2015).
<i>Salvadora persica</i> (Arak roots)	Phytochemicals like vitamin C, salvadorine, salvadore, alkaloids, trimethylamine, cyanogenic glycosides, tannins, saponins and salts, mostly as chlorides	Diminishes oocyst output through inhibition or impairment of the invasion, replication and development of <i>Eimeria</i> parasite species in the gut tissues of chickens. Reacts with cytoplasmic membranes and modifies their cation absorption, leading to damage of vital activities in coccidian cells leading to coccidian cell death. Stimulates antioxidative stress enzymes and neutralizing reactive oxygen species. This may have beneficial effects in treating coccidian infections ameliorating the degree of intestinal lipid peroxidation.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Shows anti-inflammatory and antioxidant properties. Inhibits stress-induced abnormalities in hematological parameters, demonstrating its defensive effect against stress.	(Ramadan and Alshamrani, 2015; Thagfan et al., 2017; Aljedaie and Al-Malki 2020).
<i>Senna siamea</i> leaves (cassia)	Alkaloids called cas-siarin emodin and upoleole	Shows antioxidant properties by ameliorating the degree of intestinal lipid peroxidation.	<i>Eimeria tenella</i>	Enhances body weight gain and decreases feed conversion ratio. Reduces lesion scores and oocysts excretion. Shows antioxidant and anti-inflammatory properties.	(Dakpogan et al., 2019).
Tannic acid extract	Tannic acid	Decreases oocyte numbers.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Decreases feed conversion ratio.	(Tonda et al., 2018).
<i>Trachyspermum ammi</i> (Ajwain)	Thymol and carvacrol	Shows <i>in vitro</i> anticoccidial effect by affecting sporulation (%) of <i>Eimeria</i> oocysts in dose dependent manner. Damages the morphology of oocysts in terms of shape, size and number of sporocysts. Stops the sporulation process and damages the morphology of <i>Eimeria</i> oocysts in dose dependent manner. Such higher <i>in vitro</i> anticoccidial potential of <i>T. ammi</i> extract might be due to action of its antioxidant compounds of <i>T. ammi</i> against <i>Eimeria</i> .	<i>Eimeria tenella</i> , <i>Eimeria brunetti</i> , <i>Eimeria necatrix</i> and <i>Eimeria mitis</i>	Enhances body weight gain and reduces feed conversion ratio.	(Abbas et al., 2019).
<i>Tulbaghia violacea</i> Harv	Antioxidant compounds as S -(methylthio-methyl) cysteine sulf-oxide (marasmin), bis[(methylthio) methyl] disulfide and various derivatives	Decreases the oocyst production in the birds. Induces host cell destruction associated with oxidative stress and lipid peroxidation and the ability to neutralize reactive oxygen species.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Shows antioxidant activity. Improves gut pathology, body weight gain.	(Naidoo et al., 2008).

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Table 2 (Continued)

Herbs	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Vitis vinifera</i> (Grape) seed extract	Proanthocyanidins [monomeric flavanols (catechin and epicatechin), dimeric, trimeric, and polymeric procyanidins, and phenolic acids (gallic acid and ellagic acid)]	Grape seed proanthocyanidin extract diminishes coccidiosis via the downregulation of oxidative stress (strong antioxidant). Damages the morphology of oocysts in terms of shape, size and number of sporocysts.	<i>Eimeria tenella</i> , <i>Eimeria tenella</i> , <i>Eimeria necatrix</i> , <i>Eimeria brunetti</i> and <i>Eimeria mitis</i>	Shows antioxidant activity. Improves gut pathology, and body weight gain.	(Yilmaz and Toledo, 2004; Naidoo et al., 2008; Wang et al., 2008; Abbas et al., 2020).
<i>Yucca schidigera</i>	Saponins	Diminishes coccidiosis via the downregulation of oxidative stress (strong antioxidant). Damages the morphology of oocysts in terms of shape, size and number of sporocysts.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Enhances the nonspecific immunity. Improves the productive performance (daily body weight gain and feed conversion ratio). Reduces the mortality rate. Decreases the faecal oocyst shedding. Reduces ammonia production.	(Hassan et al. 2008; Mohiti-Asli and Ghanaatparast-Rashti, 2015).
<i>Zingiber officinale</i> (Ginger)	Phenol derivative as oleoresin and gingerol	Degenerates schizonts in the glandular epithelium. Interacts with parasite through an adsorption involving hydrogen bonding. Low levels of phenol interact with proteins and form a phenol protein complex. The free phenol infiltrates into the parasite, causing precipitation and protein denaturation. The high levels of phenol cause the coagulation of proteins and lysis of the cell membrane.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> and <i>Eimeria maxima</i>	Increases body weight gain. Shows antioxidative, anti-inflammatory and immunomodulatory properties.	(Ali et al., 2019; Aljedaie and Al-Malki 2020).

virus (Rice and Reid, 1973), reticuloendothelial virus (Motha and Egerton, 1984), and reovirus (Ruff and Rosenberger, 1985a,b), increases susceptibility to coccidiosis.

Vaccinations can also increase susceptibility to coccidiosis. For example, the infectious bursal disease (IBD) vaccination increased the severity of caecal coccidiosis due to immunosuppression (McDougald et al., 1979). However, Kabell et al. (2006) showed that coccidiosis did not affect IBD vaccination of chickens, suggesting the promoting effect of concurrent stimulation of the immune system by subclinical coccidiosis and the very virulent infectious bursal disease virus (vvIBDV), activating the distribution, and replication of the vaccine strain in chicken lymphoid tissues (Kabell et al., 2006).

Chickens infected with *E. tenella*, before and after vaccination with the lentogenic F or the mesogenic Komarov vaccine strains of Newcastle disease virus (NDV), had significantly lower HI antibody titers and higher mortality after challenge with velogenic strains of NDV suggesting the immunosuppressive effect of *E. tenella* infection to NDV vaccine response (Mohammed, 1980,1982; Hegazy et al., 1986). Furthermore, coccidiosis incubation and latent disease conditions are known to be hastened and aggravated by NDV vaccination (Anonymous, 1986).

Obasi et al. (2006) reported a natural outbreak in Nigeria of acute coccidiosis in a flock of 250 broilers with 33% mortality over 4 d, which was considered to be induced by NDV vaccination. In disease outbreaks (with field exposure to NDV) on the farm (with subclinical coccidiosis) and with a higher infectious dose and involvement with more virulent strains of NDV, a more severe, sudden, and acute clinical disease (caecal coccidiosis) is expected (Shaban, 2012).

Various laboratory trials suggest that coccidiosis may predispose birds to necrotic enteritis (NE), such as *E. acervulina* (Shane et al., 1985), *E. maxima* (Williams et al., 2003), or *E. necatrix* (Baba et al., 1997). Coccidiosis promotes the onset of NE by supporting *Clostridium perfringens* growth by inducing the inflammatory reaction, increasing mucous secretions (goblet cells), which is a growth factor for *C. perfringens* (Collier et al., 2008). However, many coccidiosis cases recorded worldwide without being associated with NE (Kaldhusdal et al., 2001; Répérant and Humbert, 2002).

It is suggested that only severe coccidiosis damages the mucous membrane enough to allow a clostridial infection leading to NE. In addition, the threshold of clostridial infection is necessary for NE to become prominent (Williams, 2005). When *Eimeria* invasion occurs before *Salmonella* infection in chickens, there is a more severe and prolonged salmonellosis. The same results were reported in a study with *S. typhimurium*/*E. necatrix* (Stephens and Vestal, 1966), *S. typhimurium*/*E. tenella*, and *S. enteritidis*/*E. tenella* (Koinarski et al., 2005). These findings can be explained based on the protozoa's invasive nature against the intestinal epithelium, as they easily bind to parenchymal organs, and allows *Salmonella* propagation in these organs

Table 3. Different herbal mixtures; bioactive compounds; specific anticoccidial properties and their effects exerted on poultry and the studied coccidian species.

Herbal mixtures	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
Herbal essential oils (Eos) of <i>Oreganum compactum</i> , <i>A. absinthium</i> , <i>Rosmarinus officinalis</i> , <i>Anredera cordifolia</i> , <i>Morinda citrifolia</i> , <i>Malaviscus arboreus</i> , <i>Syzygium aromaticum</i> (eugenol), <i>Melaleuca alternifolia</i> , <i>Citrus sinensis</i> , <i>Curcuma zanthorrhiza</i> (curcumin), <i>Piper nigrum</i> (piperin) and <i>Thymus vulgaris</i> (Thymol)	-	The EOs β thujone 1,8-cineol and p-cymene from <i>A. absinthium</i> prevents <i>Eimeria</i> oocyst development, while cineol, α -pinene and bornyl acetate from <i>R. ofcinalis</i> acts as antioxidants. Limonene and linalool from <i>C. sinensis</i> , and thymol and p-cymene from <i>T. vulgaris</i> destroys <i>Eimeria</i> oocysts.	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Reduces the total intestinal lesion score. Improves the zootechnical performance body weight gain and feed conversion ratio.	(Cox et al., 2000; Oviedo-Rondón et al., 2006; Reisinger et al., 2011; Remmal et al., 2011; Abbas et al., 2012a,b; Arczewska-Włosek and Świątkiewicz, 2013; Bozkurt et al., 2013; Quiroz-Castañeda and Dantán-González, 2015).
<i>Sophora flavescens</i> Aiton, <i>Pulsatilla koreana</i> , <i>Sinomenium acutum</i> , <i>Ulmus macrocarpa</i> , <i>Quisqualis indica</i>	Phenolic compounds as flavonoids, tannins, terpenoids and essential oils, alkaloids, and saponins	The EOs β thujone 1,8-cineol and p-cymene from <i>A. absinthium</i> prevents <i>Eimeria</i> oocyst development, while cineol, α -pinene and bornyl acetate from <i>R. ofcinalis</i> acts as antioxidants. Limonene and linalool from <i>C. sinensis</i> , and thymol and p-cymene from <i>T. vulgaris</i> destroys <i>Eimeria</i> oocysts.	<i>Eimeria tenella</i>	Decreases bloody diarrhea. Increases body weight gain and reduces feed conversion ratio.	(Youn and Noh, 2001).
<i>Agrimonia eupatoria</i> , <i>Echinacea angustifolia</i> , <i>Ribes nigrum</i> , <i>Cinchona succirubra</i> (Apacox)	-	Decreases the number of <i>Eimeria tenella</i> oocytes in chickens.	<i>Eimeria tenella</i>	Decreases bloody diarrhea and increases body weight gain and reduces feed conversion ratio.	(Christaki et al., 2004).
Uncariae ramulus cum Uncaria stem and thorn) <i>Agrimoniae herba</i> (agrimony) Sanguisorbae radix (<i>sanguisorba</i> root) <i>Eclipta prostrata</i> (Yetbadetajo Hert) Rehmanniae radix (rehmannia root) Pulsatillae radix (Chinese <i>Pulsatilla</i> root) <i>Sophora flavescens</i> (flavescence sophora root) Radix glycyrrhizae (licerice root)	Uncaria alkaloids such as rhyncopyline and isorhynchophyline, etc. Agrimone, agrimonolide, organic acids phenols, agri-mol A, B, C and D, etc. b-Sitosterol, pomolic acid, suavissimoside F1 Saponins such as eclalbasaponin I, II, III and XII, etc. Saponins such as rehmaglutins A, B, C and D, acteoside, glutinosides A, B and C Triterpenoid glycosides Alkaloids such as matrine, sophoridine and isomatrine, etc., flavanoids such as isoanhydroicartin, isoxanthohumol, etc. Glycyrrhizin, flavanoids such as licochalcone A, isoglycycomarin	Shows direct inhibiting effect on the maturing of unsporulated and killing effect on the sporulated oocysts.	<i>Eimeria tenella</i>	Decreases intestinal lesions and increased body weight gain.	(Du and Hu, 2004).

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Table 3 (Continued)

Herbal mixtures	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
Polysaccharides from <i>Astragalus membranaceus</i> , <i>Carthamus tinctorius</i> , <i>Lentinus edodes</i> , and <i>Tremella fuciformis</i>	-	Polysaccharides enhances anticoccidial antibodies and antigen-specific cell proliferation in splenocytes via cellular and humoral immunity to <i>E. tenella</i> in chickens	<i>Eimeria tenella</i>	-	(Guo et al., 2004).
<i>Curcuma longa</i> , <i>Capsicum annuum</i> , and shiitake mushroom	Mixture of curcuma/capsicum/lentinus	Increases antibodies and decreases the number of oocytes in feces.	<i>Eimeria acervulina</i>	Enhances the local innate immunity (Transcriptional levels of local cytokines for IL- IL-, IL-, and IFN-).	(Lee et al., 2009).
Prebiotics or oligosaccharides (oligo-fructose) derived from chicory, onion, garlic, asparagus, artichoke, leek, bananas, tomatoes, wheat	Pyrodextrin, Inulin	-	-	Enhances immune defense against infection and reduces the mortality rate. Increases the gut microbiota and growth performance.	(Janardhana et al., 2009; Kim et al., 2011; Nabizada, 2012; Al-Sheraji et al., 2013; Sugiharto, 2014).
Capsicum oleoresin Turmeric oleoresin	-	Shows increases in NK cells, macrophages, CD4 ⁺ T cells, CD8 ⁺ T cells, and their cytokines (IFN- and IL-6). Decreases the TNFSF15 and IL-17F, leading to induction and elevation of host immunity which kills <i>Eimeria tenella</i> in chickens	<i>Eimeria tenella</i>	Increases body weight gain. Lowers feed conversion ratio and mortality.	(Lee et al., 2011).
Carvacrol, 1.8-cineole, camphor, and thymol extracted from oregano, bay leaves, and lavender	-	Reduces oocyst number and shedding in a dose-dependent manner (oocysticidal action).	<i>Eimeria tenella</i> , <i>Eimeria maxima</i> , <i>Eimeria acervulina</i> , <i>Eimeria necatrix</i> and <i>Eimeria mitis</i>	Improves performance of birds.	(Remmal et al., 2011,2013; Bozkurt et al., 2012).
Isopulegol, carvacrol, carvone, eugenol, cineol, cinnamaldehyde, carveol and thymol	-	Reduces oocyst number and shedding in a dose-dependent manner (oocysticidal action).	<i>Eimeria tenella</i> , <i>Eimeria maxima</i> , <i>Eimeria acervulina</i> , <i>Eimeria necatrix</i> and <i>Eimeria mitis</i>	Improves performance of birds.	(Remmal et al., 2011,2013; Bozkurt et al., 2012).
Mixture of leaves of <i>Azadirachta indica</i> A. Juss and <i>Nicotiana tabacum</i> L.; flowers of <i>Calotropis procera</i> Ait. F. and seeds of <i>Trachyspermum ammi</i> L.	Phytochemicals of 4 plants discussed above can be broadly divided into phenols flavonoids, tannins, terpenoids and essential oils, alkaloids, and saponins. <i>Nicotiana tabacum</i> contains alkaloids, mainly nicotine. <i>Calotropis procera</i> is rich in alkaloids, carbohydrates, glycosides, phenolic compounds/tannins, proteins and amino acids, proteolytic enzymes, flavonoids, saponins, sterols and/or triterpenes, acidic compounds and resins. <i>Azadirachta indica</i> and <i>Trachyspermum ammi</i> mentioned above	Shows a concentration-dependent anticoccidial activity.	<i>Eimeria tenella</i>	Shows anti-tumor, anti-inflammatory, antioxidant, antiproliferative, antibacterial, antiviral, and anti-parasitic properties.	(Zaman et al., 2012).

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Table 3 (Continued)

Herbal mixtures	Bioactive compounds	Specific anticoccidial effects exerted in poultry	Studied coccidian species	Other beneficial effects	References
<i>Allium sativum</i> , <i>Urtica dioica</i> , <i>Inula helenium</i> , <i>Glycyrrhiza glabra</i> , <i>R. officinalis</i> , <i>Chelidonium majus</i> , <i>Thymus serpyllum</i> , <i>Tanacetum vulgare</i> , and <i>Coriandrum sativum</i> . <i>Salvia tibonitica</i> decoction, Eucalyptus EO, Peppermint EO, and saponin	-	-	<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , and <i>Eimeria maxima</i>	Reduces the total intestinal lesion score and improves the zootechnical performance.	(Oviedo-Rondón et al., 2006; Pop et al., 2019; Sultan et al., 2019).
Herbal mixture of <i>Allium sativum</i> , <i>Urtica dioica</i> , <i>Inula helenium</i> , <i>Glycyrrhiza glabra</i> , <i>Rosmarinus officinalis</i> , <i>Chelidonium majus</i> , <i>Thymus serpyllum</i> , <i>Tanacetum vulgare</i> , <i>Coriandrum sativum</i>	Flavonoids, tannins or saponins, polyphenols. Chlorogenic acid, caffeic acid and luteolin.	Alters the process of oocyst wall formation. Inhibits sporulation by destroying the sporozoites. Alleviates the damage to the intestinal tissue during parasite invasion by reducing the cytotoxic effects caused by the reactive oxygen species and thus the lowers the lesion score.	<i>Eimeria mazi</i>	Reduces the coccidian multiplication rate. Reduces the severity of intestinal lesions. Shows immunomodulatory effects.	(Pop et al., 2019).
Herbal powder (Shi Yin Zi) consists of: <i>Cnidium monnieri</i> (L.) Cuss, <i>Taraxacum mongolicum</i> Hand-Mazz., and sodium chloride	Osthole Chlorogenic acid and caffeic acid	Inhibits coccidian oocyst sporulation.	<i>Eimeria tenella</i>	Alleviates the histopathological changes of the cecum, and the number of oocysts and mucosa cell necrosis. Improves body weight gain.	(Song et al., 2020).

(Koinarski et al., 2005). It was also noted that infestation with *E. tenella* increased the severity of *Histomonas meleagridis* infection in chickens (McDougald and Hu, 2001).

The occurrence of concurrent coccidiosis and mycoplasmosis in chickens starting from 7 wk old in 50% of samples and with colibacillosis in 4 to 6 wk old in 43.33% of samples, while sole infection with coccidiosis was in 37.5% of samples. This indicated that concurrent coccidiosis significantly affects the productivity and health status of birds (Chanie et al., 2009).

PHYTOCHEMICAL (HERBAL) REMEDIES FOR AVIAN COCCIDIOSIS

Prolonged use of anticoccidial chemicals promotes drug resistance and results in tissue residues in chickens; therefore, a healthy anticoccidial treatment based on herbs is important.

Different phytochemical/herbal remedies and/or their extracts; bioactive compounds; specific anticoccidial properties and their effects exerted on poultry and the studied coccidian species are discussed in Table 2. In addition, different herbal mixtures and their bioactive compounds; specific anticoccidial properties and their effects on different coccidian species are also presented in Table 3.

CONCLUSION

In domestic fowl, each of the 7 *Eimeria* species developing inside the chick's digestive tract in a particular location inducing everything from subclinical enteric infection to subacute mortality. *Eimeria* species, strains and their infective dose, host genetics, flock size, environmental and stress factors, and concurrent infection could influence the clinical outcome of coccidial infection. Recently herbal products have received more attention for their use in prophylaxis or therapy for avian coccidiosis. Here, we summarized the research findings of phytochemical compounds, which showed preventive, therapeutic, or immuno-modulating effects against coccidiosis. These herbal treatments are characterized by the absence of coccidial resistance development (up till now).

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DISCLOSURES

Authors declare no conflict of interests.

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