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Intervention Strategies for Controlling Poultry Coccidiosis: Current Knowledge

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ABSTRACT

Poultry coccidiosis is considered one of the most important continuous threats that frustrates the poultry industry around the world and causes serious adverse effects on poultry productivity. Accordingly, this article comprehensively reviewed the recent control strategies that are applied against such disease regarding medication, vaccination, and application of some natural products. The causative agent of coccidiosis is a protozoon parasite of the genus *Eimeria*. This parasite is characterized by the host, different parts of the intestines, and immune specificity. Chicken is the most susceptible host to intestinal infections with *Eimeria* species. Diarrhea, loss of profitability, and intestinal lesions are the most characteristic clinical picture of *Eimeria* infection. Prevention and control of such infections remain a great problem. The application of hygienic measures is still the gold standard for the prevention of avian coccidiosis. Anticoccidials medication either in the feed or water can effectively reduce *Eimeria* infection, however, the development of drug resistance to the commonly used anticoccidial drugs is incessant. Live non-attenuated and attenuated as well as recombinant and sub-unit vaccines were developed with some limitations. Therefore, using some natural alternatives, such as probiotics, prebiotics, and phytobiotics have emerged as anticoccidial compounds.

Keywords: Chicken, *Eimeria*, Intestine, Natural products, Medication, Vaccination

INTRODUCTION

The poultry industry is regarded as one of the most important growing sectors of agriculture that contributes to the world's nutrition (Mottet and Tempio, 2017). However, this industry is exposed to many serious diseases that hamper and threaten the productivity of poultry among which coccidiosis disease can be named (Blake and Tomley, 2014).

Poultry coccidiosis is considered a devastating and problematic parasitic intestinal disease that causes severe economic losses in the poultry industry worldwide. Financial losses were estimated at 3 billion dollars annually, mainly due to the costs of medications and vaccinations, mortalities, and decreasing profitability in coccidiosis-affected birds (Noack et al., 2019). The life cycle of this parasite is complex and consists of an exogenous phase in the environment and an endogenous phase in the intestine of the birds. Diseased birds with coccidiosis showed mortalities, decreased feed efficiencies, growth retardation, and suppression of cell-mediated and humoral immunity (Chapman et al., 2013). In addition, coccidiosis is usually associated with a transient drop in egg production in layer chickens and increased susceptibility to some other disease outbreaks, such as necrotic enteritis in broiler chickens (Noack et al., 2019). Avian coccidiosis is an enteric infection that is caused by a protozoon parasite of the phylum Apicomplexa and genus *Eimeria*. Most domestic avian species, especially younger ones, can be infected with specific *Eimeria* species. Chickens are highly susceptible to seven species of *Eimeria* that vary in their pathogenicity and replication site of the intestine (Chapman, 2014). Different developmental stages of *Eimeria* life cycle penetrate the intestinal cells resulting in detrimental damage, inflammation, and hemorrhages (Lillehoj and Trout, 1996).

Owing to the drastic adverse effect of poultry coccidiosis on the global industry, different prophylactic and control measures have been deployed. Strict biosecurity and hygienic measures accompanied by using preventive medicaments are the first bedrock strategies against the infection (Godwin and Morgan, 2015). Using prophylactic and therapeutic anticoccidial drugs is the most common and traditional intervention for the prevention and control of avian coccidiosis (Snyder et al., 2021). Due to the continuous development of drug resistance and bans on using anticoccidial drugs, it becomes urgent to search for non-conventional and new alternatives to control such infection searching for new alternatives and nonconventional approaches to control this costly avian disease becomes an urgent demand (Adhikari et al., 2020). These approaches may include applying live virulent and attenuated as well as recombinant *Eimeria* species vaccines (Soutter et al., 2020; Snyder et al., 2021). Vaccination can be alternated with anticoccidial drugs in the feed within rotation programs and in combination with biosecurity measures. The utilization of some natural products, such as probiotics, prebiotics, and natural herbs with their extracts is also another safe and effective alternative for coccidiosis control (Awais et al., 2019; Gordillo Jaramillo et al., 2021; Tsiouris et al., 2021).

This review summarized the epizootiology and clinical picture of poultry coccidiosis, and comprehensively showed the recent control strategies that are applied against such disease regarding medication, vaccination, and application of some natural products.

Epizootiology and clinical picture

More than 1000 *Eimeria* species have been found to infect different hosts, including animals and birds (chickens, turkeys, ducks, geese, and pigeons, Blake, 2015). Seven *Eimeria* species, including *Eimeria (E) tenella*, *E. necatrix*, *E. brunetti*, *E. maxima*, *E. acervulina*, *E. mitis*, and *E. praecox*, have been recorded in chickens. Each species of *Eimeria* has a specific developmental site in each part of the intestine (upper, middle, and lower). Many *Eimeria* species can infect poultry without cross-immunity between them. All ages of chickens are susceptible to coccidial infection; however, the infection mostly begins at a younger age (older than one week) as the immune system is immature. Older birds are relatively resistant as a result of prior exposure to coccidiosis.

Infection with *Eimeria* species usually occurs through the oral ingestion of contaminated food, water, or litter that contains large quantities of infective sporulated oocysts (Gharekhani et al., 2014). Mechanical transmission of *Eimeria* oocysts from one house to another through wild birds, rodents, insects as well as contaminated boots and clothes of personnel, equipment, or dust was recorded (Belli et al., 2006).

Infected birds voided in their droppings a large number of non-sporulated oocysts. These oocysts require certain bad housing and management system with special environmental conditions, such as warm temperature (25-30°C), high humidity (40–80%), and aeration (oxygen) for sporulation (Mohammed and Sunday, 2015). Accordingly, coccidiosis is more rampant in the intensive deep litter system than other types of housings such as cages or battery systems. *Eimeria* oocysts have thick walls of lipid and protein, thus they are stable and resist mechanical and chemical destructive agents, harsh heat and cold as well as proteolytic degradation (Belli et al., 2006; Mai et al., 2009). It has been shown that sporulated oocysts can persist in the environment for more than 2 months, but non-sporulated ones can persist for 7 months in the caecum of the host (Quiroz-Castan˜eda and Danta´n-Gonza´lez, 2015). Temperatures above 35°C and below 0°C can be lethal for oocysts. It is so difficult to decontaminate previously oocysts-contaminated poultry houses.

Eimeria species have a self-limiting life cycle characterized by host and tissue specificity. This life cycle is complex and embraces sporogony, schizogony (merogony), and gametogony. After ingestion of tetrasporocystic-disporozoites sporulated oocysts, some physical and chemical agents are secreted in the proventriculus and gizzard that help release mature infectious sporozoites form sporocysts. Consequently, the sporozoites penetrate the intestinal epithelial cells using penetration proteins and form trophozoites and then schizonts during the schizogony (merogony) stage (Blake and Tomley, 2014). Merozoites enter the epithelium and continue this merogony stage 2-3 times for increasing the cell number of merozoites at the asexual stage of reproduction. Finally, merozoites are differentiated into male microgametes and female macrogametes sexually reproduced to form zygotes (non-sporulated oocysts) voided in the droppings of the infected birds. The complete life cycle of different *Eimeria* species may take about 4-7 days (Hammond, 1973).

The severity of the clinical picture of coccidiosis is dependent on the species of *Eimeria*, the number and pathogenicity of the ingested sporulated oocysts, the host's age and immunity along with the environmental management. Many species of *Eimeria* in chickens are of high pathogenicity, such as *E. tenella*, *E. necatrix*, *E. brunetti*, *E. acervulina*, and *E. maxima*, while *E. praecox* and *E. mitis* are of low pathogenicity (Jadhav et al., 2011). The small intestine and caecum are the target sites of *Eimeria* species that take 5-6 days incubation period till the appearance of signs. (Musa et al., 2010). Affected birds may show general signs of depression, huddling, and ruffling, reduced food intake, and watery-whitish or bloody diarrhea (Blake, 2015). Consequently, poor weight gain, dehydration, and death can occur. A sub-clinical form of coccidiosis is frequently observed without specific intestinal signs or lesions. It is often not detected but mostly results in poor feed conversion and reduced weight gain of the flock.

The inflammation or damage lesions caused by *Eimeria* species in different parts of the gut depend mainly on their degree of pathogenicity (Morris et al., 2007). These lesions include thickening of the intestinal wall, mucoid to bloody exudates, mucosal petechial to ecchymotic hemorrhages, necrosis, and hemorrhagic enteritis or typhlitis. Affected caecum may show the development of the caecal core. Secondary colonization by some bacteria, such as *Clostridium perfringens* (Helmbolt and Bryant, 1971), or *Salmonella typhimurium* (Baba et al., 1982), may be seen in the damaged intestines. Moreover, the severity of *Histomonas meleagridis* infection could be increased in case of coinfecion with *E. tenella* (Mcdougald and Hu, 2001). Accordingly, intestinal coccidiosis is difficult to be differentiated from other similar lesions of some diseases, such as necrotic enteritis, ulcerative enteritis, salmonellosis, and histomoniasis (Hafez, 2008). A coccidiosis 'break' indicates immunosuppression due to concomitant infection with immunosuppressive viral diseases which interferes with the development of immunity and aggravates coccidial infection (Mcdougald et al., 1979).

Applied control strategies

Management and hygienic measures

Application of management and hygienic measures is crucial for successful prophylaxis or even treatment of coccidiosis especially when drug-resistance strains of *Eimeria* are predominated. The management protocol includes all parameters that can keep good litter quality, such as appropriate installation and management of watering systems, provision of adequate feeding space, maintaining suitable stocking density, and supplying adequate ventilation. Birds should be separated from the environment and from other mechanical carriers of *Eimeria* such as rodents and insects. Restriction of traffic between farms is essential. It has been shown that ammonia gas produced from ammonium salt and sodium hydroxide is active in destructing *Eimeria* oocysts. Liquid or vapor forms of 5% ammonium hydroxide revealed high efficacy against *E. tenella* oocysts (Chroustova and Pinka, 1987). Disinfection with 37% formol and 12% sodium dodecylbenzene sulphonate or with calcium hydroxide and ammonium sulphate combinations are very efficient against *Eimeria* oocysts (Gumara˜es et al., 2007). Moreover, cresol compounds are also used as a good disinfectant against different stages of *Eimria* species (Daugschies et al., 2002).

However, it is believed that oocysts in the litter of birds are useful for the early establishment of immunity to avoid later outbreaks of coccidiosis (Allen and Fetterer, 2002). Therefore, cleaning and disinfection should be skipped under certain conditions to repopulate the litter with drug-sensitive *Eimeria* strains and to keep the survival of vaccine strains between vaccinated and non-vaccinated birds.

Reducing *Eimeria* infection of chickens can be achieved via reducing sporulation of oocysts in the environment, mainly through maintaining dry litter and keeping ventilation in houses (Etuk et al., 2004). Sanitary management of litter is a very important factor to control coccidial infection among consecutive flocks. In this regard, it is of utmost importance to completely remove contaminated litter after chicken marketing, and provide fresh and dry bedding before chick placement. However, different litter treatments reduce oocyst count and output. The used litter could be treated among flocks, and a small number of fresh shavings could be added (Coufal et al., 2006). Treatments including fermentation or addition of 800 g/m^2 calcium oxide to the litter efficiently reduced the count and sporulation of *Eimeria* oocysts (Beninca et al., 2021). In addition, poor management of litter can exacerbate coccidiosis, prevent the taking of a sufficient number of oocysts of the vaccines, and limit the cycling of oocysts (Attree et al., 2021). Managing litter moisture and house humidity are critical for sporulation of oocysts and eventually, the success of the vaccine through on-farm cycling (Williams, 2002).

Medication

The global mainstream agents used for controlling avian coccidiosis are anticoccidial drugs. Anticoccidials could be classified into synthetic or chemical compounds (such as sulphonamides, amprolium, amprolium ethopabate, nicarbazin, halofuginone, clopidol, robenidine, dinitolmide, pyridones, aprinocid, quinolone, methyl benzoquate, diclazuril, and toltrazuril) and polyether ionophorous compounds (ionophores; including narasin, lasalocid, bacitracin, maduramicin, semduramicin, virginiamycin, avilamycin, monensin, and salinomycin). They were effectively used in different combinations and concentrations for broiler and layer chickens as well as turkeys according to the manufacturer's instructions

(Shivaramaiah et al., 2014). The withdrawal period of these compounds varies from one to five days (Hafez, 2008).

Anticoccidial drugs target different developmental stages of the protozoon, such as the sporozoites or merozoites. Few anticoccidials show equal efficiency against all species of *Eimeria* (Mcdougald, 2003). The ideal anticoccidial drug should mostly affect all the developmental stages of *Eimeria* species, do not disturb the host's immune response, and has no tissue residues. Besides, it should permit a small leakage of the protozoon to enable the host to build up a degree of immunity. However, anticoccidials prevent treated chickens from building up natural immunity and some are not completely efficient to destroy all the developmental stages of the protozoon. Consequently, *Eimeria* species quickly became resistant to the used drugs leading to frequent severe disease outbreaks.

Synthetic anticoccidials

Synthetic anticoccidials are effective and commonly used in the field. Early successful treatment of coccidiosis was achieved after using low concentrations of sulphaquinoxaline in the feed (Delaplane et al., 1947). Sulfonamides have efficient coccidioststic and coccidiocidal activities (Li and Bu, 2014). In the protozoa, sulfonamides are the competitive antagonist of para-aminobenzoic acid, a precursor of folic acid, which is an essential coenzyme for the synthesis of deoxyribonucleic acid (Harfoush et al., 2010). Moreover, sulfonamides proved effective antibacterial potency, so they prevent secondary bacterial infections which often occur after coccidiosis (Yegani and Korver, 2008). A major side effect of sulphonamides is their narrow safety margin, which leads to intoxications, especially after treatment of coccidiosis outbreaks.

Nicarbazin was introduced to the USA in 1955 and it was extensively used in broilers production (Chapman, 1994). It acts by inhibition of succinate-linked NAD reduction in mitochondria and transhydrogenase and accumulation of Ca2 ions (Dougherty, 1974). Accordingly, it inhibits the first and second generations of the schizont of the parasites. However, it is not used for layer chickens due to its adverse effects on the egg quantity and quality.

Amprolium also acts by competitive inhibition of thiamine uptake and completely blocks the absorption of thiamine. It is efficacious against the first generation of schizogony and the gametogony where the demand for thiamine is at its highest (James, 1980) allowing the development of immunity (Reid, 1975). Ethopabate is often used in combination with amprolium to improve efficacy. Some studies compared the efficacy of using sulfonamides and amprolium and the results proved that both medicaments were efficient against *Eimeria* infection with variable degrees (Khan et al., 2021). Ethopabate and sulphonamides affect the second generation of schizonts.

Quinolone group includes buquinolate, decoquinate, and nequinate (benzoquate). At very low concentrations, these drugs acted by inhibition of *Eimeria* respiration through blocking the electron transport in their mitochondria (Wang, 1975) and also stopping the development of sporozoites (Reid, 1973). Similarly, the pyridone group contains meticlorpindol compound which inhibits electron transport in mitochondria of the protozoon.

Toltrazuril, a triazinetrione derivative is used in drinking water as a prophylactic and therapeutic medicament. It affects all intracellular schizogony and gametogenic stages of all *Eimeria* species in chickens (Shivaramaiah et al., 2014). Toltrazuril interferes with the nucleus division and the mitochondrial activity, which are responsible for the respiratory metabolism of the protozoon (Noack et al., 2019). Moreover, it destructs the so-called wall-forming bodies in the macrogamete and consequently induces vacuolization in all intracellular developmental stages. It produces cidal changes in the plastid-like organelles at multiple levels without impairment of natural immunity development (Hackstein et al., 1995). It has been found that toltrazuril treatment of mice induced reduction of some respiratory enzymes, such as nicotinamide adenine dinucleotide oxidase, succinate-cytochrome C reductase, succinate oxidase, and dihydroorotate-cytochrome C reductase (Harder and Haberkorn, 1989). Treatment of coccidiosis infected broiler chicks with toltrazuril induced improvement in feed intake, weight gain, and food conversion rate, besides reduction in oocyst number (Badrawy, 2012).

Diclazuril is also involved in the synthesis of nucleic acid and may affect the schizogony and gametogenic phase of the parasite (Verheyen et al., 1988). Moreover, the drug can affect the synthesis of the oocysts wall resulting in the formation of an abnormally thickened, incomplete oocyst wall as well as non-sporulated oocysts necrosis for some *Eimeria* species (Verheyen et al., 1989).

The exact mode of action of robenidine, a guanidine derivative, is not well known. But it can show inhibition of oxidative phosphorylation of mitochondria (Wong et al., 1972). Besides, a quinazolinone derivative, halofuginone, inhibits the first generation of the schizogony stage.

Ionophorous anticoccidials

In the 1970s, monensin was the first ionophore coccidiostats introduced to the poultry field, and as reported, it inhibits *Clostridium perfringens* associated with necrotizing enteritis (Martel et al., 2004). Salinomycin also showed antibacterial effects against coliforms, *Streptococci* (George et al., 1982), and *Salmonella typhimurium* (Ford et al., 1981). Ionophores disrupt ion gradient across the parasite cell membrane. Resistance to ionophores develops very slowly with a tendency to increase the level of tolerance and they have some influences on the intestinal microbial populations (Dibner and Richards, 2005). Marginal to the poor effect of different ionophores on many *Eimeria* species was reported (Mathis, 1999). However, it has been found that the combination of antibiotics and ionophores is likely responsible for lower mortality in the medicated flocks (Thabet et al., 2017; Kogut, 2019). Ionophores are incompatible with some antibiotics like erythromycin, chloramphenicol, and tiamulin, and some sulphonamides and antioxidants (Dowling, 1992). Despite ionophores may no longer be acceptable for use, they are still permitted for broilers in some European countries. In other countries, using prophylactic anticoccidial or antibacterial drugs is forbidden according to the legislation for “drug-free” broiler chickens (Gaucher et al., 2015).

Despite the acceptance and success of anticoccidials in managing coccidiosis in the poultry industry, there is great pressure to reduce their dependence for controlling such infection (Tsiouris et al., 2013). Not surprisingly, the widespread and continuous long-term use of anticoccidials, especially in feed, generates the development of resistant *Eimeria* strains against most of the commercially used products (Abbas et al., 2011). In addition, the accumulation of drug residues in the meat, eggs, and by-products of poultry induces an adverse effect on public health safety (Peek and Landman, 2011).

Application programs

There are different programs for applying anticoccidials. The continuous program means using the same anticoccidial drugs until the development of drug resistance problems or until the introduction of new drugs in the field. However, long exposure to the drug leads to loss of sensitivity, so it should be kept short if possible. A drug rotation program, with continuous monitoring of the oocysts in the droppings or the litter, is very crucial to avoid the cross-resistance between anticoccidial drugs. The rotation program involves changing the anticoccidial drug every 2 months or giving it for 2 fattening periods, and it is very effective if drugs with a different mode of action follow each other. The shuttle program uses two or more anticoccidial drugs during the grow-out period of the flock (ionophore/chemical). For instance, one drug is used for the starter phase, while another one is used during the grower and finisher phases. However, it should be taken into consideration the withdrawal period of the used drug during the finisher period. This program is also very important to prevent drug resistance development. Changing the anticoccidial drug at each restocking in one operation is termed a switch system.

The resistance to anticoccidial medicaments is detected by the anticoccidial index method (Jeffers, 1974). This index depends on the detection of the survival and the relative weight gain percentages, the lesion score, and the oocyst count along with the pathological, parasitological, and production traits (McManus et al., 1968). However, the difference in weight between day 0 and day 7 after *Eimeria* challenge and then subtracted the average score of dropping abnormality (0-4), divided by 10 is another evaluation criteria (Jeffers, 1974). Besides, the former protocol was modified and assigned as a cut-off for drug sensitivity (Chapman and Shirley, 1989).

Application of less intensive rotation and shuttle programs and incorporating other methods in disease prevention, such as vaccination, especially in broiler breeders, or using natural products are promising to reduce the development of anticoccidial drug resistance.

Vaccination

Searching for alternative strategies to prevent coccidiosis is increasing as a result of the rapid development of anticoccidial drug resistance, the deficiency of new anticoccidials, the sensitivity of turkeys to ionophore toxicity, and the trend toward reducing using antibiotics in feed (Hafez, 2008). Vaccines against coccidiosis were not developed in the poultry industry till the 1960s. Now, the development and the use of these vaccines as well as the knowledge about the induced immunity in the vaccinated host are increasing (Williams, 2002).

Live vaccines against coccidiosis are given to the birds for the stimulation of immunity to the specific *Eimeria* species present in the vaccine (Price et al., 2015). This immune response can be achieved after trickle infection of birds with either a single high dose or multiple low doses of *Eimeria* species vaccine (Long et al., 1986). It is very important to withdraw the anticoccidial drugs from the feed before vaccination with a drug-sensitive live vaccine to avoid vaccination failure.

The available vaccines contain live *E. acervulina*, *E. maxima*, *E. tenella*, *E. necatrix*, *E. brunetti*, *E. mitis*, and *E. praecox* oocysts. Recycling of oocysts present in these vaccines through litter reinfection is essential for the development of the flock's immunity (Price et al., 2016). Therefore, the application of live vaccines in layer chickens is difficult. Moreover, live vaccines may revert to their virulence by repeated fecal-oral recycling in the susceptible host and cause severe clinical picture of coccidiosis with high mortalities (Williams, 2002).

Live non-attenuated vaccines

In 1950, the first generation of the live wild-type (non-attenuated, virulent) vaccine containing sporulated *E. tenella* oocysts was developed. It has been used in the USA and other countries for many years. Coccivac® vaccine is regarded as the first commercially available type of virulent vaccine. Variants (Coccivac-B and Coccivac-D) types are different mixtures of *Eimeria* species; while type "T" is used for turkeys and was introduced in the 1970s (Milbradt et al., 2014). Furthermore, Immucox® and Immuncox – T® were developed in Canada and have been used. Other live non-attenuated vaccines such as CoxATM®, Advent ™, and Inovocox™ have been developed recently. It has been found that CoxATM® contains a mixture of wild-type *Eimeria* species and it is relatively tolerant to anti-coccidial ionophores (Vermeulen et al., 2001). Moreover, Advent™ has more viable sporulated oocysts than other vaccines, while Inovocox™ is used *in ovo*. Live virulent vaccines give a specific immunity to the homologous *Eimeria* strain that is present in the vaccine after repeated administration in low doses. There is little or no immune protection against infection with a heterologous or different *Eimeria* species, and even infection with a different strain of the same species can escape immune protection (Blake et al., 2011). Nevertheless, by the time, other *Eimeria* species oocysts were incorporated in these vaccines to give broad-spectrum immune response (Williams, 2002). These live virulent vaccines are administrated as a direct spray for day-old chicks in the hatchery, spraying of feed, or in the drinking water in an edible gel (Jenkins et al., 2013). Strict application protocol should be applied (Chapman et al., 2002). In order to diminish the risk of coccidiosis outbreaks following vaccination, attenuated vaccines have been developed. However, the uniform up-taking and distribution of oocysts is not always obtained. Application of chemical anticoccidials after vaccination was recommended to decrease the possibility of disease outbreak after vaccination pressure and control the inherent pathogenicity of the parasites (Quiroz-Castan˜eda and Danta´n-Gonza´lez, 2015).

Live attenuated vaccines

As a result of the disadvantages of live virulent vaccines, the second generation of vaccines using live attenuated lines of *Eimeria* oocysts named precocious development has been developed at the end of the 1980s (Shirley and Bednrik, 1997). Precocious *Eimeria* strains mean those lines with a shortened prepatent period of the endogenous life cycle due to the lack of one or more secondary schizogony stages, compared to strains with the normal life cycles (Mathis et al., 2017). As a result of the disappearance of the last generations of schizogony, the number of schizogony generations is decreased, and consequently, the number of the produced oocysts is reduced and the immunizing potential is maintained (McDonald et al., 1986). This vaccine was introduced commercially in the European Union as Paracox® and Livacox® products. This attenuation can be achieved by serial passages of the protozoon in chicken embryos. Attenuated vaccines contain a mixture of different sporulated oocysts of *Eimeria* species. It has been shown that most attenuated lines notably highly pathogenic species of *E. brunetti* and *E. necatrix* were less fecund than their wild-type equals (Shirley et al., 1986). The attenuated anticoccidial vaccine is given orally like a live virulent type. Although these precocious lines of live vaccines displayed low pathogenicity, they maintained some immunogenicity (McDonald and Ballingall, 1983) which called for their use with adjuvants (Ahmad et al., 2016).

Recombinant vaccines

The demand for the development of recombinant or sub-unit vaccines emerges (Blake et al., 2017). Recombinant vaccines against coccidiosis include different *Eimeria* species antigens which have immunogenic properties to stimulate the effective immune response. There are different studies regarding the use of this type of vaccine for controlling chickens coccidiosis (Yin et al., 2015). The recombinant vaccine is highly appreciated as it gives protection against many *Eimeria* species. However, the genetic diversity of antigens present in recombinant vaccines and the ineffectiveness of the vaccine to compete for co-infection of *Eimeria* species have led to different modifications of it. Accordingly, sub-unit vaccines emerged. Subunit vaccines comprise purified antigenic determinants obtained from *Eimeria* species. They rely on DNA recombinant techniques and contain protective antigens or recombinant proteins of different stages of *Eimeria* life cycle (sporozoites, merozoites, and gametes). The native antigens are micronemes, rhoptries, or refractile bodies of *Eimeria*. A sub-unit vaccine, such as CoxAbic®, has been prepared from purified native protein isolated from the gametocyte of *E. maxima* (Wallach et al., 1995). Although this vaccine inhibits oocytes development, it provided only 53% protection against *Eimeria* challenge (Sharman et al., 2010). Lal et al. (2009) showed that the specific proteins of *E. tenella* oocysts, sporozoite, and second-generation merozoite in each stage and many other proteins were shared in all stages. During the invasion of the protozoon, RON2 and RON5 proteins are expressed and may have a role in the host adhesion during the invasion process. *In silico* analysis was useful to detect epitopes from the sporozoites and merozoites as different epitope mapping of T-cell mediated antigenic determinants (Ahmad et al., 2016). Finger and Michael (2005) reported that intramuscular twice vaccination of broiler breeder chickens with sub-unit *E. tenella* vaccine provided maternal antibodies to the offspring and the developed immunity to *Eimeria* species has been demonstrated with *E. acervulina*, *E. tenella*, *E. maxima*, and *E. mitis*. Multivalent T-cell epitopes of *E. tenella*, *E. necatrix*, *E. acervulina*, and *E. maxima* vaccines were effective in improving the body weight gain, decreasing lesion scores and oocysts shedding, and increasing the anti-coccidial index (Song et al., 2015a). Moreover, multivalent sub-unit vaccine that included recombinant antigens from the previous *Eimeria* species has been shown partial protection against the disease caused by these species (Song et al., 2015b). Up to now, recombinant or sub-unit vaccines show limited potentiality as no antigen can induce a potent protective immune response against *Eimeria* infection. In addition, more immunological studies are required to investigate the host-parasite interactions at the molecular and cellular levels. In the future, a good knowledge of the proteome of *E. tenella* genome can allow the preparation of potential immunogens (Reid et al., 2014).

Anticoccidiosis vaccines have been used commercially in European Union since the 1990s, especially for breeder and layer flocks, followed by their use for broilers chickens (FEFAC, 2007).

Vaccines can replace drug-resistant field *Eimeria* strains with drug-sensitive vaccine strains. This is observed in the renovation of sensitivity to some ionophores (such as salinomycin and monensin) and synthetic chemicals like diclazuril. Nowadays, the rotation of vaccines with conventional anticoccidial drugs is used. For instance, chemical anticoccidials that are used to a single cycle of the flock can effectively reduce the oocysts load, and then in the following cycles, vaccines are used to repopulate the flock with anticoccidial-sensitive oocysts, which are highly sensitive to the chemicals and ionophores programs. Ionophores could be used after the vaccination cycles in the vaccine-repopulated flock. The addition of essential oils to the diet enhanced the productive performance of anti-coccidiosis-vaccinated broiler chickens (Lee et al., 2020).

Assessment of anticoccidial vaccines

The ideal anticoccidial vaccine should be safe, stable, easy to administer and it should also indicate the rapid onset of immunity particularly for broiler chickens, and long duration of immunity, especially in layers. Assessment of anticoccidial vaccine efficacy is based on the measurement of different evaluation criteria. These criteria include reduction of the clinical disease picture and the intestinal lesion score (Johnson and Reid, 1970), improving the weight gain, growth rate, and egg production (Williams and Catchpole, 2000), as well as decreasing the oocysts count in the droppings or litter (Hamzic et al., 2015). A quantitative polymerase chain reaction (PCR) has been developed to quantify the oocyst counts and the number of *Eimeria* genomes in the tissue's samples (Vrba et al., 2010). Deep sequencing or *Eimeria* species 18S rDNA PCR amplicons is also a highly sensitive recent technique for the detection of the parasite (Hinsu et al., 2018). Some studies have used the anticoccidial index as a means of evaluating the vaccine efficacy with different cut-off values (Zhai et al., 2016). Evaluation of the immune response to the tested anticoccidial vaccine faces some difficulties as the protozoon of *Eimeria* is an intracellular parasite and the production of antibodies is not a reliable correlate of protection against coccidiosis (Lillehoj and Ruff, 1987). Although the level of circulating *Eimeria* species-specific immunoglobulin Ig (Y), IgM, and IgA were serologically detected (Gilbert et al., 1988). *Eimeria* infection depends mainly on the stimulation of cell-mediated immunity, so measuring this type of immune response to anticoccidial vaccines is more important than measuring humoral immunity.

In ovo vaccination

Nowadays, advanced industrial technologies regarding vaccine deliveries have been developed in poultry production systems (Saeed et al., 2019; Attree et al., 2021). The *in ovo* application of vaccines is applied against several diseases of poultry including coccidiosis (Saeed et al., 2019). Vaccines are inoculated into 18-days-old embryos in the hatchery. This technique is attractive for the mass administration of *Eimeria* vaccines (Watkins et al., 1995). Such approach for vaccines application shows many advantages including early protection of chickens with minimal interference with maternal antibodies, accurate pre-hatch vaccine delivery before exposure to environmental challenge, stimulation of innate and adaptive immunity, reduction of bird's stress, and improvement of bird's health (Sundar et al., 2016). Early age protection against certain *Eimeria* species can be achieved via *in ovo* application of a single dose of live vaccine containing oocysts of *E. acervulina*, *E. tenella*, and *E. maxima* (Inovocox™) (Dalloul and Lillehoj, 2006). Injection of the later vaccine *in ovo* induced significant positive effect on the hatchability and the hatched chick quality (Sokale et al., 2016) as well as improved the growth performance parameters and reduced the mortalities in hatched broiler chickens (Sokale et al., 2017). Moreover, *in ovo* inoculation of recombinant proteins and cytokine adjuvants conferred protection against *E. tenella* and *E. acervulina* (Lillehoj et al., 2005) and *E. maxima* (Lee et al., 2010). *In ovo* vaccination with EtMIC2 recombinant gene of *E. tenella* was found to stimulate the intestinal protective immunity against this infection (Ding et al., 2005).

Limitations of anticoccidial vaccines.

Vaccination against coccidiosis in chickens shows several limitations and obstacles, such as high production costs, time-consuming, adverse effects on feed efficiency and body weight gain, and the possibility of the insufficient immune response or clinical coccidiosis as a result of dosage errors (Dalloul and Lillehoj, 2006). The genomic studies of *Eimeria* species especially *E. tenella* have indicated a wide antigenic variability that leads to the rapid development of vaccine resistance. Besides, production of either live virulent or attenuated anticoccidial vaccines is limited by some factors, including the need for chickens' infection to produce oocysts, quality control tests for ensuring vaccine safety, short shelf life time of the vaccines, loss of infectivity with time affecting their expiry, and the need for cold environment condition for storage. Another point of concern is the reversal of virulence of coccidiosis live vaccines. The inaccurate addition of anticoccidial medicaments to the feed hinders effective vaccination of drug-sensitive strains and vaccination of diseased birds. However, stoppage of oocysts production following vaccine challenge is very critical to obtain sterile immunity and prevent vaccine resistance (Blake et al., 2017).

Natural controlling

As a result of raised awareness and demand of consumers for chemical-free animal products, the necessity to find more acceptable, and more environmentally friendly natural compounds alternatives against avian coccidiosis have been increased (Bozkurt et al., 2013). Some of these natural alternatives are probiotics, prebiotics, and phytobiotics (phytogenics or botanicals). These natural alternatives are applied in the feed or water or recently inoculated *in ovo* during embryogenesis (Saeed et al., 2019).

Probiotics

Probiotics refer to beneficial bacteria or even yeast that are mostly used in the feed to improve the immune system and decrease the bacterial intestinal pathogens load. The effect of different types of probiotics on *Eimeria* species infection of poultry is summarized in Table 1. *Lactobacillus*-based probiotic reduced the shedding of oocysts and increased T and B cell specific cytokines against *E. avervulina* infection (Dalloul et al., 2005). Similarly, *Pediococcus* and *Saccharomyces*-based probiotics revealed improving in performance parameters after a challenge with *E. tenella* and *E. acervulina* (Lee et al., 2007). In addition, *Saccharomyces* and *Lactobacillus*-based probiotics can enhance the immune response and performance parameters after a challenge with *Eimeria* in broiler chickens (Awais et al., 2019). Probiotics composed of *Bifidobacterium animalis* and *Lactobacillus salivarius* alleviate the damaging effects of *Eimeria i*nfection but enhance the performance parameters of infected chickens (Ritzi et al., 2014). Furthermore, single or mixed combinations of probiotics could reduce coccidiosis lesion scores. Exogenous enzymes combined with probiotics containing *Bacillus* species reduced the intestinal damage and performance loss caused by *Eimeria* challenge (Dersjant-Li et al., 2016). The combined effect of the probiotics with the vaccines, anticoccidials, or even with the plant extracts have also been demonstrated with successful results (Chen et al., 2016; Wang et al., 2019).

Table 1. The effect of different types of probiotics on *Eimeria* infections in poultry

Probiotic bacteria	Anticoccidial action	Reference
A mixture of lactic acid bacteria (*Lactobacillus* species)	*Lacto-bacillus* species treatment could enhance intestinal health and integrity, feed digestion and absorption, and body weight gain as a result of the competitive exclusion against *Eimeria* species.	Behnamifar et al. (2019)
	These bacteria improve the permeability of the intestinal cells, regulate the mucosal barrier by mucin in the intestinal wall, promote the balance of gut microbiota, increase nutrient utilization, and thus hinder the intestinal colonization and invasion of protozoon.	Royan (2019)
	Eimeria species adhere to the intestinal cell surface receptors. However, lactic acid bacteria absorb receptors in the epithelial cells, compete for the parasite and prevent its intestinal invasion. This attachment hampers the perforation of sporozoites into the intestinal mucosa, resulting in reduced proliferation and consequently oocyst shedding.	Alagawany et al. (2018)
	Competitive exclusion of the parasites at the attachment receptor sites, lactic acid bacteria co-aggregate with the parasite and produce some antimicrobials such as lactic acid, hydrogen peroxide, and bacteriocins which stimulate the immune system.	Jarujareet et al. (2018)
	The growth-promoting effect of *Lactobacillus*-based probiotics in *Eimeria*-infected chickens is owing to the enhancement of both cellular and humoral immune responses that restrict the gut invasion with the parasite. *Lactobacillus*-based probiotics produce cytokines (IL-2, IL-6, and IFN-c) and local (mucosal) immunoglobulin Ig (A), which are important for challenging coccidiosis. Cytokines are a natural protein that is essential for stimulation and regulation of immunity as well as hindering siderophores secretion and restricting iron availability to facilitate parasite invasion.	Khan et al. (2019)
Bacillus cereus	• It competes with the parasite via improving the ability of beneficial bacteria to adhere to the gut epithelium and occupy most of the cell receptors, and accordingly inhibit the parasite's growth. • This species helps in the digestion of indigestible fibers and releasing of some substances like butyrate and fatty acids, which are essential for extra nutrients and energy. • It is also essential for stimulating the proliferation of the intestinal epithelium.	Leung et al. (2018)
	It enhances the host immune response via the regulation of T-helper cells that provides protection against *Eimeria* challenge.	Gu et al. (2019)
Bacillus subtilis	It modifies the composition of the gut microbiota, improves the growth performance and nutrient digestion via increasing the number of *Bacteroidetes* and other normal inhabitant bacteria in broilers. Besides, it lowers the bacterial diversity in the caecum via changing microbial communities and increasing predominant species.	Erdoğmus et al. (2019)
	It enhances the host immune response via the regulation of T-helper cells that provide protection against *Eimeria* challenge.	Wang et al. (2019)
Enterococcus faecium	• *Enterococcus faecium* could increase the number of beneficial intestinal microflora and modulate their composition. • In addition, it has an immunomodulatory effect in chickens after infection with *Eimeria* species through increasing the production of anti-inflammatory cytokines and other immune mediators such as IL-1b, IL-6, IL-10, and IFN-c, which leads to reducing of the severity of the intestinal lesions.	Wu et al. (2019)
Pediococcus	*Pediococcus* alone and/or combination *Saccharomyces* increase the immune response against *E. acervulina* and *E. tenella*, with protection against growth retardation and oocyst shedding.	Lee et al. (2007)

Prebiotics

Prebiotics are non-digestible feed ingredients that enhance the growth of probiotics and their activities in the gut of birds (Bindels et al., 2015). Mannan oligosaccharides, fructooligosaccharides, β-glucans, arabinoxylooligosaccharides, soy oligosaccharides, isomatooligosaccharides, inulin, and pyrodextrins are the common types of prebiotics that used in the poultry industry (Nopvichai et al., 2019; Ocejo et al., 2019). Dietary addition of mannan oligosaccharides originated from the cell wall of *Saccharomyces cerevisiae* (yeast) that can reduce the severity of *E. tenella* (Elmusharaf et al., 2006), and *E. acervulina* infections in the challenged birds (Elmusharaf et al., 2007). Prebiotics may have similar anticoccidial mechanisms to probiotics. They suppress coccidiosis probably through indirect regulation of increased probiotics and host immunity. Prebiotics mediated the immune response owing to their interaction with gut immune cells. Furthermore, they enhance gut colonization with probiotics and their products that interact with immune cells and consequently suppress pathogens (Sugiharto, 2014). The host can produce bacteriocins and other immunomodulators that stimulate macrophages to neutralize the pathogens (Alloui et al., 2013). Bozkurt et al. (2014) demonstrated that prebiotics can diminish the coccidial infection in chickens but reserve oocyst production that might act as a source of a live vaccine for non-infected birds.

Phytobiotics

Products that are produced or extracted from plants, essential oils, or oleoresins could be defined as phytobiotics (Gadde et al., 2017; Mohammadi Gheisar and Kim, 2017; Skoufos et al., 2020). Herbs produce a variety of phytochemicals as alkaloids, phenolics, polysaccharides, polyacetylenes, ethanol, petroleum, ether and acetone extracts, terpenoids, ground powder, essential oils, and other large numbers of bioactivities (Blake and Tomley, 2014). Phytobiotics proved their strong coccidiostatic and coccciocidal efficacy in terms of a significant reduction in birds' mortalities, intestinal lesions, and improvement of the performance (Habibi et al., 2016). Phytobiotics exert a wide range of beneficial actions as alternative natural anticoccidial preparations. They increase the digestive secretions and food intake, maintain the gut health, stimulate the immune response, as well as they have growth-promoting, antimicrobial, antiinflammatory, and antioxidant properties (Jitviriyanon et al., 2016; Giannenas et al., 2018; Zhai et al., 2018). Production of superoxide dismutase enzyme by phytobiotics enhances their antioxidant activity. (Idris et al., 2017) and mitigation of Alpha-1-acid glycoprotein level which is a moderate acute-phase protein that is secreted from the hepatocytes in response to *Eimeria* infection (O'Reilly et al., 2018; Gordillo Jaramillo et al., 2021). Increasing the levels of phenolic compounds in chicken meat is associated with the strong antioxidant capacity (Ramos et al., 2017). There are about 68 herbs and phytocompounds with proven suppression of *Eimeria* species that have been demonstrated. Table 2 illustrates the commonly used phytobiotics and their action against *Eimeria* species infection in poultry.

The *in vitro* activity of a mixture of carvacrol, curcumin, and *Echinacea purpurea* extract showed inhibition of the invasion of epithelial cells by *E. tenella* sporozoites (Burt et al., 2013). The efficacy of garlic active principle (allicin) *E. tenella* sporozoites showed successful inhibition of the protozoon *in vitro* (Alnassan et al., 2015). Besides, a mixture of thymol, carvacrol, and saponins has a strong *in vitro* anticoccidial effect (Felici et al., 2020). A recent study by Sidiropoulou et al. (2020) revealed an anticoccidial activity of oregano and garlic essential oils *in vitro*.

Furthermore, combined phytochemicals supplementation can boost the anticoccidial effects in birds, compared to the time they are administered alone (Felici et al., 2020; Sidiropoulou et al., 2020). For example, the addition of mixed herbs of *Holarrhena antidysenterica*, *Berberis aristata*, *Syzygium aromaticum*, *Polygonum aviculare*, and *Allium sativum* to the diet of broiler chickens protected birds from *E. tenella*, *E. maxima*, and *E. acervulina* infection through enhancement of intestinal microbiome and increasing the number of *Bacillales* and *Lactobacillales* (Tsiouris et al., 2021).

The meat quality of broiler chickens is affected by challenges with *Eimeria* (Chodová et al., 2018). However, dietary supplementation of broilers with phytobiotics may improve the carcass trait after exposure to coccidiosis (Tauer et al., 2019).

Regardless of the phytobiotics success against coccidiosis, the little understanding about their mode of actions as well as their safety and toxicity make limitations in their field usage.

Advanced industrial technologies

Some modifications in the physical cage environment during brooding of pullets could be applied (Price et al., 2013). A mesh floor consists of a thick paper of fiber trays made of egg carton material that could be put over a portion (40%) of the cage floor. This method reduces the possibility of oocysts multiplication on the floor. In addition, modification a manure belt to rotate and go through a scraping area where manure is scraped off the belt into a manure disposal area. Moreover, regular checking of litter moisture contents and controlling of environmental humidity surrounding chickens are critical preventive measures.

Understanding the genetic markers of *Eimeria* species is very essential to detect susceptibility, tolerance, and resistance traits. Such an approach has a great impact on the breeding decisions which help the control of coccidiosis in the future (Boulton et al., 2018). For instance, the susceptibility to *E. tenella* challenge varies according to breeds, where Egyptian Fayoumi breeds are highly resistant but White Leghorn breeding lines are susceptible (Pinard-van der Laan et al., 2009).

Table 2. The effect of different types of phytobiotics on *Eimeria* species infection of poultry

Phytobiotic	Active compound	Anticoccidial action	Reference
Artemisia annua *Artemisia sieberi*	Artemisinin Phytochemicals, flavonoids, and phenols	• Directly, artemisinin degenerates the iron-peroxide complex and generates reactive oxygen species which directly inhibits sporulation and cell wall formation in *Eimeria* species, leading to an intervention in the life cycle of the parasite and reduction of the lesion score. • Moreover, artemisinin has an adverse effect on the gametocyte of *E. tenella* through limiting of sarcoplasmic-endoplasmic reticulum calcium ATPase enzyme expression. • Indirectly, other compounds of the plant establish the growth of other beneficial intestinal microflora that improve the digestion and absorption of food as well as they enhance the immune response.	Jiao et al. (2018)
Garlic (*Allium sativum*)	Allicin Sulfur Propyl thiosulfinate Propyl thiosulfinate oxide	• Allicin and sulfur induce alterations in broiler intestinal microbiota and have antioxidant activity against *Eimeria* oocysts in broiler chickens. • They inhibit the sporulation of *E. tenella* effectively *in vitro*. Also, they improve the growth performance and intestinal microbiota, and decrease the clinical picture and the fecal oocyst output of *Eimeria in vivo*. • The highest capacity of the intestinal villi and crypts was reported after dietary supplementation of *Eimeria* infected broilers with garlic.	Ali et al. (2019)
		Dietary supplementation of *Eimeria* infected broilers with a combination of garlic and ginger (*Zingiber officinale*) improved the intestinal morphology and the integrity as well as the mucosal architecture in terms of increasing villus height and decreasing crypt depth.	Majed et al. (2019)
		Propyl thiosulfinate and propyl thiosulfinate oxide modify the expression levels of 1,227 transcripts related to intestinal intraepithelial lymphocytes in chickens. Besides, they activate NF-κB transcription factor that plays an important role in the regulation of immune response after infection. Accordingly, these compounds increase the resistance to *Eimeria* species infections by boosting the humoral immunity or stimulating splenocyte proliferation which directly leads to the destruction of sporozoites.	Hussein et al. (2021)
Curcuma longa (turmeric)	Curcumin (Diferuloylmethane)	• Curcumin has a strong anticoccidial activity via destructing of sporozoites, the interference with *Eimeria* life cycle, enhancing the host humoral immunity, and maintaining gut integrity. • In addition, it affects the microbial population by increasing the abundance of *Lactobacilli* and reducing the population of Selenihalanaerobacter in the chickens' gut.	Yadav and Jha (2019)
		Curcumin has antioxidative characters through inhibition of nitic oxide induction by macrophages stimulated with lipopolysaccharide and interferon. Nitic oxide may promote the development of *Eimeria* lesions.	Lee et al. (2020)
Oregano (*Origanum vulgare*)	Essential oils Carvacrol Thymol Eugenol	• These compounds interfere with the life cycle of *Eimeria* species by destroying sporozoite membrane, decreasing the number of oocysts in the litter, increasing the growth performance and intestinal barrier function, as well as altering the gut physiology. • Moreover, they increase the volatile fatty acids concentration in the caecum following the challenge with coccidiosis vaccine in broilers.	Pop et al. (2019)
		These compounds enhance the carcass traits of broiler chickens after exposure to coccidiosis.	Tauer et al. (2019)
Bidens pilosa	Polyacetylene Flavonoid	• The anticoccidial action of *Bidens pilosa* is related to the presence of some phytochemicals, such as 70 aliphatics, 60 flavonoids, 25 terpenoids, 19 phenylpropanoids, 13 aromatics, 8 porphyrins, and 6 other compounds. • Polyacetylenes and flavonoids showed anti-parasitic effects via disruption of the life cycle of *Eimeria* and enhances T-cell mediated immunity.	Yang et al. (2019)
		The plant exhibits anticoccidial activity in chickens infected with *E. tenella* as demonstrated by reduction of mortalities, oocyst count, and intestinal lesions, increasing body weight and gut microflora, and improving the intestinal villus to crypt ratio.	Chen et al. (2020)
Aloe vera *Aloe excelsa*	Acemannan	The polysaccharide acemannan has an immunomodulatory effect through binding with mannose receptor on macrophages, stimulating cells for production of some inflammatory cytokines like IL-1 through IL-6 and TNF-α and finally inhibiting *Eimeria* infection.	Akhtar et al. (2012)
		Treatment with Aloe vera showed increased weight gain and decreasing droppings oocyst count of infected chickens.	Babak and Nahashon (2014)
Cinnamon (*Cinnamomum zeylanicum*)	Cinnamaldehyde Acids Numerous essential oils	It improves chicken growth performance and alters caecal microbiota composition.	Yang et al. (2020)
		Cinnamaldehyde and Oleoresins (Capsicum and Turmeric) can regulate host innate immunity against *Eimeria* species in chickens by enhancing and elevation of T helper cells and cytokines (FN-c and IL-6) and body weight gain.	Lee et al. (2011)

Beet (*Beta vulgaris*)	Betaine	• Betaine stabilizes and protects the metabolism of the intestinal epithelial cells in which *Eimeria* species multiply. • It can protect cells against the stress of osmosis via stabilization of cell membranes and enabling osmotic pressure maintenance in the intestinal cells with normal metabolic activity. • It affects the developing stages of *Eimeria*. Betaine and/or combination with salinomycin inhibited the invasion of sporozoites and the second generation schizonts for *E. acervulina* and *E. tenella*. • Betaine increases the lymphocytes and phagocytes in the intestine of *Eimeria*-infected chickens. • The palliative effect of betaine on the coccidiosis appeared as an improvement of weight gain and feed efficiency.	Klasing et al. (2002)
Wheat bran (*Triticum aestivum*) Sugar Cane (*Saccharum officinarum*)	Arabinoxylans	Arabinoxylans protect chickens against *Eimeria* infection through stimulation of natural (adaptive) cell-mediated immune response. This protection was indicated by improving body weight gain and diminishing oocyst shedding, intestinal lesion score, and anticoccidial indices.	Awais and Akhtar (2012)
Pine tree (*Pinus radiata*)	Tannins	Concentrated tannins penetrate *Eimeria* oocyst wall and damage the cytoplasm through the inactivation of endogenous enzymes responsible for the sporulation of the oocyst. Accordingly, abnormal shapes of sporocysts and inhibition of the life cycle of *E. tenella*, *E. maxima*, and *E. acervulina* can occur.	Molan et al. (2009)
Green tea (*Camellia sinensis*)	Selenium and polyphenols	They inactivate the enzymes responsible for *Eimeria* oocyst sporulation.	Molan and Faraj (2015)
Carica papaya	Papain	• Papain may have a proteolytic destructive activity against *Eimeria*. • It has an inflammatory suppression by vitamin A.	Nghonjuyi et al. (2015)
Olive tree (*Olea europaea*)	Maslinic acid	Maslinic acid was found to reduce the lesion, the oocyst, and the anticoccidial indices in *Eimeria* infected chickens. Its mechanism as an anticoccidial plant extract is well not known.	De Pablos et al. (2010)
Guar bean (*Cyamopsis tetragonoloba*)	Saponins	Saponins could bind with sterol molecules of the parasite cell membrane and lyse oocysts.	Hassan et al. (2008)
Grape seed	Proanthocyanidin	• Proanthocyanidin has polyphenolic antioxidant character. It alleviates coccidiosis by downregulation of oxidative stress via increasing the superoxide dismutases in the host blood and decreasing the nitric oxide. • It has been shown that grape seed proanthocyanidin reduced *E. tenella* infection in terms of improvement of the intestinal pathology, and body weight, and reduced mortality in broiler chickens.	Wang et al. (2008)
Berberis lyceum *Linum usitatissimum* *Ageratum conyzoides* *Vernonia amygdalina*	Berberine	Berberine inhibits *E. tenella* sporozoites by induction of oxidative stress. The later causes the imbalance of oxidant or antioxidant species in the host which is often seen in coccidiosis. Once *Eimeria* sporozoites invade the intestinal epithelial cells of the host, the reactive nitrogen species and the reactive oxygen species are produced, leading to the death of non-sporulated oocysts.	Nweze and Obiwulu (2009)
Tremella fuciformis *Astragalus membranaceus Radix* *Carthamus tinctorius* *Lentinus edodes*	Polysaccharides	• Polysaccharides augment the anticoccidial antibodies and antigen-specific splenocytes proliferation in splenocytes through cell-mediated and humoral immunity against coccidiosis. • Besides, polysaccharides stimulate lymphocytes proliferation through the regulation of DNA polymerase activity. • Polysaccharides treated vaccinated birds showed better growth and lower *Eimeria* oocysts count when compared to non-treated vaccinated ones.	Guo et al. (2005)
A mixture of cinnamaldehyde, carvacrol, *Capsicum Oleoresin*, and *Turmeric Oleoresin*		This mixture exhibits immuno-stimulatory activity through increasing in NK cells, macrophages, CD4+ T cells, CD8+ T cells, and their cytokines (IFN-γ and IL-6) and decreasing in TNFSF15 and IL-17F, leading to the destruction of *E. tenella* in chickens.	Lee et al. (2011)
Oriental Plum fruit (*Prunus salicina*)	Phenols	Phenols significantly increased the transcription of IFN-γ and IL-15 and splenocyte proliferation, resulting in enhancing immunity against coccidiosis. Dietary addition of it to chickens feed significantly reduced *E. acervulina* infection in chickens in terms of increased body weight gain and reduced fecal oocyst shedding.	Lee et al. (2008)
Mushroom (*Fomitella fraxinea*)	Lectins	• Lectins boost both cellular and humoral immune responses of chickens against coccidiosis and other infectious pathogens and toxins. Besides, it enhances the growth performance parameters. • When inoculated lectins in 18-day-old embryos can protect week-old chicks after *Eimeria* challenge against weight loss with a reduction in oocysts shedding compared to untreated embryos.	Dalloul et al. (2006)
Dichroa febrifuga	Febrifugine (alkaloid) Halogenated derivative of Febrifugine "Halofuginone"	Febrifugine is a strong anti-coocidal chemical and proved its efficacy against *E. tenella* infection in chickens.	Zhang et al. (2012)
Areca Nut *(Areca Catechu)*	Arecoline Guvacine (Alkaloids)	It enhances immunity through the production of IL-2 and reduces the caecal lesion scores.	Wang et al. (2018)

Emblica officinalis *Echinacea purpurea*	Tannins and chicoric acid	• Tannins and chicoric acid promote the humoral immune response in chickens against coccidiosis. The mechanism of boosting the immune response is not well known. • The weight gain and lesions enhanced after a mixed infection with different *Eimeria* species.	Kaleem et al. (2014)
Coal tar	Gentian violet	Gentian violet reduced *Eimeria* lesion score lesion scores and improved the weight gain in infected birds, especially in combination with anticoccidial drugs.	Sharkey (1998)
Citric extracts	Organic acids	These acids inhibited different *Eimeria* species in terms of reduction of lesion scores and oocyst production	Tamasaukas et al. (1997)

CONCLUSION

As the world's poultry industry continues to grow, attention toward controlling coccidiosis increases to combat such very important reported disease of chickens. Infections with *Eimeria* species are often associated with severe economic losses. Medication or vaccination alone is not enough for the complete eradication of the disease. However, the previous strategies should be accompanied by improvements in management, sanitation, and hygiene as well as using of some supportive natural feed additives such as probiotics, prebiotics, or phytobiotics. Regular monitoring programs are crucial for the early detection of *Eimeria* strains developing resistance. In addition, controlling avian coccidiosis demands many communal efforts with advanced industrial technologies to open new lines of investigations. The modifications in the physical cage environment during brooding of pullets could be applied. Regular checking of litter moisture contents and controlling of environmental humidity surrounding chickens are critical preventive measures. Genetic selection is a long-term approach that should be applied throughout generations of different avian breeds.

DECLARATIONS

Competing interests

There are no competing interests to declare.

Ethical considerations

Plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been checked by the author.

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