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AVIAN COCCIDIOSIS: RECENT ADVANCES IN ALTERNATIVE CONTROL STRATEGIES AND VACCINE DEVELOPMENT

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ABSTRACT

Coccidiosis induces huge economic losses to poultry production. Its control through anticoccidial live vaccines and drugs has been very successful with some limitations because of the cost of production of live vaccines, drug resistance, and residues representing public health concerns. Consequently, there is a crucial need for drug-free production of foods. Useful strategies include environmental, immunological, and genetic approaches; feed additives are recent attitudes involving probiotics, synbiotics, organic acids, phytobiotics as essential oils, antioxidants, and nanobiotics (nanoparticles). A combination of such additives is a recent useful trend. Transgenic *Eimeria* parasite could fill in the gap in the control of chicken coccidiosis as an efficient anticoccidial vaccine with improved protective efficacy using multiple vaccine antigens. Alternatives justify further studies as therapeutic or prophylactic anticoccidial agents. Full biological and toxicology profiles are crucial for the promising materials which deserve to be applied on a larger scale.

***Keywords*:** Vaccination, Transgenic *Eimeria*, Botanicals, Essential oils, Probiotics, Synbiotics, Organic acids, Nanoparticles.

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INTRODUCTION

Poultry plays an important role in the food industry in terms of meat and eggs fulfilling the demand of the populations of the world (Belova et al. 2012). The total poultry production market in the world differs from geographical regions which increased in Asian countries as compared to Australia and New Zealand. In recent years, the world total chicken production market dominated over by China, USA, Brazil, Russia, Mexico, India, and Pakistan (Food and Agriculture Organization 2014, Putri et al. 2018). The poultry production reached up to 42 billion broilers annually; however, coccidiosis induces economic losses worldwide reaching up to US$ 3 billion due to poor growth performance and treatment intervention costs (Blake and Tomley 2014). Avian coccidiosis is a highly pathogenic protozoan disease infecting 5-70% commercialized poultry production systems (Du and Hu 2004), especially in developing countries like Egypt and Pakistan (Al-Gawad et al. 2012, Abbas et al. 2017).

The intestinal health of birds is very important depends on biosecurity, management, pathogens, microbiota balance, water quality, and excess of nutrients (Oviedo-Rondón et al. 2019), however, disruptions in the gastrointestinal tract (GIT) caused by parasites (Khater 1993, Abbas et al. 2015) are adversely reflected on digestion, absorption, metabolism, and immunity of birds (Svihus 2014).

Major *Eimeria* species infecting chicken include *E. brunetti* , *E. acervulina*, *E. maxima*, *E. necatrix*, *E. mitis*, *E. praecox*, and *E. tenella* (Abbas et al. 2015). *Eimeria* spp. penetrate the intestinal cells of the host at different sites damaging the intestinal walls resulting in great economic losses due to poor absorption, reduced weight gain, bloody diarrhea, poor feed conversion ratio, and dehydration (Alzahrani et al. 2016, Pawestri et al. 2020) Moreover, stress

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caused by routine viral vaccinations influences the incidence and severity of protozoal diseases, especially *Eimeria* spp. on non-treated Balady (native breed) chickens (Ramadan et al. 2015).

Eimeria life cycle includes sporogony, an exogenous stage, and schizogony, an endogenous stage, (Blake and Tomley 2014). Sporulation of oocysts occurs under standard environmental conditions like humidity, oxygen, and favorable temperature that maximally require 24 to 36 hours. Infection occurs after the ingestion of sporulated oocysts found in litter, feed, and water systems (Sundar et al. 2017). Excystation occurs in the digestive tract by a chemical process where sporozoites are emerged out from sporocysts which invade the intestine. Merozoites converted into schizonts through asexual reproduction and merozoite formations occur from schizonts through merogony. Merozoites penetrate the epithelial cells and convert to micro and macrogametes through the second merogony/schizogony stage. Zygote development occurs through the fusion of micro and macrogametes. Encystation of zygote led to the formation of the oocyst. The oocyst comes out in the feces via the rupturing of the host cell at the maturation stage. Clinical signs appear followed by great economic losses (Dalloul and Lillehoj 2005; Ali et al. 2014a, 2015).

Antimicrobial feed additives as antibiotic growth promoters (AGP) had been used in poultry production to inhibit bacterial infections and promote growth; however, there is an increased pressure to remove AGP in poultry production. Some natural feed additives induce positive effects on broiler chickens' intestinal health and improve growth performance if combined with complementary biosecurity practices in case of AGP-free poultry production (McKnight et al. 2019). Successful control of coccidiosis occurs through anticoccidial vaccines and drugs (Abbas et al. 2012, Kadykalo et al. 2017, Akanbiand and Taiwo 2020). However, with some limitations because of the cost of production of live vaccines, and drug resistance and residues representing a public health concern (Peek and Landman 2011, Mund et al. 2017). Therefore, the present review aims to focus on the current situation of coccidial control and shed more light on alternative control strategies to treat and prevent coccidiosis as environmental, immunological and genetic control, as well as feed additives including probiotics, synbiotics, organic acids, phytobiotics like essential oils, antioxidants, and nanoparticles.

1. Conventional Control

1.1. *Anticoccidial drugs*: Anticoccidial drugs are the main pillar in the coccidiosis control program including chemicals as Amprolium, Clopidol, and Halofuginone which directly involved in the metabolism of parasites especially coccidian species. The other class of anticoccidial drugs is Ionophores such as Salinomycin, Maduramycin, and Sulphanilamide arresting the ion transport channels and hinder the osmotic balance of the parasite (Abbas et al. 2011a, 2012). However, the excessive use of anticoccidial drugs has resulted in the development of resistant strains of *Eimeria* species (Rahman and Mohsin 2019). Furthermore, the continuous usage of such drugs led to the toxic effects on birds (Sundar et al. 2017) and food residues inducing deleterious effects on human health (Mund et al. 2017).

1.1.1. *Development of Resistance:* Factors responsible for the development of anticoccidial drug resistance could be classified into genetic, biological, and operational factors. Genetic factors include the diversity of populations according to their genetic makeup, numbers of genes, and resistance alleles (Pinard-van der Laan et al. 2003). Biological factors include host-parasite relationships (Sangster 2001). Operational factors, for instance, drug quality, composition, dose, frequency, and method of application (Abbas et al. 2011a), and the condition of the bedding, which remains wet in places, creating a nursery of sporulated oocysts for permanent re-infection of the animals despite therapy promoting permanent contact between the drugs and the coccidia and thus the development of resistance (De Gussem 2011). The chemical structures of some anticoccidial drugs and compounds are shown in Fig 1.

1.1.2. *Managing Anticoccidial Resistance*: Strategies to reduce resistance to anticoccidial drugs represent a crucial need. Reducing permanent re-infections by improving husbandry conditions in poultry under anticoccidial prevention or treatment reduces the drug resistance of *Eimeria* spp. Most poultry producers may use rotation (Blake and Tomley 2014), a combination of anticoccidial drugs (Peek and Landman 2011) or even a shuttle program to shift from one chemical to another in the same season to minimize resistance.

Many attempts during the last two decades have been made to develop efficient novel approaches for the prevention and treatment of coccidiosis that would be economically applicable and could avoid the development of resistance. Such options will be discussed in the following sections.

2. Environmental Control

Poor management and unhygienic conditions increase the incidence of poultry coccidiosis (Khan et al. 2006). Adaptation of better environmental practices plays an important role in managing and reducing the occurrence of diseases. The best poultry housing practices include managing wet litter, routine cleaning, and prevention of overcrowding to reduce stress and the chance of coccidia infection (Fanatico 2006) at the farm level.

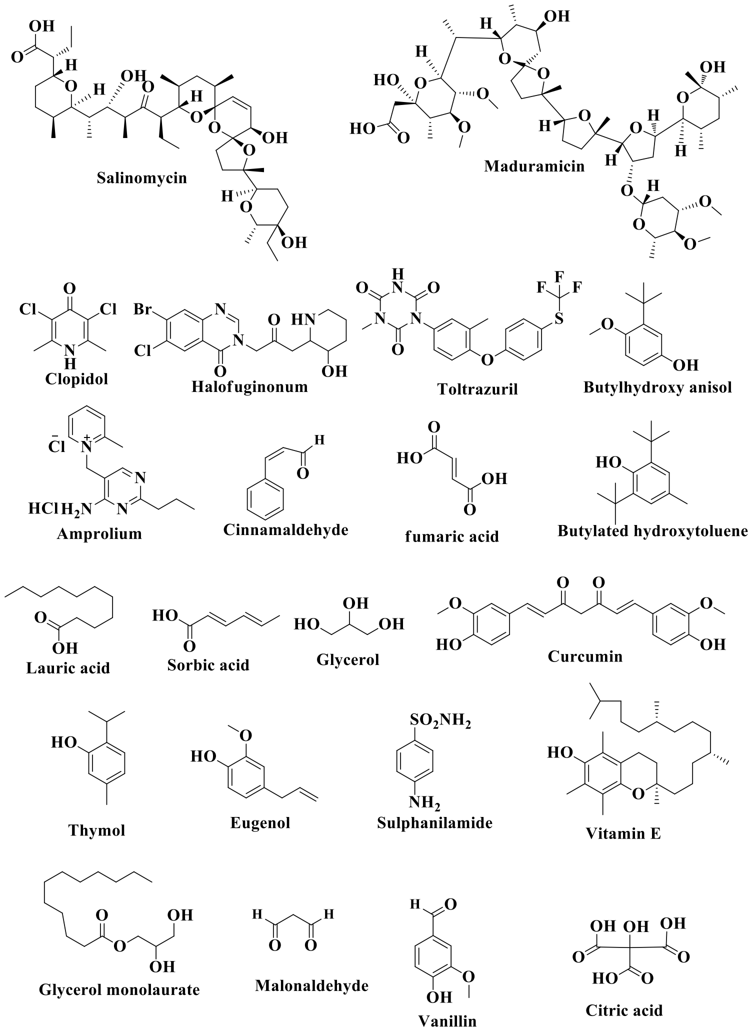

Fig. 1: Chemical structures of some anticoccidial drugs and compounds.

3. Immunological and genetic manipulations

3.1. *Vaccines*: The first successful commercial anticoccidial vaccine was produced in 1952 containing live, non-attenuated *E. tenella* oocysts. After that in 1974, precocious lines of coccidia were developed to facilitate the development of the first attenuated anticoccidial vaccine. Even though attenuation of coccidia by embryo adaptation was first recorded in the UK in 1972, an embryo-adapted line of *E. tenella*, in the Czech Republic in 1992, was incorporated with precocious lines of some other species under the trade name Livacox®. Currently, the formulations of commercially available live vaccines for poultry are based upon the scientific principles established for the CocciVac®, Paracox®, or Livacox® vaccines (Williams 2002).

Vaccination is an effective and successful method against coccidiosis because vaccines provide a high level of protection against coccidiosis and replace the populations of *Eimeria* which reduces the drug resistance problem in chickens (Fitz-Coy 2005, Peek and Landman, 2005, Akanbi and Taiwo 2020). The problem is the promising vaccines in one country might not be effective in the other parts of the world because of geographical variations of *Eimeria* strains and the complexity of *the Eimeria* life cycle. This challenged scientists to prevent vaccination failures with complete oocysts and the identification of potentially immunogenic protein as a promising candidate for vaccine production (Blake et al. 2011, Zhang et al. 2014). Furthermore, the use of live vaccines may also trigger coccidiosis outbreaks in poorly managed production systems.

Even though non-attenuated and attenuated live vaccines were developed with satisfying outputs, they represent a great risk of inducing coccidiosis and/or selection of highly pathogenic strains by genetic recombination with wild strains (Chapman and Jeffers 2014). Although attenuated vaccines are safe, the cost of their productions is high due to the reduced fecundity of precocious parasite (Williams 2002), and 2-3 cycles of *Eimeria* are necessary for maximum acquired immunity (Blake et al. 2017). Treatment with UV- irradiated oocysts significantly reduced oocyst shedding and maintained cecal mucosal integrity; moreover, the body weight was higher in chickens inoculated with irradiated oocysts than their non-irradiated counterparts (El-Ashram et al. 2019).

The effect of a local isolate and Houghton strain of *E. tenella* on clinical and growth parameters following challenges in chickens vaccinated with IMMUCOX and LIVACOX vaccines indicated that the vaccinated chickens overcame the effect of the virulent challenge by *E. tenella* including blood loss, reduction in feed intake and conversion ratio as well as weight loss (Akanbi and Taiwo 2020).

3.2. *Immunogenic protein*: A good alternative includes identification of potentially immunogenic protein as candidates for a vaccine against avian coccidiosis; the first identified antigens are proteins secreted by some organelles of *Eimeria* parasite (Blake et al. 2011, Zhang et al. 2014) followed by complementary DNA expression library immunization screening known vaccine antigens from *Eimeria* sporozoites (Yang et al. 2017). From both origins, more than 20 proteins were used in vaccination trials, with good protection against homologous and heterologous challenge (Blake et al. 2011, Li et al. 2013, 2018, Hoan et al. 2014, Liu et al. 2018), although the protection is higher with the recombinant antigens (Kundu et al. 2017, Li et al. 2018); fortunately, some of them are commercially available. The protection inhibits parasite invasion; increases body weight gain, anticoccidial index, antibody (IgG) titer, CD4+ T cells, and IFN- responses; and reduces oocyst shedding and gut lesion, reviewed by Abiodun and Matthew (2020).

Proteomic analysis of *E. tenella* as unsporulated and sporulated oocyst, sporozoite, and 2nd generation merozoite revealed specific proteins in each stage whereas some other proteins are shared in all stages. During the parasite invasion, proteins RON2 and RON5 are expressed. Such proteins have been identified in *Toxoplasma gondii* and *E. tenella* and they may have a role in host adhesion during the process of invasion (Lal et al. 2009). *In silico analysis*, several epitopes resulted in a significantly predicted efficacy when a collection of epitope mapping of T-cell mediated antigenic determinants was applied to investigate promising epitopes from the sporozoite and merozoite stages (Ahmad et al. 2016).

3.3. *Transgenic Eimeria spp.:* The benefits of the identification of immunodominant antigens and their insertion into transgenic *Eimeria* spp. include host specificity and the large size of the genome, which can tolerate the insertion as well as expression of other antigens (Clark et al. 2012, Marugan-Hernandez et al. 2016, Fatoba and Adeleke 2020). Furthermore, vaccination with *E. tenella* elongation factor-1α recombinant protein induces protective immunity against infections with *E. tenella* and *E. maxima* (Lin et al. 2017).

The stable and transient transfection systems are previously recognized in some other parasites like *Plasmodium falciparum* and *Toxoplasma gondii* (Qin et al. 2014). A stable transfection entails the integration of foreign DNA into the genome of a parasite via a homologous recombination mechanism where the foreign DNA expressed in the type of plasmid (Suarez et al. 2017).

Transfection protocols were developed for *Eimeria* parasites with sporozoites of *E. mitis*, *E. tenella*, and the merozoites of *E. necatrix* (Clark et al. 2008, Liu et al. 2008, Suarez and McElwain 2010, Qin et al. 2014, Duan et al. 2019). Even though transgenic *Eimeria* was produced though the restriction enzyme-mediated integration technique (Clark et al. 2008, Duanet al. 2019), such methodology might damage some crucial regions of the *Eimeria* genome (Qin et al. 2014, Fabota and Adeleke 2020). Such constraint could be improved with the use of a recent technology like CRISPR/Cas9 system which is non-applicable so far for *Eimeria* (Fabota and Adeleke 2020).

Currently, the transgenic *Eimeria* parasite as a vaccine delivery vehicle is highly appreciated. Transfection of antigens from different *Eimeria* species into the genome of a single transgenic species offers heterologous protection plus protection against parental infection and there is no interference in the expression of exogenous EmIMP1 and endogenous Et-IMP1 in the transgenic parasite (Tang et al. 2018, 2019). The vaccination with double transgenic *Eimeria* has improved body weight; elevated cellular responses and level of interferon-gamma (IFN-γ)-secreting lymphocytes; and reduced cecum lesion scores and oocyst output. The benefits of this new technology not only control coccidiosis however also some other parasitic and viral diseases (Marugan-Hernandez et al. 2016, Tang et al. 2016).

4. Feed additives

Feed additives used for controlling avian coccidiosis are summarized in Fig.2.

4.1. *Probiotics and Synbiotics:* Probiotics are beneficial living microorganisms like bacteria and yeast whereas prebiotics are indigestible fibers serving as food for probiotics. Probiotics such as *Lactobacillus* and *Bifidobacterium* spp. are popular in the agriculture industry because they stimulate immunity, increase feed digestibility, and control coccidiosis accordingly (Zhao and Kim 2015). Nonetheless, several factors as slow growth rate, sensitivity to high temperatures and acidic gut environment, less colonization in the small intestine, plus costly mass production would limit their use (Grant et al. 2018).

In contrast, *Bacillus* spp. are effective and reliable probiotic as they sustain high temperatures, low pH and, bile salts, which enable them to survive the extensive food processing steps (Shivaramaiah et al. 2011). They are beneficial in improving the growth rate of chickens through promoting gut health by stimulating the production of cytokines, chemokines, and tight junction (TJ) proteins (Lee et al. 2014) and reducing enteric disease occurrence such as *Eimeria maxima*, necrotic enteritis, and salmonellosis infection in chickens because of their antimicrobial peptides (Lee et al. 2010, Sumi et al. 2015). Some studies have even reported that a few selected *Bacillus* strains promote greater growth in chickens compared to AGPs and control coccidiosis (Chaudhari et al. 2020).

Lactobacillus-based probiotic enhanced immunity level against *E. acervulina* infection in broiler chicks (Dalloul et al. 2003). MitoMax, a commercial probiotic-containing *Saccharomyces boulardii*, and *Pediococcus acidilactici*, resulted in a humoral immune response (Lee et al. 2007). Symbiotic is a combination of probiotics and prebiotics. A symbiotic, Clostat [(HC SP Dry®, Kemin, Belgium), contains *Bacillus subtilis* 2 x 108 CFU/gm (as probiotic) + Lactose 99.8% (as prebiotic)] not only treated coccidiosis, however also increased body weight, gain, feed conversion ratio, serum total protein, albumin, and globulin; and reduced serum total cholesterol and triglycerides. So Clostat as a synbiotic has positive effects when administered either alone or in combination with diclazuril in broilers chickens infected with *E. acervulina* (Ali et al. 2015).

4.2. *Organic acids*: Acids have been used for different uses to treat birds with results surpassing the commercial drugs (Khater and Ramadan 2007, Khater et al. 2013, Adhikari et al. 2020). Organic acids are found naturally in animal and plant tissues as well as in the intestinal tract of animals, due to microbial fermentation. Organic acids are interconnected to the inhibition of bacterial growth (Khan and Iqbal 2016) and induced protective immunity against coccidiosis (Abdullahi et al. 2020)

Among the organic acids, short-chain fatty acids (SCFAs) are potential alternatives to AGPs (Ali et al. 2014a). SCFAs, such as butyric acid (BA), acetic acid, and propionic acid, are the products of bacterial fermentation of undigested carbohydrates in the intestine (Sakata 1987). Acetic (ethanoic) acid has antimicrobial properties (Chaveerach et al. 2004) and demonstrated excellent effects against chickens infected with *E. tenella* improving feed intake, weight gain, and reduced oocyst count. Its effect was comparable to amprolium, a reference commercial drug (Abbas et al. 2011b).

Glycerol monolaurate (GML), a compound formed from lauric acid and glycerol provides very promising results (Fortuoso et al. 2019). Butyric acid glycerides (BAG, Lactobutyrin) and clopidol had the potential to lower the severity and pressure of coccidial infection and maintain very low oocysts production, which is crucial for re-infection and maintaining immunity stimulated by the initial infection (Ali et al. 2014a). So, diet supplementation of SCFAs could be used for AGPs and anticoccidials free programs help in growth-promoting, antimicrobial, and immune stimulant effects (Ali et al. 2014a,b).

Organic acids have a bacteriostatic or bactericidal effect that may be because of a reduction in the intracellular pH through the entry of undissociated acids into the bacterial cell and consequent dissociation in the cytoplasm. Butyric acid has shown an increased expression of intestinal tight junction hence decreasing intestinal permeability. On the other hand, lactic acid bacteria ferment carbohydrates and produce lactic acid which lowers the pH and inhibits the growth of pathogenic microorganisms, for instance, *E. coli*, *Salmonella typhimurium*, and *C. perfringens*, reviewed by Adhikari et al. (2020). The mode of action of short SCFAs is summarized in Fig.3.

4.3. *Phytobiotics*: Botanicals are highly acceptable among consumers as they are a natural new class of additives based on plants and we call them here "*phytobiotics*". They enhance productivity through managing diarrhea and the elimination of pathogens in the gut and improve digestibility and nutrient absorption **(**Kubkomawa et al. 2013). Plant extracts including essential oils have several uses as safe antiparasitic alternatives comparable to commercial drugs used to treat birds (Seddiek et al. 2011, 2013, 2014; Khater et al. 2014). Botanicals, in general, comprise the complex structure of molecules reducing the risk of developing resistance (Khater 2012, 2013). They are highly efficient as synthetic drugs and vaccines and help in organic poultry production (Kiran et al. 2018; Abbas et al. 2019). A herbal complex (leaves of *Azadirachta indica* and *Nicotiana tabacum*, flowers of *Calotropis procera* and seeds of *Trachyspermum ammi*) significantly reduced the negative performance and pathogenic effects associated with *E. tenella* challenge at a level that was comparable with amprolium when using against a largely susceptible recent field isolate (Zaman et al. 2012). *Allium spp*. is widely used as a feed additive (Kothari et al. 2019). A commercial herbal formula contains *Allium sativum*, *Urticadioica*, *Inula helenium*, *Glycyrrhiza glabra*, *Rosmarinus officinalis*, *Chelidonium majus*, *Thymus serpyllum*, *Tanacetum vulgare*, and *Coriandrum sativum*, effectively controlled experimental coccidiosis in chickens and can be used successfully as a natural anticoccidial drug (Pop et al. 2019). Sugarcane (*Saccharum officinarum* L.) bagasse (left after juice extraction) derived polysaccharides act as an immunomodulatory and anticoccidial agent in commercial broilers (Awais et al. 2018).

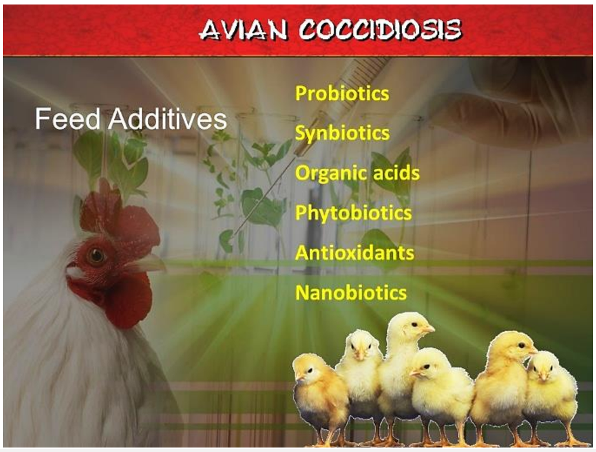

Fig. 2: Feed additives used for controlling avian coccidiosis

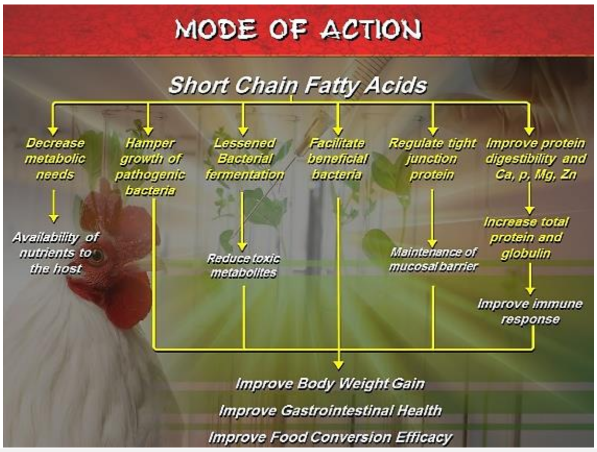

Fig. 3: The mode of action of short of short chain fatty acids

Different mushrooms possess diverse therapeutic properties including antibacterial and antiparasitic effects. Supplementation of two mushrooms, *Tremella fuciformis*, and *Lentinus edodes*, resulted in reduced oocyst shedding and improved weight gain in chickens infected with *E. tenella* (Guo et al. 2005). Cocciban, an herbal product, (1000 g/ton) effectively controlled a mixed infection with *Eimeria* spp. resulted in higher feed efficiency, body weight gain, and mean percent livability (78.33%) in the treated groups than the other infected groups, however lower than that of the healthy control group (Srinivasu et al. 2020). The organic feed additive Calica+ improves growth performance and shows anticoccidial effects in broilers (Martel-Kennes et al. 2019).

A blend of carvacrol, cinnamaldehyde, and capsicum oleoresin stimulate cell-mediated immunity as it induced an increase in natural killer cells, macrophages, CD4, CD8 T cells, and cytokines like IFN-γ and IL-6 that stimulate the innate as well as the adaptive or humoral immune response (Naidoo et al. 2008). Considerable work has been done on anticoccidial drug development from indigenous plants (Abbas et al. 2012) and some other studies have been summarized in Table 1.

4.3.1. ***Essential Oils*:** Essential oils were used since the Egyptian Pyramids (Khater 2017) as fragrances, and favoring, natural remedies, insecticides, and repellents (Khater 2013, 2014; Khater et al. 2009, 2011,2018). Such oils are complex mixtures of volatile organic compounds produced as secondary metabolites in plants. Steam distillation of aromatic plants yields essential oils. Recently, there has been an emerging interest in using plant-based essential oils in controlling coccidiosis with promising results (Qureshi et al. 2017). Three main plant families possess antiparasitic properties as *Asteraceae*, *Lamiaceae*, and *Apiaceae*. The plant products and essential oils obtained from *Allium cepa*, *Echinaceae purpure*, and *Origanum vulgare* found to be effective against *Eimeria* species. The EOs of *O. vulgare* has been enormously studied for controlling *E. maxima*, *E. acervulina*, *E. tenella*, and mixed infection with *Eimeria* in poultry (Idris et al. 2017).

From previous applications, oil bends prepared according to the rules of aromatherapy providing a unique mixture with additive or synergistic effects (Khater et al. 2018; Khater and Geden 2018, 2019). The essential oil blends, mixtures of phytochemical compounds, help in reducing necrotic enteritis as they have selective antimicrobial effects, acting against *Clostridium perfringens* proliferation and helping control of coccidia infection (Guo et al. 2004). A blend of castor oil and cashew nut shell liquid oil improved weight gain and feed conversion ratio in broilers chickens challenging with *E. maxima*, *E. acervuline*, and *E. tenella* (Murakami et al. 2014).

Cinnamaldehyde has been used as a supplement in both in vitro and in vivo disease challenge trials against coccidiosis (Lee et al. 2011). An in vitro followed by an *in vivo* study has shown a higher stimulation of EtMIC2 (purified recombinant protein) antibody response in *E. tenella* and cinnamaldehyde group compared with only *E. tenella* group (Lillehoj et al. 2011). Supplementation of diets with cinnamaldehyde induced morphological modification of intestinal mucus cells and affected expression of metabolism-related intestinal genes, for instance, IL-1β, IL-6, IL-15, and IFN-γ mRNA, were found to be increased thus reducing *E. acervulina* and *E. maxima*-induced bodyweight loss as well as *E. acervulina* oocyst shedding and increasing in anticoccidial immunity (Naidoo et al. 2008).

Essential oils are immune stimulate because of their anti-inflammatory, antioxidant, and cytoplasmic damage activities (Abbas et al. 2012) which reflected into the proliferation of immune cells, elevated expression of cytokines, and an increased antibody titer; enhancing innate and adaptive immunity, including both cell-mediated and humoral immunity; and an increase in natural killer cells, macrophages, CD4, and CD8 T cells and their cytokines like IFN-γ and IL-6 (Bozkurt et al. 2013).

Table 1: Phytobiotics with anticoccidial effects

Plant Name	Family	Common Name	*Eimeria* Species	References
Rumex nervosus	Polygonaceae	Oseille Sango	*Eimeria tenella*	Qasem et al. (2020)
Camellia sinensis	*Theaceae*	Green Tea	Mixed	Zhang et al. (2020)
Azadirachta indica	Meliaceae	Neem	Mixed	Chukwuma et al. (2019)
Phyllanthus amarus	*Phyllanthaceae*	Hurricane weed	*E. tenella*	Brice et al. (2019)
Jatropha curcas	*Euphorbiaceae*	physic nut; pig nut; fig nut; purging nut	*E. tenella*	Brice et al. (2019)
Trachyspermum ammi	*Apiaceae*	Ajwain	Mixed	Abbas et al. (2019)
Bidenspilosa	*Asteraceae*	black-jack, beggar ticks	*E. tenella*	Yang et al. (2019)
Combretum micranthum	*Combretaceae*	Kinkeliba	*E. tenella*	Dakpogan et al. (2019)
Morinda lucida	*Rubiaceae*	Brimstone tree	*E. tenella*	Dakpogan et al. (2019)
Areca catechu	*Arecaceae*	Areca palm	*E. tenella*	Wang et al. (2018)
Beta vulgaris	*Chenopodiaceae*	Chukander, beet	Mixed	Abbas et al. (2017a)
Pinus radiata	*Pinaceae*	Monterey pine	Mixed	Abbas et al. (2017b)
Brucea javanica	*Simaroubaceae*	Kosam	*E. tenella*	Lan et al. (2016)
Cassia sieberiana	*Fabaceae*	Sindia	Mixed	Fall et al. (2016)
Combined Aqueous Extracts of *Azadirachta indica and Khaya senegalensis*	*Meliaceae*	Neem and Mahogany (Senegal mahogany)	Mixed	Gotep et al. (2016)
Plantago asiatica	*Plantaginaceae*	Plantain or fleaworts	*E. tenella*	Hong et al. (2016)
Azadirachta indica	*Meliaceaae*	Neem	Mixed	Hema et al. (2015)
Artemisia herba-alba	*Asteraceae*	Wormwood	*E. tenella*	Messaï et al. (2014)
Moringa oleifera	*Moringaceae*	Moringa	Mixed	Ola-Fadunsin et al. (2013)
Aloe vera	*Asphodelaceae*	Aloe	*E. maxima*	Yim et al. (2011)
Carthamus tinctorius	Asteraceae	Sunflower	*E. acervulina*	Lee et al. (2009)

4.4. *Antioxidants*: Antioxidants are molecules that interact with free radicals and terminate their oxidative reaction and prevent cellular damage. Free radical oxidative species are produced during the host's cellular immune response to invasion by *Eimeria* species (Allen et al. 1997) playing an important role in defending against parasitic infections, however their high concentrations cold lead to tissue damage and cytotoxicity aiding the pathology of infection. As a result, a severe coccidial infection includes pathogenic oxidative stress and impaired ecological oxidative balance which manifested though weight gain, feed conversion ratio, oocyst production, and alterations in the caecum (Georgieva et al. 2006).

Lipid peroxidation is one of the best parameters used for indicating the level of reactive oxygen species (ROS)-induced systemic biological damage (Popova and Popov 2002). Malondialdehyde (MDA), a lipid peroxidation end-product, is isolated in urine, blood, and tissues and is used as a biomarker for radical-induced damage (Day 1996). Chickens possess both enzymatic and non-enzymatic antioxidant mechanisms of defense that prevent ROS formation or limit their toxic effects (Fridovich 1978). Superoxide dismutase (SOD) and catalase (CAT) are antioxidant enzymes involved in endogenous antioxidant defenses against ROS (Fridovich 1975).

The enzyme changes reflect an impaired antioxidant status of chickens during the course of coccidial infection and the occurrence of oxidative stress after infection; the antioxidant status of broiler chickens infected with *E. tenella* revealed increased blood plasma MDA and CAT and decreased SOD when compared to healthy chickens (Georgieva et al. 2006). Coccidiosis significantly reduced growth performance ($P<0.05$) and increased nitric oxide (NO) and MDA, however, did not change the hepatic activity of glutathione peroxidase (GPX) (Pourali et al. 2014).

4.4.1. *The benefit of antioxidants*: The antioxidant system includes enzymatic antioxidants as SOD, GPX, (CAT (B), and non-enzymatic antioxidants like vitamin E, vitamin A, Selenium, etc. The role of antioxidants in poultry production has been reviewed (Masood et al. 2013; Surai 2020). Toltrazuril, a highly effective anticoccidial, limits the degree of lipid peroxidation as a part of its mode of action. The anticoccidial effect of salinomycin was potentiated by the antioxidant butylated Hydroxy Toluene (BHT) (Seddiek et al. 2008) and butylated Hydroxy Anisole (BHA) (Ali et al. 2014b).

Antioxidant compounds ameliorate the degree of intestinal lipid peroxidation and reduce the severity of *E. tenella* infections accordingly (Allen et al. 1998). Curcumin from the rhizomes of *Curcuma longa* eliminates free radicals and protects cells from lipid peroxidation (Khan et al. 2012). Cinnamaldehyde enhances performance as it protects the intestinal mucosa through increasing antioxidant enzyme levels; exerts anti-inflammatory and antimicrobial effects (Petrolli et al. 2012; Pirgozliev et al. 2018); stimulates the secretion of salivary enzymes and pancreatic amylase, helping in digestion (Petrolli et al. 2012). Feed supplements are used in the poultry industry to reduce the oxidative stress like Selenium, Zinc, Copper, Vitamin E, Manganese, and butylated hydroxytoluene (Georgieva et al. 2011a, 2011b; Bortoluzzi et al. 2020). Antioxidant compounds have a cellular protective action against oxidative stress and reduce the severity of infections via altering the degree of intestinal lipid peroxidation (Allen et al. 1998). Some more important antioxidants in poultry production have been summarized in Table 2.

Table 2: The anticoccidial potential of antioxidants

Antioxidants	*Eimeria* Species	Anticoccidial and other efficacy	References
Curcumin and a commercial microencapsulated phytogenic supplement containing thymol, cinnamaldehyde, and carvacrol in broiler chicken feed	Mixed	Increased the crypt/villus ratio, a marker of improved intestinal health and performance. These additives generate improved meat quality by increasing polyunsaturated fatty acids that are beneficial to health and by reducing lipid peroxidation, increasing the meat shelf life.	Galli et al. (2020)
Tulbaghia violacea (35 mg/kg), *Vitis vinifera* (75 mg/kg) and *Artemisia afra* (150 mg/kg)	*E. tenella* *E. maxima* *E. avervulina*	Feed conversion ratios similar to toltrazuril, and higher than the untreated control. *T. violacea* significantly decreased the oocyst production in the birds.	Naidoo et al. (2008)
Garlic powder (GP) and total sulfur amino acid (TSAA)	Mixed	Decrease fecal oocyt output	Pourali et al. (2014)
Grape seed proanthocyanidine extract (natural polyphenolic antioxidant)	*E. tenella*	Reduction in mortality and improved bird performance was observed	Wang et al. (2008)
Xanthohumol (XN), a prenylated flavonoid, obtained from the hops plant	*E. acervulina* *E. maxima*	Anticoccidial activity against different *Eimeria* species in chickens Reduction in lesion scores suppress parasite development within the host	Allen (2007)
Camellia sinensis	*E. maxima*	Rich in flavonoid, has anticoccidial effects due to their antioxidant properties	Jang et al. (2007)

4.5. ***Combination of Feed Additives*****:** Improvement in feed efficiency and growth performance occurred when broilers were supplemented a combination of feed additives like organic acids and essential oils. Acids, in their undissociated form, can lower the internal pH and disturb the bacterial metabolism. On the other hand, essential oils have great hydrophobicity property which increases the bacterial membrane permeability facilitating the influx of organic acids into the cytoplasm (Oviedo-Rondón et al. 2010, Smyth et al. 2018). Hence, such combination may result in a synergic or additive beneficial effect because of modulation of the intestinal microbiota and acting as an antibiotic growth promoter alternative on growth performance, intestinal morphology, and gut microflora in broilers (Liu et al. 2017).

Recently, broilers feed on a supplement of a protected blend consisted of organic acids as fumaric, sorbic, malic, and citric acids plus essential oils like thymol, vanillin, and eugenol reflected in improved intestinal integrity; greater expression of mucin 2, claudin1, and occludin genes when compared to those of the challenged control group; and increased intestinal health, nutrient digestibility, and growth performance (Stefanello et al. 2020). A combination of probiotics (PrimaLac) along with mushroom (*Lentinus edodes*) showed a positive effect on health enhancement in broiler chicken (Willis et al. 2007).

Specific essential oil blends and probiotics used as feed additives have been shown to promote healthy digestive microbes resulting in improved poultry production (Oviedo-Rondón et al. 2010). Synbiotics and essential oils are potential alternatives to antibacterial and anticoccidial drugs in poultry production; synbiotics (*Bacillus subtilis, B. licheniformis, Saccharomyces cerevisiae,* beta-glucan, and mannanoligosaccharides) and essential oils (oregano, anise, and citrus peel) ameliorated the negative effect of necrotic enteritis and coccidiosis in broiler chickens by promoting better intestinal health (Abd El-Haleem et al. 2019). As vaccination represents a stress factor that increases coccidial infection (Ramadan et al. 2015), some researchers have reported enhanced protection levels of vaccines, against coccidiosis in broiler chicks, when used in combination with botanicals and probiotics (Ritzi et al. 2016). As a result, such combinations of feed additives could be used efficiently in AGP and anticoccidial free programs (Stefanello et al. 2020).

4.6. *Nanobiotics*: Nanoparticles are a recent trend (Govindarajan et al. 2016a, 2016b) and could be supplemented in a bird's diet (Fisinin et al. 2018) and we would call them here as "*nanobiotics*". Silver nanoparticles have many used (Murugan et al. 2015, Roni et al. 2015) were used as an additive in poultry feeds as an inorganic antibacterial agent used for many years for its capability of killing about 650 types of pathogens (Jeong et al. 2005). For broiler chickens, nanoparticles of selenium are a highly bioavailable and non-toxic alternative as it increased absorption and diffusion of materials into organs and tissues, and increased antioxidant capacity (Gangadoo et al. 2020).

Despite its usage for the prevention and treatment of coccidiosis, toltrazuril has poor aqueous solubility (25 °C, 0.41 µg/mL) and its dose escalation for systemic administration remains challenging. As a result, Zhang et al. (2018a) engineered a Tol mixed nanomicelle (TMNM) delivery system depends on sodium deoxycholate–Brij C20 polyethylene ether–triton x100 (NaDC–Brij58–Tx100) as surfactants, via a film hydration method, significant increases in the drug solubility and bioavailability. More studies about nanobiotics have been summarized in Table 3.

Table 3: The anticoccidial encapsulated and nanoparticles

Nanoparticles	*Eimeria* Species	Efficacy	References
Encapsulated essential oils containing thymol and carvavacrol	Unspecified	Dietary EEO counteracted coccidiosis-vaccine-induced depression in body weight gain and feed intake; decreased the concentrations of the volatile fatty acids; affected gut morphology in chickens; increased serum catalase activity; and altered gut physiology in broiler chickens.	Lee et al. (2020)
Encapsulated cinnamaldehyde and citral alone or in combination	Mixed	Reduced both incidence and severity of necrotic enteritis	Yang et al. (2020)
Phenylboronic acid-conjugated chitosan micelles		Anticoccidial efficacy and reduced intestinal damage	Zhang et al. (2018b)
Ginsenoside-based nanoparticles (ginsomes)	*E. tenella*	The adjuvant ginsomes can promote subunit vaccine to induce a strong immune response and protective effects.	Zhang et al. (2012)
Silver nanoparticles	*E. tenella*	Coccidiostat, 50% fewer oocysts in the fecal samples compared to the control group	Chauke and Siebrits (2012)
Eimeria recombinant profilin in conjunction with nanoparticle adjuvants,	*E. acervuline* *E. tenella*	Immunization of chickens with the recombinant prof lin subunit vaccine in conjunction with adjuvants increases protective mucosal immunity against *E. acervuline* infection	Jang et al. (2011)
Recombinant protein vaccine Silver	Mixed	Good antibody response and has more efficiency to protect birds against the challenge of *Eimeria* oocysts	Dalloul and Lillehoj (2006)

Conclusion: Poultry production plays an important role in curtailing malnutrition and poverty plus enhancing economic growth. However, coccidiosis is still a global challenge for profitable production due to drug resistance and residues; constraint comes from the consumer, and the ever-increasing need for the drug-free production of foods. Various strategies as vaccination, nutrition, and husbandry have been used to control avian coccidiosis in the postantibiotic era. Transgenic *Eimeria* parasite could fill the gap in the control of chicken coccidiosis as an efficient anticoccidial vaccine with improved protective efficacy using multiple vaccine antigens.

A common alternative to improve birds' intestinal health is to formulate diets with feed additives and their combinations shown better results with less toxic effects in poultry coccidiosis. Such compounds have immunomodulatory and therapeutic effects against coccidiosis. The promising results by alternatives discussed here deserve to be applied on a larger scale in AGPs and anticoccidial free poultry farms and to be formulated to overcome the synthetic drug resistance and residues. More efforts need to be done to evaluate the biological, chemical, and toxicology properties of additives providing bright opportunities for therapeutic or prophylactic anticoccidial agents and organic poultry production reflected on improving the health, wealth, and national economy.

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