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Natural Alternatives to Controlling Coccidiosis

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Abstract: Coccidiosis is a parasitic disease caused by apicomplexan protozoa of the genus *Eimeria*, and today it may be difficult to appreciate the devastating effects that these parasites once had on poultry flocks. Indeed, without adequate means of control, both by chemotherapy and vaccination. The main problem with *Eimeria* infections is that they are caused by more than one species that attack different regions of the intestine. The use of several drugs, alone or in combination, has proven to be an effective alternative in the struggle against avian coccidiosis. However, the emergence of drug resistant strains, especially after a prolonged use of a drug, is a real problem. Thus, vaccines are the only preventative methods. Due to this, new alternatives have emerged, most of which are natural compounds extracted from plants or produced by microorganisms. Some of these compounds are antioxidants that damage the parasite, thus preventing the infection. Others, such as essential oils, disrupt the structure of oocysts preventing the dispersion of the parasite. From this perspective, *Eimeria* parasites should be controlled by several ways, implying the use of a toolkit yet to be available Many of these natural compounds are used as diet supplements with varying effects that include immune stimulation, anti-inflammatory and antioxidant activities, and cytoplasmic damage.
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Introduction

Although good husbandry can help in reducing the risk of transmission of coccidiosis-causing parasites, additional measures are essential to accomplish a complete control of the disease **(McDonald and Shirley, 2009)**. Some efforts have focused on the development of anticoccidial compounds that attack both the sexual and asexual stages of the parasites (stages that occur within the host) rather than targeting the most infectious stage, the oocyst (**Chapman et al., 2010)**. The agents used for the prevention and control of coccidian infections are termed anticoccidial drugs. These drugs can either be coccidiostatic or coccidiocidal agents. The former comprises drugs that prevent the replication and growth of coccidial populations, whereas the latter includes drugs that destroy coccidial populations. In general, coccidiocidal drugs have been more effective than coccidiostatic drugs. This has been the case because when coccidiostatic medication is withdrawn, arrested parasites may continue their life cycle and goon to contaminate the environment with infective oocysts **(McDougald and Fitz-Coy, 2009)**. Two categories of drugs are employed in the poultry industry, those being ionophorous compounds (ionophores) and synthetic drugs (chemicals). Generally, ionophores cause the death of the parasite by interfering with the passage of ions across the cell membrane, whereas chemicals act by inhibiting different biochemical pathways of the parasite (**Chapman et al., 2010**). Synthetic drugs were the first to be discovered and comprise a diverse array of molecules that are absorbed into the blood stream of the host and kill developing parasites in the epithelial cells of the villi in the intestines. One of the oldest synthetic drugs is nicarbazin (coccidiostatic agent). The molecular mechanism of nicarbazin is based on inhibiting the development of the first and second generations of the schizont stage of the parasites. There are some molecular mechanisms proposed for nicarbazin's avian adverse effect, but no research group to date has conducted *in vivo* research **(Aslian et al., 2014)**. Nicarbazin is one of the most successful drugs and is still widely used today **(Stotish et al., 1978 and Chapman, 1994)**. Another coccidiostatic synthetic drug with a wide range of action is amprolium and has been shown to inhibit the uptake of thiamine by second generation schizonts of *E. tenella*.

Quinolone drugs inhibit cellular respiration by blocking the electron transport chain in the parasite mitochondrion thus arresting the parasite in the early stages of development **(James, 1980 and Wang, 1976)**. Ionophores, which are byproducts of bacterial fermentation, have a unique mechanism of action. They are known to affect cellular processes involving cation (mono and divalent) transport through the cell membrane thus affecting the osmotic balance **(Chapman et al., 2013, Witcombe and Smith, 2014)**. These compounds are considered as coccidiocidal because of their ability to preferentially move ions, usually sodium, which results in highly toxic conditions to the cell **(McDougald,2013).** Besides properties mentioned, ionophores show a broad spectrum of bioactivity ranging from antibacterial, antifungal, antiparasitic, antiviral, and tumor cell cytotoxicity **(Rutkowski and Brzezinski, 2013 and Łowicki and Huczy´nski, 2013)**. Since the discovery of sulfonamide sixty-five years ago as a potent compound to control *Eimeria* infections, the development of anticoccidial drugs has continued in earnest. The use of several drugs, alone or in combination, has proven to be an effective mechanism in the struggle against avian coccidiosis. However, the emergence of drug-resistant strains, especially after prolonged uses of a drug, is a real problem **(McDougald and Fitz-Coy, 2009).**

To combat resistance, shuttle and rotation systems of drugs are employed. In the shuttle program, the different drugs are used during a period of juvenile growth to market size growth, whereas in the rotation program, the type of drug used is switched after one or several grow-out periods or seasonally **(De Gussem, 2007)**. However, even with the shuttle and rotation programs there is no method to fully prevent drug resistance. This has been observed when ionophores, such as monensin orlasalocid, are used in the field and drug resistant parasites emerge (**Martin et al., 1997**). Due to the constant pressures by government agencies and consumers to ban the use of drugs in animals intended for human consumption, other alternatives to the control of coccidiosis are now available. The demand for alternative methods has constantly increased in European countries, Australia, and the US **(Sharman et al.,2010 and Farrant,2001).** Consequently, the development and use of vaccines and other alternatives have showed a significant increase. Immunity to *Eimeria* is stimulated by the initial developing parasite stages, particularly the schizonts, and is subsequently boosted and maintained by multiple reexposures to oocysts in the litter. Accordingly, the recycling of infection, following the administration of live oocysts, is critical for the development of protective immunity **(Chapman and Cherry, 1997).** Two types of vaccines are currently used with the aim of controlling coccidiosis in a chemical-free way: unattenuated and attenuated vaccines. Their effectiveness is based on the recycling of what are initially very low doses of oocyst and on the gradual buildup of solid immunity **(Allen and Fetterer, 2002)**. The use of live unattenuated vaccines (Coccivac, Advent, Immucox, and Inovocox) is limited due to the risk induced by the live parasites, so their use is accompanied by chemical treatments to control the inherent pathogenicity of the parasites. However, this practice is no longer required due to the improved methods of administration of the oocysts **(Williams, 2002)**. The success of live attenuated vaccines (Paracox and Hatch Pak Cocci III) is based on the fact that there is a lower risk of disease occurring because there is a reduction in the proliferation of the parasites and as a result less damage to the intestine of the bird **(Sharman et al.,2010)**. Today, attenuation of *Eimeria* species is based on precociousness. This refers to populations of parasites that complete their life cycle up to 30 h faster than parasites from the same parent strain, resulting in parasites with attenuated virulence and a significant reduction in their reproductive capacity **(McDonald and Shirley,2009, Shirley and Bedrn´ık,1997, Innes and Vermeulen,2006).** Today, precocious lines are described for all species of *Eimeria* **(Williams,2002)**. Although the species-specific nature of immunity induced by exposure to live *Eimeria* (whether attenuated or unattenuated) is significant to control coccidiosis, there still is a requirement for the development of a fully effective anticoccidial vaccine, mainly because *Eimeria* species distribution can vary between poultry farms and specific screenings should be performed before vaccine administration. Additionally, the anticoccidial drug resistance observed in birds around the world has directed the search for natural products with efficient anticoccidial activity **(Abbas et al., 2011). For** more detailed information about vaccines, the follow published reviews are good resources **(Chapman et al.,2013 and Chapman, 2014).**

Natural Alternatives to Controlling Coccidiosis

There is a current interest in the use of so-called natural products, which include fungal extracts, plant extracts, and probiotics to reduce problems caused by coccidiosis **(Chapman et al.,2013**). Many of these natural compounds are used as diet supplements with varying effects that include immune stimulation, anti-inflammatory and antioxidant activities, and cytoplasmic damage **(Abbas et al.,2012).**

1. Fats.

It has been reported that sources of fat containing high concentrations of docosahexaenoic acid, eicosapentaenoic acid, and linolenic acid (known as n-

3 fatty acids) from fish oils or flax seeds reduced the severity of *Eimeriatenella* infections in young broiler chicks. Diets supplemented with 2.5 to 10% fish oil, 10% flax seed oil, or 10% linseed oil significantly decreased cecal lesions, which allowed a maintained weight gain in birds. In addition, a reduced parasite invasion rate and development were also observed in the caeca of infected chicks. Unfortunately, the effect of these fatty acids was only observed in *E. tenella* infected animals but not in *E. maxima* infected animals **(Allen et al.,1996 and 1997**). In fact, diets with low levels of linolenic acid do not show protection against *E. tenella* infection **(Allen et al., 2000).** These results suggest that these diets induce an oxidative stress that is detrimental to parasite development, and this may be because sporulated oocysts and sporozoites of *E. tenella* are deficient in superoxide dismutase, an enzyme that would protect them from reactive oxygen species **(Michalski and Prowse, 1991)**.

2. Antioxidants.

Cells are constantly exposed to environmental damage or to damage caused by the cells themselves. In response to this damage, antioxidant molecules are important to control and reduce oxidative stress caused by increased levels of reactive oxygen species and free radicals that caninitiate chain reactions in the cell, resulting in the death or in serious damage to the cell **(Masood et al., 2013)**. In the poultry industry, the use of antioxidants from natural sources can help in restoring the balance of oxidants/antioxidants, leading to an improvement of birds infected with coccidiosis. Fruits and other plant materials provide a good source of an antioxidant due to their high content of phenol compounds **(Karre et al, 2013)**. Most of the antioxidants available are found as dietary supplements. One of the most studied antioxidant is vitamin E, known to delay lipid peroxidation in muscles and improvement quality. Various fruit and herb plants such as plum, cranberries, pomegranate, bearberry, grape seed extract, pine bark extract, rosemary, oregano, green tea, and other spices function as antioxidants in meat and poultry products **(Karre et al, 2013 and Dkhil, 2013)**. Curcumin, present in *Curcuma longa*, could reduce these verity of an infection of the upper and middle part of the small intestine caused by *E. acervulina* and *E. maxima* **(Allen et al.,1998). Naidoo et al. (2008)** used the antioxidants properties of several plant extracts and compared those to the drug toltrazuril. They reported that *Tulbaghiaviolacea*, *Vitisvinifera*, and *Artemisia afra*, used in doses of 35 g/kg, 75mg/kg, and150mg/kg, respectively, exhibit an activity similar to that observed in the control drug. Artemisinin, an extract isolated from *Artemisia annua*, is effective in reducing oocyst shedding output from *E. acervulina* and *E. tenella* but not *E. maxima* infections when broiler chickens are fed the extract at concentrations of 1 or2.5mg/kg. The extract's mechanism of action is thought to involve oxidative stress **(Arab et al.,2006).**

3. Essential Oils.

Most of the alternative therapies offered in the treatment of coccidiosis are focused on attacking the stages of the parasite that are different from the oocyst. The use of essential oils as part of formulations or diets to control coccidiosis has been reported. Recently, *in vitro* destruction of *Eimeria* oocysts was reported after a three hours contact period with essential oils from artemisia, thyme, tea tree, and clove **(Remmal et al.,2011)**. Out of ten essential oils tested, only those four present with a LC50<1mg/mL for oocysts. Oocysticidal activity of the commercial oils carvacrol, carvone, isopulegol, thymol, and eugenol was also evaluated.

The lysis was monitored in suspensions of oocysts from *E. tenella* (45%), *E. maxima* (32%), *E. acervulina* (10%),*E. necatrix* (6%), and *E. mitis* (7%) through the release of internal substances at 273 nm (**Remmal et al.,2013).** Although the mechanism of action of essential oils is still unknown, these two reports are an example of the use of natural substances as agents for the destruction of the most resistant structure of the parasite, the oocyst. Nevertheless, the economic factor for obtaining these products could be an impediment for their extensive use in farms.

4. Herbal Extracts and Medicinal Plants.

Extracts from plants have also been shown to exhibit anticoccidial effects. **Youn and Noh (2001)** assessed the effect of 15 different herbs against *E. tenella* in one-day old broiler chickens. They found that survival rates in the groups treated with *Ulmusmacrocarpa*, *Pulsatillakoreana*, *Torilis japonica*, *Artemisia asiatica*, and *Sophoraflavescens* were higher than those of the infected control. Bloody diarrhea in the *S. flavescens* and *Sinomeniumacutum*-treated groups was milder when compared to the control-treated groups. Lesion scores in the groups treated with *U. macrocarpa* and *P. koreana* were significantly lower than those of the control group. In summary, the data of survival rates, bloody diarrhea symptoms, lesion scores, bodyweight gains, and oocyst excretions indicate that *S. flavescens* was the most effective, followed by *P. koreana*, *Sinomeniumacutum*, *U. macrocarpa*, and *Quisqualisindica*.

A comparison between *Artemisia sieberi* extracts and ionophoremonensin was assessed to compare their anticoccidial effect on 21-day old broiler chickens infected with *E. tenella*, *E. maxima*, *E. necatrix*, and *E. acervulina* **(Kheirabadi et al., 2014).** This study showed that chickens challenged by coccidiosis and treated with *A. sieberi* extract had a decreased number of oocysts per gram of feces and had improved growth performance parameters such as feed intake and weight gain, among others, when compared with the effects observed with moneys in treatment. The extract could be an alternative therapeutic agent against avian coccidiosis under field conditions. Similar results were observed with an extract of *A. sieberi* obtained using petroleum ether and recovered as a novel granulated extract. One-day old broilers challenged by *E. tenella* on day 21 and treated with this extract showed a significant reduction in mortality, diarrhea, lesion scores, and oocyst number in feces. The authors suggest that this new formulation is a promising herbal medicine that can be used as a prophylactic or therapeutic product to control avian coccidiosis **(Kaboutari et al.,2014)**. The extraction of compounds from herbal material is common. Recently, Ola-Fadunsin and Ademola **(Ola-Fadunsin and Ademola, 2013)** used *Moringaoleifera* acetone extract and assessed its anticoccidial activity. They used this extract to treat broiler chickens naturally infected with several *Eimeria* species. The parameters assessed were inhibition of oocyst output, fecal score, weight gain, and mortality, and in all cases tested, positive results were obtained. Additionally, evaluation of hematological indices showed a significant increase in packed cell volume, hemoglobin concentration, and red blood cell count of the treated birds. Some plants used against *Eimeria* also possess activities against other protozoan parasites such as plasmodia and trypanosomes, which makes the plant or its extracts a feasible phytomedicine **(Nweze and Obiwulu, 2009).** For plants such as *Ecliptaalba*, other biological activities, in addition to anticoccidial activities, are reported, such as antimicrobial, analgesic, antiviral, anti-inflammatory, and others **(Michels et al.,2011)**. Different diet supplementation with plant-derived phytonutrients, carvacrol, cinnamaldehyde, and capsicum oleoresin has been used to examine their immunomodulatory effects on broiler chickens infected with *E. acervulina* **(Lillehoj et al., 2011)**. The results of this study provide evidence that these phytonutrientspossess immune enhancing properties in chickens, which offers the possibility of developing effective drug free alternative strategies to control poultry coccidiosis **(Lillehoj et al., 2011).**

5. Immune Response Modulators.

Enhanced immune responses were observed in one-day old chickens fed with a lyophilized powder extracted from plums. These chickens show an increased body weight gain, a reduced fecal oocyst shedding rate, and an increase in the mRNAs for IFN-5 and IL-15. Furthermore, chickens fed with plum exhibited a greater spleen cell proliferation **(Lee et al., 2008)**. In this search for natural products, the use of probiotics and prebiotics emerges as an alternative to the use of antibiotics on a large scale. The use of these products have been shown to prevent the establishment of pathogens in the intestinal tract of chickens, thus increasing weight gain, feed conversion ratio, and livability, in addition to acting as immune response modulators **(Gustafson and Bowen,1997 and Lee et al.,2007)**. Probiotics are defined as live microbial feed supplements designed to benefit the host by improving the intestinal microbial ecology **(Fuller, 1989).** The commercial probiotic Mito-Max, containing *Pediococcusacidilactici* and *Saccharomycesboulardii*, was evaluated as an alternative control method to prophylactic drugs against coccidiosis **(Lee et al.,2007)** fecal oocyst shedding rates. Diet enriched with lactobacilli has also been used, acting as immunomodulators to stimulate the gut-associated bacteria in neonatal chicks, thereby protecting them from disease without decreasing growth performance. This has been proposed as a possible substitution to antibiotics **(Sato et al.,2009)**. Probiotics, in combination with vaccines, were used to observe the immune response in broilers. **(Stringfellow et al., 2011)** observed an increase in lymphocyte proliferation on day14 in addition to higher levels of heterophil oxidative bursts at day 7. These results confirm that probiotic treatments are very useful in modulating the immune response.

In addition to probiotics, a number of nonspecific immunomodulatory agents have been used to enhance immune responses against several pathogens in the poultry industry. For instance, heat-killed *Mycobacterium phlei* exhibited an immunotherapeutic potential in broiler chickens infected with *E. tenella*. Broilers treated with *M. phlei* showed a significant body gain weight and caecal lesion score. Additionally, these bacteria can act as immunostimulant agents and have beneficial roles against caecalcoccidiosis **(Bera et al.,2010)**. Arabinoxylans derived from wheat (*Triticumaestivum*) have also been shown to have immunostimulatory and protective effects against coccidiosis in broiler chickens **(Akhtar et al., 2012).** Recently, a number of herbal complexes and botanicals, such as the fungi *Lentinulaedodes* and *Tremella* and the plants *Aeglemarmelos*, *Eclipta alba*, *Oleaeuropaea*, *Pinusradiata*, and *Echinacea purpurea*, have been shown to contain active ingredients with mechanisms of action that include immunestimulation, whether alone or in combination with vaccines **(Abbas et al., 2012) (Allen, 2003).** Most recently, the efficacy of in-feed preparations including five dietary supplement regimens (anticoccidial salinomycin, probiotic, prebiotic, multienzyme, and essential oils mixture) were evaluated in *Eimeria* spp. infected broilers **(Bozkurt et al., 2014)**.

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