INTERNATIONAL JOURNAL OF AGRICULTURE & BIOLOGY
ISSN Print: 1560–8530; ISSN Online: 1814–9596
12–317/ZIP/2012/14–6–1014–1020
http://www.fspublishers.org

Review Article

Options for Integrated Strategies for the Control of Avian Coccidiosis

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ABSTRACT

Avian coccidiosis is one of the serious infectious diseases of poultry caused by different species of genus *Eimeria*. Though some anticoccidial vaccines are in the market with controversial efficacy, farmers mainly rely on the prophylactic and therapeutic use of chemicals for the control of avian coccidiosis. Frequent use of anticoccidial drugs, however, has resulted in the development of resistance in the Eimerian species. Increasing awareness about public health hazards associated with drug residues in food chain has also added to the constraints in using the synthetic drugs for treatment and control of diseases in animals. Therefore, there is a renewed interest in using alternatives for safe, effective and economical control of avian coccidiosis. Some of the alternatives focused in the current review include acids, vitamins, probiotics, mushrooms, amino acids, nonsteroidal anti-inflammatory agents, natural feed additives, essential oils and botanicals having anticoccidial properties. This review may, in given situations, be helpful in planning integrated control strategies for avian coccidosis.

Key Words: Anticoccidials; Alternatives; Poultry; Coccidia (or Eimeria); Coccidiosis; Drug resistance

INTRODUCTION

Commercial poultry farming is expanding day by day and contributing in the provision of affordable and high quality proteins (Ahmad *et al*., 2010; Ghafoor *et al*., 2010). However, this sector is still confronted with many enteric diseases like coccidiosis which are hindering its progress (Saima *et al*., 2010; Hafez, 2011).

Avian coccidiosis in an intestinal protozoan disease caused by various species belonging to genus *Eimeria*. According to a recent estimate (Chapman, 2009), the United States poultry industry costs about US$127 million annual losses just because of coccidiosis and proportionally similar losses may be faced by the poultry producers in various parts of the world. Thus, in commercial poultry systems, coccidiosis is thought to be the one of the most expensive infectious diseases. Thus far, chemoprophylaxis and anticoccidial feed additives have controlled the disease but situation has been complicated by the emergence of drug resistant strains against commonly used drugs (Abbas *et al*., 2008; Abbas *et al*., 2011a).

Vaccination by using live coccidial oocysts has been another effective approach for coccidiosis control (Shirley & Lillehoj, 2012), but, in poorly managed production systems particularly in case of broiler birds, live vaccines may result in the onset of severe reactions ultimately affecting the performance and production of flocks (Chapman, 2000). As a result of this drawback of live vaccines, attenuated vaccines, having reduced pathogenicity, have been developed, but these are expensive to produce. The other draw back of using vaccines is diversity of *Eimeria* strains in different geographical distributions. Therefore, vaccine strain, effective in one geographical area may not be effective in the other area.

Because of development of drug resistance and pathogenicity associated problems with live vaccines, poultry producers all over the world are moving towards alternative control of avian coccidiosis. Cost effective alternative strategies are being sought for more effective and safer control of avian coccidiosis (Abbas *et al*., 2011b, 2011c; Abbas *et al*., 2012; Arczewska-Wlosek & Swiatkiewicz, 2012; Zaman *et al*., 2011) which are discussed in the following sections.

Acids: Acids are known to have antibacterial, antifungal, and antiprotozoal activity particularly at low pH. Many acids like formic acid, butyric acid, anacardic acid, acetic acid and hydrochloric acid are found effective in controlling avian coccidiosis (Shobha & Ravindranath, 1991; Garcia *et al*., 2007; Abbas *et al*., 2011b, c). In an experimental study, Garcia *et al*. (2007) found formic acid to have positive

To cite this paper: Abbas, R.Z., Z. Iqbal, A. Khan, Z.U.D. Sindhu, J.A. Khan, M.N. Khan and A. Raza, 2012. Options for integrated strategies for the control of avian coccidiosis. *Int. J. Agric. Biol*., 14: 1014–1020

effects like increase in height of villus, depth of crypt and surface area of villus in broiler chickens experimentally challenged with *E. tenella*. The broiler growth performance and immune response were determined by using different doses of liquid dl-2-hydroxy-4-methylthio butanoic acid (LMA). In an arrangement of LMA with 4 graded levels 140%, 120%, 100% and 80% of methionine, broiler requirements were suggested by Chinese feeding standards for chickens; humoral immunity, cellular immunity and growth performance were determined. It was observed (Zhang & Guo, 2008) that in broiler chickens, methionine deficiency led to decrease in feed utilization; humoral and nonspecific immuno-competence were also decreased. However, use of LMA for methionine deficiency corrected these problems.

Organic acids like acetic acid have also been reported to have antimicrobial and anticoccidial effects (Chaveerach *et al*., 2004; Van Immerseel *et al*., 2004; Abbas *et al*., 2011b). Acetic acid is a weak organic acid which gives vinegar and is a partially dissociated acid in an aqueous solution. Only a few reports are available regarding the protective effects of acetic acid against avian coccidiosis (Abbas *et al*., 2011b). Organic acids showed promise in altering bacterial activities and cecal environment in chicken. Furthermore, a number of reports (Manickam *et al*., 1994; Runho *et al*., 1997; Yeo & Kim, 1997; Gunes *et al*., 2001; Abbas *et al*., 2011b) also showed the positive effects of organic acids on performance parameters such as weight gains and feed consumption. Recently, Abbas *et al*. (2011b) has shown the anticoccidial effect of acetic acid both in terms of improved performance (weight gain and feed consumption ratio) and pathological parameters (lesion scores, oocyst scores & mortality).

Some strong acids like hydrochloric acid, in low concentrations, are also being used for the control and treatment of avian coccidiosis (Abbas *et al*., 2011c). Furthermore, the acids when used at low concentrations also result in better performance by improving the solubility of the feed ingredients, digestion and absorption of nutrients but higher concentrations result in negative impact on weight gains and feed intake (Owings *et al*., 1990; Adams, 1999; Vesteggh, 1999).

Anacardic acid shows antimicrobial (Himejima & Kubo, 1991) and antitumor (Kubo *et al*., 1993) activities in addition to having effective molluscicidal (Kubo *et al*., 1986) effects. The feed supplementation with 0.4% cashew nut shell oil and 0.2% anacardic acid was found to be effective in controlling coccidial infection. Furthermore, it was also reported that anacardic acids with four concentrations $C_{15:3}$, $C_{15:2}$, $C_{15:1}$ or $C_{15:0}$ showed uncoupling effects of alkyl side chains (similar to the classical uncoupler 2,4-dinitrophenol) on the ADP/O ratio, state 4 and respiratory control ratio in succinate-oxidizing rat liver mitochondria (Toyomizu *et al*., 2000). Considering that proton electrochemical potential mediats the oxidative phosphorylation, as chemiosmotic hypothesis described, in mitochondria anacardic acids could act as ionophores and/or as protonophores (Toyomizu *et al*., 2003). Anacardic acids administration has dual effect as anticoccidial and/or anti-inflammatory drugs due to its possible protonophores/ ionophore properties.

So far, the exact anticoccidial mode of action of acids is not fully understood but it is thought that after entering into the microbial cell, the acids ionize to release H^+ ions, resulting in a decrease of intracellular pH. This influences microbial metabolism, inhibiting the action of important microbial enzymes and forces the cell to use energy to export the excess of protons H^+, ultimately resulting death by starvation. In the same matter, the protons H^+ can denature acid sensitive proteins and DNA of the microbial cell (Russell & Diez-Gonzalez, 1998).

Vitamins: Vitamins play a significant role in the development of chicken immune system and thus enabling them to fight against various stresses (Khan *et al*., 2010; Ajakaiye *et al*., 2011). Essential nutrients such as vitamins may affect both humoral and cell-mediated immune responses. Vitamin A differentiates the epithelial cells, which is highly essential for maintaining the integrity of mucosal surface of intestine (Chew & Park, 2004). Deficiency of vitamin A increases the chances of enteric diseases like coccidiosis and it also impaires the local immune defences within the gut lymphoid tissues of broiler chickens (Dalloul *et al*., 2002). Due to this effect, there was a significant reduction in intraepithelial lymphocyte subpopulations, mainly CD4+ T cells. The alteration in intraepithelial lymphocyte subpopulation leads to lower the ability of resistance against *E. acervulina*. Furthermore, it was reported (Dalloul *et al*., 2002) that the deficiency of vitamin A also affects the systemic immune system by reducing the ability of splenic T lymphocytes to respond to *in vitro* mitogen stimulation, which resulted in lower IFN-gamma secretion. In fact dietary vitamin A levels can affect gut immunity in broiler chickens, and its deficiency may lead to immunosuppression at those sites that make the birds more susceptible to coccidiosis.

Probiotics: Probiotics are 'live microorganisms, which when administrated in adequate amounts confer a health benefit on the host' (FAO, 2002). In poultry production, probiotics are identified for their ability to reinstate the intestinal microflora after being disrupted by antibiotic treatment or enteric infections (Line *et al*., 1998; Pascual *et al*., 1999). In addition, they are also known for their capacity to enhance the immune system and used against allergies and other immune diseases (Dalloul *et al*., 2003a, b; Kabir *et al*., 2004; Koenen *et al*., 2004).

Recently, Lee *et al*. (2007a) reported the increased resistance of birds against coccidiosis and a partial protection against growth retardation with a Pediococcus-based commercial probiotic (MitoGrow®). In another study, Pediococcus and Saccharomyces-based probiotic (MitoMax®) given to birds challenged with 5000 oocysts of either *E. acervulina* or *E. tenella*, less oocyst shedding and a better antibody response was found in probiotic fed birds compared to non-probiotic controls. These results suggest that MitoMax® when included in the diet, may improve the resistance against coccidiosis by enhancing the humoral immune response in birds (Lee *et al*., 2007b). Furthermore, Lactobacillus-based probiotic has optimistic influence on cellular immunity (Dalloul *et al*., 2005).

Mushrooms: Mushrooms contain antibacterial and antioxidant properties, thus, having the health-supporting benefits. Recently, Willis *et al*. (2007) conducted an experiment to determine the health and growth of broiler chicken by using the combination of probiotics (PrimaLac) and extract of Shiitake mushroom (*Lentinus edodes*). The results indicated that this combination was not effective for weight gain but showed positive effect on health enhancement. Furthermore, Guo *et al*. (2004, 2005) explored the immunoprotective effects of polysaccharide extracts of two mushrooms, *Tremella fuciformis* and *Lentinus edodes*, with an herb *Astragalus membranaceus* in the chickens infected with *E. tenella*. Both *Lentinus edodes* and *Astragalus membranaceus* fed groups showed lower cecal oocyst output. Likewise, it has been reported (Dalloul *et al*., 2006) that a mushroom lectin (FFrL) extracted from *Fomitella fraxinea* has the immuno-potentiating effect on cell-mediated immunity and subsequent protection against coccidiosis. As mushrooms have immunomodulatory activity, they can be used as effective growth promoting and immunostimulating agents in poultry.

Nonsteroidal anti-inflammatory drugs: The use of nonsteroidal anti-inflammatory drugs may be another effective approach for the control and treatment of avian coccidiosis but so far a very limited work has been done on this aspect. Ibuprofen is a nonsteroidal anti-inflammatory drug which inhibits the biosynthesis of prostaglandins with pro-inflammatory and immunosuppressive properties and is therefore proposed as a candidate molecule for the treatment of coccidiosis in broiler chickens (Vermeulen *et al*., 2004). A number of trials were performed to find out the anticoccidial activity of Ibuprofen. In all experiments, Ibuprofen was administered via drinking water and it was found that coccidial lesion scores and oocyst shedding were reduced when Ibuprofen was provided at a dose of 100 mg/kg body weight. However, at this dose, Ibuprofen did not show any significant effect on the degree of sporulation and infectivity of *E. acervulina* oocysts.

Natural feed stuffs: The use of natural feed additives has also been reported to provide protection against coccidiosis. Among natural products, fat rich diets such as fish oils, flaxseed and its oil, when fed to chickens from first day of age, are effective to control caecal coccidiosis (Allen *et al*., 1996a). Fat diets are a rich source of n-3 fatty acids (n-3 FA). Allen *et al*. (1996b) showed that n-3 FA rich diets (fish oil & flaxseed oil diets) significantly reduced the development of both sexual and asexual stages of *E. tenella*, characterized by cytoplasmic vacuolization, chromatin condensation within the nucleus, and lack of parasitophorous vacuole delineation (Danforth *et al*., 1997). Later, these findings were confirmed by the same effect of n-3 FA diets on other parasites (Allen *et al*., 1998). These diets (n-3 FA diets) are detrimental for the development of parasite because of inducing oxidative stress (due to the high concentration of easily oxidized double bonds). Therefore, the anticoccidial effect of n-3 FA against caecal coccidiosis (*E. tenalla*) is directly related to the concentrations of double bonds in n-3 FA ethyl esters (Allen & Danforth, 1998). However, n-3 FA diets are particularly effective against *E. tenella* because the developmental stages, sporulated oocysts and sporozoites, of this *Eimeria* spp. are deficient in superoxide dismutase enzyme, which would protect them from reactive oxygen damage. Allen *et al*. (2000) further supported the oxidative-stress hypothesis and observed that the antioxidant-stabilized diets supplemented with up to 10% flaxseed could not protect against *E. tenella*. Sources of fats, such as n-3 FA, can be used in combination of anticoccidial drugs or vaccines for the effective control of *E. tenella*. But further research is needed to explore the knowledge about the missing information about their mode of action and immunomodulatory effects.

Glycine betaine or betaine is extensively originated in nature and has been in use as anticoccidial agent in broiler chickens (Boch *et al*., 1994). The cells are protected from osmotic stress by betain accumulation and permit them to carry on activities of regular metabolism, in situations that would generally deactivate the cell (Petronini *et al*., 1992; Ko *et al*., 1994). In avian species coccidia is related with an enteric disease, and ionic and osmotic disorders are associated with this disease (Virtanen, 1995). These disorders may be worsened by using ionophorous anticoccidial drugs (Virtanen, 1995). Betaine, because of its osmoprotectant effects against osmotic stress, stabilizes cell membranes and thus enabling the maintenance of osmotic pressure in cells and ultimately maintain and ensure normal metabolic activity (Ko *et al*., 1994). Because of this osmoprotection, a number of studies (Augustine *et al*., 1997; Allen *et al*., 1998; Fetter *et al*., 2003) have been conducted to find out protection against avian coccidiosis. Betain showed not only intestinal protection against coccidiosis but also showed improved weight gains. However, to get maximum protection, authors suggested to use betain in combination with anticoccidial drugs.

Essential oils: Essential oils (EOs) are the combination of fragrant, volatile compounds, named after the aromatic characteristics of plant materials from which they are isolated (Oyen & Dung, 1999). EOs have been reported to have immunomodulatory effects that play a vital role in treating infectious diseases, especially when these oils have no adverse effect on the host (Awaad *et al*., 2010). Most of the EOs inhibit nitric oxide production in macrophages (de Oliveira Mendes *et al*., 2003). Nitric oxide is a potent intracellular parasite killing mechanism in macrophages and it is well known fact that macrophages are pivotal in the innate immune response (Dogdan, 2001). Oregano EOs have shown an antioccidial effect both in terms of better production (weight gain & feed conversion ratio) and reduced pathogenic effects (mortality, lesion scores, oocyst excretion) against experimentally induced *E. tenella* infection in broiler chickens (Giannesnas *et al*., 2003). But, this anticoccidial effect was lower as compared to commercial anticoccidial drug 'laslalocid'. However, in another study (da Silva *et al*., 2009), the anticoccidial effect of Oregano EOs was similar to anticoccidial effect exerted by ionophores antibiotics. Later, Oregano EOs were used in combination with some other plants EOs and extracts. This combined use of Oregano EOs increased the spectrum of their activity against both bacteria and *Eimeria* species (Bona *et al*., 2012). The effect of EOs on improvement in feed effeciency and ultimately better weight gains could be attributed to their positive effects on nutrient digestibility (Hernandez *et al*., 2004; Jamroz *et al*., 2005).

The carvacrol and thymol compounds, the primary components of Oregano EOs, are thought to impart anticoccidial activity by maintaining the intestinal integrity (Greathead & Kamel, 2006; da Silva *et al*., 2009).

Prebiotics: Prebiotic is a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in colon, and thus improves host health (Gibson & Roberfroid, 1995). The positive influence of prebiotics on the intestinal flora has been confirmed by a number of studies (Van Loo *et al*., 1999). Mannanoligosaccharides (MOS), derived from the cell wall of the yeast *Saccharomyces cerevisae*, are widely used as prebiotics to promote gastrointestinal health and performance. Mode of action of MOS is thought to block the binding of pathogens to mannan receptors on the mucosal surface and stimulate the immune response (Spring *et al*., 2000). In poultry, MOS enhance the development of *Bifidobacteria* spp. and *Lactobacillus* spp. in the intestinal tract of young chickens and suppress the number of enterobacteriacea members (Fernandez *et al*., 2002). Dietary MOS (1 g/kg feed) were found effective against, artificially induced, light infection of *E. tenella* (Elmusharaf *et al*., 2006). Later on, it was also observed that a dietary supplementation of MOS, at a concentration of 10 g/kg feed, reduced the oocyst excretion and diminished the severity of lesions caused by *E. acervulina*. But this anticoccidial effect was also observed against light infection induced by subclinical doses of sporulated oocysts (Elmusharaf *et al*., 2007). However, further research is required to validate whether MOS has anticoccidial activity when used at higher concentrations in feed in combination with higher challenge doses.

Botanicals: Recently, research on botanicals is getting great attention for the control and treatment of enteric diseases caused by both microbes and parasites (Alawa *et al*., 2010; Jung *et al*., 2011; Badar *et al*., 2011). Several poultry scientists all over the world are also actively engaged in research into the use of plants and plant derived products to fight and reduce the heavy economic losses in poultry industry caused by coccidiosis. Recently, Abbas *et al*. (2012) has provided an excellent review on the anticoccidial effects of various botanicals, herbal complexes and commercially available botanical products, against avian coccidiosis, along with their doses, active compounds, and mechanism of action. A number of botanicals were discussed but the candidate plants with anticoccidial properties include *Aloe* spps. (Marizvikuru *et al*., 2006; Yim *et al*., 2011), *Artemisia* spp. (Allen *et al*., 1998; Arab *et al*., 2006; Brisibe *et al*., 2008; de Almeida *et al*., 2012), *Azadirachta indica* (Tipu *et al*., 2002; Abbas *et al*., 2006; Biu *et al*., 2006; Toulah *et al*., 2010), *Beta vulgaris* (Ko *et al*., 1994; Augustine *et al*., 1997; Kettunen *et al*., 2001; Klasing *et al*., 2002), *Camellia sinensis* (Jang *et al*., 2007); *Curcuma longa* (Allen *et al*., 1998; Abbas *et al*., 2010; Khalafalla *et al*., 2011), *Echinacea purpure* (Allen, 2003), *Origanum vulgare* (Giannesnas *et al*., 2003), *Saccharum officinarum* (El-Abasy *et al*., 2003), *Triticum aestivum* (Allen *et al*., 1998) and *Yucca schidigera* (Alfaro *et al*., 2007). Most recently an herbal complex containing *Allium sativum*, *Salvia officinalis*, *Echinacea purpurea*, *Thymus vulgaris* and *Origanum vulgare* has also been found effective against many species of *Eimeria*, in broiler chickens, in terms of reducing oocyst output (Arczewska-Wlosek & Swiatkiewicz, 2012).

Most of the above mentioned plants have been reported to have antioxidant compounds like saponins, flavonoids, papaine, n-3 fatty acids, vernoside and tannins, and therefore may be lethal to the parasites by inducing oxidative stress.

Integrated coccidiosis control program: It is clear from the scientific literature that rapidly increasing problem of drug resistance and treatment failure will give rise to use of alternative control strategies in an integrated avian coccidiosis control program in future. Integrated control refers to the intelligent use of alternative control methods like; use of botanicals, vaccine, pre- and pro-biotics and immunemodulatory compounds in order to minimize the use of chemical compounds. In case of avian coccidiosis, alternation of drugs has been practiced with vaccines for many years. The suggestion that vaccination be combined with chemotherapy is not new, but efforts have not been made to develop an integrated control program by adopting other alternatives as well. Plant, bacterial, and other substances claimed to alleviate coccidiosis either directly or indirectly by improving health and immune status have been evaluated individually. So far, there is no data available on integration of these strategies into one coccidiosis control program. The future research in the area of botanicals and alternative control strategies should be focused on integration of already proven alternatives into an effective control program so that farmer could control coccidiosis in an effective manner with minimal use of drugs.

CONCLUSION

In the face of development of drug resistance almost all over the world and drug residues in food, there is an urgent need to take a shift towards alternative ways for the effective and long term control of avian coccidiosis. Using alternatives, mentioned in this review, provide a novel approach for controlling wide spread drug resistant *Eimeria* strains in intensive poultry production systems. Most of the alternates enhance the immunity of the birds and thus could play a vital role to minimize or eliminate the burden of anticoccidial chemotherapeutic agents in poultry production. Integration of the alternates proposed above for the treatment and control of avian coccidioisis may be one of the viable options. However, there is need of large scale experimental trials to establish the efficacy of alternative agents because most of these studies lack the sufficient replication, proper experimental designing and appropriate controls.

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(Received 23 June 2012; Accepted 01 October 2012)