

Review

Control of Avian Coccidiosis: Present and Future Strategies for Natural Alternatives of Therapeutics

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Abstract. Avian coccidiosis has great economic impacts on poultry enterprise. Coccidiosis is caused by *Eimeria* species mostly affecting epithelium of the bird's intestines causing enteric problems. Prominent clinical outcomes are bloody diarrhoea, poor FCR, weight gain and growth rate with high morbidity and mortality rate. For the control of coccidiosis various strategies have been adapted including chemical agents and feed additives. But due to their repeated use, drug resistance to *Eimeria* species emerged thus badly affecting their efficacy. Moreover, these chemical agents have adverse effects on bird's health and meat quality. Therefore, alternatives are used nowadays including natural and herbal products having the desired efficacy without harmful effects. Natural products and their anticoccidial activity have been reviewed in this study. This group comprises herbal extracts, fatty acids, fungal extracts, probiotics and immune response immunomodulators with proven anticoccidial activity. Additionally, poultry industry and economic cost of coccidiosis as well as classical strategies used in the control of avian coccidiosis are also reviewed.

Keywords: coccidiosis, natural alternatives, poultry, probiotics, herbal extracts

Introduction

Commercial poultry farming is one of the most flourishing industries in the world and it provides the cheapest source of animal proteins to human beings (Ahmad *et al.*, 2011). In Pakistan, out of total meat production, 19% is contributed by poultry (Ahmad *et al.*, 2010). Poultry farming is increasing day by day at commercial level however, due to certain diseases like coccidiosis, its development is affected in Pakistan and other countries of the world (Saima *et al.*, 2010). Coccidiosis is mainly caused by single celled protozoan of genus *Eimeria* of phylum Apicomplexa with complex life cycle. In commercial poultry farming, the incidence of coccidiosis ranges from 5 to 70% (Du and Hu, 2004). *Eimeria* species mostly affect the epithelial cells of bird's intestine, resulting in enteric problems leading to bloody diarrhoea, poor growth rate and high mortality with heavy economic losses up to three billion dollar per annum worldwide (Dalloul and Lillehoj, 2006). So far seven species of genus *Eimeria* (*E. mitis*, *E. maxima*, *E. acervulina*, *E. necatrix*, *E. brunetti*, *E. tenella* and *E. praecox*) have been identified that are responsible

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for coccidiosis in chickens by residing in different parts of their intestines. The most devastating species is *E. tenella* that causes ceacal coccidiosis in chickens. Ceacum is the predilection site for *E. tenella* sporozoites that invades its mucosa through villi of epithelial cells and results in severe damage to epithelium, reduced weight gain, blood in faeces, poor feed efficiency and ultimately death of birds that leads to heavy economic losses (Zaman *et al.*, 2012). Sub-clinical form of avian coccidiosis manifests as immunosuppressant in the birds that result in outbreak of secondary bacterial diseases. During rainy seasons, there is high incidence of coccidiosis (Etuk, 2010). The hot and humid weather positively hastens prevalence of disease by providing favourable conditions to the infective oocyst.

Various strategies in the past have been adopted to overcome avian coccidiosis including use of synthetic chemicals and anticoccidial feed additives. However, with the passage of time and repeated use of these drugs there is emergence of anticoccidial drug resistance in *Eimeria* species (Abbas *et al.*, 2012). Along with this Nogueira *et al.* (2009) has also reported that harmful effects of these chemicals on bird's health status and

consumption of affected meat by humans are the major constraints. Another technique for the control of coccidiosis is the use of live vaccines but this practice may lead to development of clinical disease in the broiler under poor management (Chapman, 2000). Owing to increasing drug-resistant parasite strains, the use of these chemical agents proved ineffective and there is need of time to introduce alternatives for the control of disease (Abbas *et al.*, 2012; Tacconelli, 2009). Resistance development in target parasites, high cost, and toxic effects of chemotherapeutic drugs are the main constraints. Therefore, for the prevention of coccidiosis, current circumstances demands alternatives. Natural and synthetic biological compounds considered as appropriate agents (Patwardhan and Gautam, 2005), to sustain bird health without affecting performance. Plant based biological active compounds are thought to be promising candidates due to their availability and powerful efficacy with no or minimal residual effect in consumers (Patwardhan and Gautam, 2005). To cure health related issues almost 64% of human population use plant based drugs worldwide (Farnsworth, 1999).

During last decade, various authors have reported that plant and herbal products have protective and therapeutic effects against experimental coccidial infections in birds (Lorrain *et al.*, 2010; Nweze and Obiwulu, 2009). It has been reported that 50% synthetic drugs have been made from compounds of plants. In this regard, one of the important source is cereals. In humans and other animal models, studies have shown that dietary cereal fibres may have a great effect on different physiological parameters. Cereals based carbohydrates are mainly reported as antitussive, antioxidant, antimutagenic, anti-inflammatory, anti-cancerous and immunomodulators (Zhou *et al.*, 2010). Cereals, fungi and yeast cell wall contain β -glucans as principle structural components with molecular weight 2000 kDa approximately. These polysaccharides enable the host to develop resistance against viral, parasitic, fungal and bacterial diseases by enhancing immune system, lysosomal enzyme activity, phagocytosis and IL-1 production (Estrada *et al.*, 1997). Botanicals may act as best and safe alternative source to anticoccidial drugs for the prevention of coccidiosis (Abbas *et al.*, 2012). A variety of botanicals including *Triticum aestivum*, *Hordeum vulgare*, *Emblica officinalis*, *Aloe vera* and *Avena sativa* have shown effective biological responses. *Oryza sativa* also known as Asian

rice, belonging to family *Poaceae* is an annual plant, which has shown immunostimulant effect through increased allergic reactions, inhibited mast cell degradation in rat (Ghatak and Panchal, 2012; Oka *et al.*, 2010), increased nitric oxide, TNF- α and interleukins in murine macrophages (Park *et al.*, 2013) as well as increased lymphocytic proliferation, TNF- α and interferon- γ (Ghoneum and Jewett, 2000). The denatured bran of this plant results in arabinoxylan by means of enzymatic hydrolysis, a polymer of xylose and arabinose (Ghoneum, 1998). Alternatives are not only natural products but they also contain valuable molecules to which resistance has not yet developed. Herbal and medicinal plants, fungal extracts and probiotics could have additional significant benefits such as palatability, low cost, low toxicity and non-residual properties (Table 1-3). Currently interest has been developing in the use of these natural products to reduce the chances of coccidiosis.

Review of literature. Favourable results have been obtained by using natural alternatives in avian coccidiosis as described in the following review literature:

Antioxidants. Fats and oils. Deficiency of vitamin A in poultry increases susceptibility to coccidiosis and other enteric infections. Alterations in intraepithelial lymphocytes due to vitamin A deficiency increase susceptibility of birds to coccidiosis (Dalloul *et al.*, 2003). Fats contained higher concentrations of linolenic acid, eicosapentanoic acid and reduced severity of coccidiosis in young broilers. Feed supplemented with 10% linseed oil, 10% flax seed oil and 10% fish oil markedly reduced ceecal lesions. Fats decreased parasitic infestation and provided immunity against *Eimeria* (Allen *et al.*, 2000). Antioxidants have been divided into two categories; i.e., fat soluble (Vitamin E and carotenoids) and water soluble (Vitamin C, uric acid, glutathione and lipoic acid). Fat soluble antioxidants hinder lipid peroxidation and protect cell membranes while water soluble reacts with free radicals existing in cytosol and blood plasma (Surai, 2007). Utilisation of botanical antioxidants is correlated in control of coccidiosis because coccidial infections are associated with lipid peroxidation of mucosa of intestines and antioxidants prevent such lipid peroxidation (Naidoo *et al.*, 2008). Coccidiosis infections promote lipid peroxidation in broilers and dietary alpha tocopherols at 316 mg/kg improved oxidant/

antioxidant system in victim birds (Masood *et al.*, 2013). Antioxidant nature of ground corn showed that corn inhibited generation of lipid hydro peroxides and their secondary products. This activity was assumed due to bound hydroxyl-cinnamates like *p*-coumaric acid and ferulic acid (Bauer *et al.*, 2013).

Antioxidant potential of corn bran. Corn husk derived arabinoxylans have been reported to possess an immunostimulatory effect, characterised by increased cytokines production and natural killer cells activity (Ogawa *et al.*, 2005; Zhang *et al.*, 2004). Bauer *et al.* (2013) reported the antioxidant potential of ground untreated corn fibre and wheat bran against lipid oxidation based on oxidative products inhibition. It was concluded that corn fibre had higher antioxidative effect at 800 mg/kg emulsion concentration which inhibited lipid hydroperoxides formation than wheat bran based on molar formulated oligosaccharides products through enzymatic treatment and methanolic extraction.

Herbal extracts and medicinal plants. Cereals derived β -glucans not only have antitussive and adipogenic activity, but they are also very important in tumor regression. Morikawa *et al.* (1985) conducted a study on wheat derived β -glucans. Results of their study showed about 100% increased polymorphonuclear leukocytes activity against tumor cells. Immuno-modulatory properties of oat derived β -glucans are not new, about two decades earlier a study was conducted by Estrada *et al.* (1997), that investigated the role of β -glucans on mice immune system. Results of their study revealed the release of TNF- α , IFN- γ , IL-4, IL-2 and IL-1 from peritoneal macrophages. Oat is an important plant that has an extensive list of biological effects. It contains proteins, fats, total digestible nutrients, minerals and vitamin (thiamine). Oat is one of the beneficial grains, which is used as nutritional compound in both humans and animals. Oat can be used as an antioxidant compound due to abundant amount of two main enzymes; alcalase and tryptic that actively transform proteins into peptides and these peptides perform antioxidant activity (Hussain *et al.*, 2002). In emergency circumstances and scarcity period oat can be used to form hay or silage. Due to this reasons it is commonly used in the diet of young animals, poultry, dairy cows and horses (Hussain *et al.*, 2002).

In another study, Yun *et al.* (2003) reported that oat β -glucans were dynamically responsible for the enhance-

ment of resistance in mice, against *E. vermiformis* and *S. aureus*. To support his idea he conducted *in vitro* and *in vivo* studies that enabled the immune system to increase phagocytic activity. Results of their study were satisfactory that fecal oocyst shedding reduced by 28% in intragastric and 39% in intraperitoneal group of mice (C57BL/6) that were initially infected with *E. vermiformis* as compared to control group. Moreover, oat cell wall polysaccharide, arabinoxylans and β -glucans are much important regarding health point of view. These carbohydrates are mainly effective against tumor growth and stimulate immune system (Vetvicka, 2011). *Avena sativa* locally known as jodar, javi or jai is an important cereal grain that has positive impact on consumer's health. Regarding their chemical structure, in recent years Havrlentova *et al.* (2011) reported that oat contained an important polysaccharides, β -glucans. It was concluded that one of the characteristic feature was their chemical structure β , 1-4 linkage due to which these were effective against bacteria, viruses and other pathogens. Additionally, these had anti-tumor activity and also act as free radical scavengers. Oat derived β -glucans may have some additional properties. A study was conducted by Vetvicka (2011), investigating the immunomodulatory and adipogenic activity of oat β -glucans. Moreover, it was found that these were helpful in wound healing process and also decreased the skin irritation.

Beta vulgaris. *Beta vulgaris* belongs to the family Chenopodiaceae and commonly known as red beet. *B. vulgaris* is a traditional plant in India and many countries including Pakistan and extensively used to treat as a therapeutic agent in hypertension, in diabetes and cancer due to its antioxidant properties. Roots of *B. vulgaris* have also been reported to be rich in antioxidant compounds (Shrishailappa *et al.*, 2007). Its juice has been found to reduce the xenobiotic-oxidative stress in rats by rejuvenating the activity of the majority of antioxidant enzymes in liver (Kujawska *et al.*, 2009). The active compounds present in *B. vulgaris* root include folic acid (15.8 mg/g), betacyanins and betaxanthines prevent active oxygen-induced, free radical scavengers and help in radical-mediated oxidation of biological molecules. *B. vulgaris* methanolic extract bears anticancerous and immunomodulatory activities (Tripathy and Pradhan, 2013).

Camellia sinensis. *Camellia sinensis* (green tea) is an important plant which contains natural flavonoids.

These flavonoids are known to have antioxidant properties due to which it can be used as an excellent anticoccidial agent. Furthermore, it also contains lipids, volatiles compounds, amino acids (especially l-theanine), carbohydrates, alkaloids, carotenoids and minerals which are helpful against several diseases. It reduced fecal oocyst shedding and improved weight gain when supplemented in feed of broilers (Jang *et al.*, 2007). *Camellia sinensis* also has anti-inflammatory antiproliferative anticancer antibacterial, antiviral trypanocidal agent and also showed inhibitory effect against ovine *Babesia* (Chen *et al.*, 2008).

Eclipta alba. *Eclipta alba* which is also known as *Eclipta prostate* having white flowers is renowned to use as diuretic and tonic agent in treatment of various hepatic diseases. In an experiment, there was appreciable weight gain observed in broiler birds infected with *Eimeria* which were orally treated with *Coumestans* obtained from *Eclipta alba* at the rate of 120 ppm. It also resulted in 80% reduction in excretion of oocysts and treated birds did not show any signs of toxicity such as hepatic and muscular lesions but, at higher dose rate (180 ppm), signs of toxicity were observed in birds (Michels *et al.*, 2011).

Aloe vera. Aloes are known medically most important plants and are used to treat many disease conditions due to their therapeutic properties. More than 360 species of aloes are identified but *A. excelsa* is well known species that has excellent anticoccidial properties, comparable with sulphachlopyrazine sodium monohydrate. Supplementation of *A. excelsa* in feed improved mean weight gain and reduced oocysts expulsion in broiler birds (Gadzirayi *et al.*, 2005). Another important species of aloe plant is *Aloe vera* which is also known to have anticoccidial properties. Recently, Akhtar *et al.* (2012) has conducted a study to evaluate the anticoccidial and immunomodulatory effects of both aqueous and ethanolic *Aloe vera* extracts against coccidiosis in broiler birds and reported excellent results of *Aloe vera* in terms of improved immune response and increased weight gain in birds against mixed *Eimeria* infection. So, it can be effectively used as an immunomodulatory agent against avian coccidiosis. In a study, supplementation of *A. vera* in feed showed remarkable effect in lowering gut lesions and oocyst excretion of *Eimeria* in faeces of broiler chickens (Yim *et al.*, 2011).

Pinus radiata. *Pinus radiata* belongs to family Pinaceae which is commonly used as Monterey pine or radiata pine, has phenolic compounds due to which it has been as traditional medicinal plant in various countries such as Europe and North America. Molan *et al.* (2009) evaluated the *in vitro* efficacy of *Pinus radiata* aqueous extracts on prevention of oocysts sporulation of different *Eimeria* species. Inhibition bioassay was used to investigate the effect of PBE on the sporulation of *Eimeria* oocysts. The results of study revealed that incubation of unsporulated oocysts in water containing 500 µg PBE per mL caused the prevention of sporulation of these oocysts by 28-84% as compared to control tubes. Furthermore, 12% of *Eimeria* oocysts showed abnormal sporocysts in size, shape and number. This study suggests that pine bark extract can be used for control of coccidiosis in broiler birds.

Ageratum conyzoides. The Asteraceae or Compositae (referred to as the aster, daisy, sunflower family) is a widespread family of flowering plants having phenolic compounds. Due to this property it has been used against ceacal coccidiosis as well as acute toxicity and given orally at dose rate (250-300 mg/kg to 500-1000 mg/kg). Reportedly causing increased weight gain and increased red blood cell count (Nweze and Obivulu, 2009).

Curcuma longa. Turmeric (*Curcuma longa*) is a rhizomatous herbaceous perennial plant of ginger family. Effectiveness of turmeric (*C. longa*) crude powder and salinomycin sodium against occurrence of coccidiosis in broiler has been reported that feed consumption, body weight gain and feed conversion ratio were better in birds supplemented with 3% turmeric powder than untreated group (Mashhadan, 2015). Reduction in oocyst excretion and bloody diarrhoea was almost similar to the anticoccidial drug "salinomycin sodium" (Abbas *et al.*, 2010).

Saccharum officinarum. Sugarcane (*Saccharum officinarum*) belonging to the genus *Saccharum* is one of the several species of tall perennial true grasses of warm temperate to tropical regions of South Asia Melanesia. The effectiveness of sugar cane juice and bagasse were reported to counter broiler coccidiosis. Water and ethanolic extracts were used to evaluate the therapeutic efficacy of sugar cane. It showed good results in terms of reduced oocyst shedding and mortality rate was also low (Akhtar *et al.*, 2012). Similarly, higher

weight gain and antibodies response observed in challenged birds but relative lymphoid organ weight ratio was not significant. However, ethanolic extract was more effective than water extract (Awais *et al.*, 2011).

***Ocimum basilicum*.** Plants belonging to genus *Ocimum* have 50-150 species of shrubs and herbs found in different sub-tropical and tropical areas of Africa, Asia, South and Central America. Among these species, *Ocimum basilicum* has over 50 therapeutic activities and has been reported to treat large number of disease conditions. It is antiseptic, antibacterial, febrifuge and aneurostimulant (Onwurah *et al.*, 2011). Another study was conducted to determine the effect of basil in broiler coccidiosis. The study revealed that provision of this plant extract to diseased birds showed good results with respect to feed conversion ratio, live weight gain, oocyst count and hematological parameters. However, the effect on mortality and daily feed intake were not statistically significant. This study recommended prophylactic and curative dose as 5 and 15 g, respectively in feed and water (Onwurah *et al.*, 2011).

***Artemisia annua*.** *Artemisia annua*, also known as sweet wormwood or sweet annie. The dietary effect of *Azadirachta indica* and *Artemisia annua* has been observed on broilers performance and anticoccidial potency against *E. tenella* post infection trial. Three parameters; feed conversion ratio, average body weight gain and feed intake were focused for the evaluation of anti-coccidial activity of both plant extracts in challenged groups. Significant results were observed in orally infected bird's group with *A. indica* (10%) or *A. annua* (5%) incorporation in broiler diet (Hady and Zaki, 2012).

***Thonningia sanguinea*.** *Thonningia sanguinea* is a renowned plant used as traditional medicine in African countries. Antioxidant and antiprotozoal activity of this plant has been observed against different diseases in birds. The results of study showed that dose more than 2.5 mg/mL significantly inhibited the invasion of bovine kidney cells by the sporozoites of *E. necatrix* and *E. tenella*. This study demonstrated that *Thonningia sanguinea* can be effectively used in feed for the control of coccidiosis in broiler birds (Severin *et al.*, 2012).

Immune response modulators. Immunostimulatory and therapeutic potential of rice bran. Rice is also

known as an important immunostimulant and therapeutic agent against avian coccidiosis. Martinez *et al.* (2015) described the increased cytotoxic potential of natural killer (NK) cells by means of rice bran derived Arabinoxylans (MGN-3) against murine neuroblastoma. For this study, NK cells activity by means of MGN-3 addition was evaluated for their phenotypic, cytotoxic and cytometric bead potential on cultured cell lines both *in vivo* and *in vitro*, respectively for two weeks. MGN-3 showed significantly increased activity for CD25 and CD69 receptors without alteration of induced self antigens and other non-catalytic receptors. Moreover, carcinoma cells growth was also inhibited due to increased NK cells cytotoxicity. These results concluded the immunoregulatory efficacy of NK cells and their beneficial remedial application for neural carcinoma. Fang *et al.* (2012) elaborated the anti-inflammatory and therapeutic results of acid hydrolysed feruloylated oligosacchrides (FO) from rice bran at dose rate of 0.1-100 µg/mL through increased TNF- α , IL-1 β , IL-6 and PGE2 production in RAW264.7 macrophages. Ani *et al.* (2013) concluded that feeding rice milling waste (RMW) improved growth rate through increased feed intake in broiler chicks. Rice is also known as an important immunostimulant and therapeutic agent against avian coccidiosis. Choi *et al.* (2014) reported the immunomodulatory activity of rice bran derived arabinoxylans through increased natural killer (NK) cell activity and modulated cytokine production in humans. Ghoneum *et al.* (2014) evaluated anticancer effects of rice bran derived arabinoxylan on cultured nonmetastatic MCF-7 human and metastatic 4T1 mice breast cancer cells. MGN-3 increased apoptosis, DNA damage and inhibition of cellular proliferation in 4T1 cells. It was also concluded that rice bran derived arabinoxylans have a potent chemotherapeutic effect against metastatic breast cancer.

Ani *et al.* (2013) conducted a study to evaluate comparative effects of feeding rice milling waste (RMW) and Roxazyme G2® enzyme on the performance of broiler chicks. Enzyme supplementation significantly reduced feed intake and improved the performance of birds in terms of average daily weight gain, protein efficiency ratio and feed cost. Enzyme supplementation significantly reduced feed intake and improved the performance of birds in terms of average daily weight gain, protein efficiency ratio and feed cost. These results

concluded that feeding rice milling waste (RMW) improved growth rate through increased feed intake in broiler chicks. Rohman *et al.* (2014) described the nutritional significance of rice for diabetic patients in Asia. Besides other cereals, there is an increased dietary intake of rice due to glucose rich contents. Similarly, rice derivatives including its bran and oil in traces have also been reported to exhibit beneficial effects on health. Fat free rice bran would be resulted on further processing of rice husk. Fat free fraction of rice bran contained carbohydrates rich contents. These contents of rice derivatives exhibit their therapeutic potential against cardiac diseases and cancer in terms of hypocholesterolemic and hypoglycemic effects.

Immunomodulatory potential of barley. Yun *et al.* (1997) evaluated the immunostimulant potential of oat derived β -glucans (1 \rightarrow 3, 1 \rightarrow 4) at dose rate of 0.2 mL intraperitoneally in CD-1 mice in terms of increased number of macrophages in peritoneal fluid and improved survival in 3 days pre-exposure to *S. aureus*. Moreover, its subcutaneous dose of 0.1 mL or administered intraglutely 0.3 mL daily for 10 days in immunosuppressed and infected C57BL/6 mice with coccidiosis reduced fecal oocyst output by 23 and 34%, as well as increased total antibody titers against sporozoites and merozoites. On the whole oat β -glucans showed immunostimulatory effects in terms of increased humoral and cellular immune responses against *E. verniformis* infection in mice.

These results suggested an immunostimulant potential of oat β -glucan against coccidiosis. Pelizon *et al.* (2005) evaluated the immunostimulatory effect of *Saccharomyces cerevisiae* derived β -glucans at dose rate of 20 μ g I.P. in female C57BL/6 mice by increased IL-12, TNF- α and natural killer spleen cells. β -glucans are soluble non-starch and complex polysaccharides abundantly found in bacterial, fungal, oats and barley cell walls which play their vital role in anti-microbial immunomodulation. Angeli *et al.* (2009) examined the mutagenicity of barley derived β -glucans in hep G2 hepatocytes at concentrations of 100 and 200 mg/mL, respectively. Chan *et al.* (2009a) concluded the receptor based mode of action of β -glucans with respect to natural or acquired immunity in terms of lymphocytic proliferation and differentiation in reticuloendothelial system (RES). Talati *et al.* (2009) suggested that barley supplementation could reduce total cholesterol, triglycerides and the low

density lipoprotein levels in humans. Takeshi and John (2010) described anti-inflammatory and immunostimulant potentials of 1 g barley derived arabinoxylans against irritable bowel syndrome (IBS) in humans in terms of improved gastrointestinal symptoms and increased NK cell activity. Samuelsen *et al.* (2011) concluded the low immunomodulatory response of barley derived arabinoxylans and β -glucans *in vitro*. Besides other cereals, barley is also known to have immunomodulatory potential against various diseases. Khoury *et al.* (2012) concluded the therapeutic significance of oats and barley derived β -glucans against obesity and metabolic syndrome through maintenance of enteric health in humans. Jacob and Pescatore (2012) reported the improved feeding values of barley litter through reduced intestinal viscosity while poultry farming. Gao *et al.* (2012) suggested that oat derived β -glucans supplementation decreased cholesterol level of serum and less enteric microbial activity with low immunomodulation in humans.

Immunomodulatory and therapeutic potential of wheat bran. Vahouny *et al.* (1985) evaluated an increased intestinal goblet cell secretory potential through 10% wheat bran dietary supplementation. Kruis *et al.* (1986) evaluated the supportive therapeutic efficacy of wheat bran in terms of superior symptomatic effect against human irritable bowel syndrome (IBS). Watzl *et al.* (1990) evaluated the phagocytic stimulant potential of wheat bran derived polysaccharides extract at dose rate of 10^{-2} mg/mL for human polymorphonuclear leukocytes. Roccatello *et al.* (1990) examined an increased *in vitro* cytotoxic activity of human peripheral blood mononuclear cells particularly of neutrophil chemokinesis by means of gliadin and glyc-gali at dose rate of 5 and 50 μ g/mL, respectively. Takahashi *et al.* (1999) examined the inhibitory effect of microfibril wheat bran on azoxy-methane at dosage rate of 20% (w/w) and 10 mg/kg against colon carcinogenesis in female CF1 mice, respectively. Neyrinck *et al.* (2008) suggested the therapeutic value of wheat bran derived arabinoxylans against obesity and metabolic disorders at dose rate of 10% with decreased macrophages, IL-6 and CD68 mRNA in adipose tissues in mice. Cao *et al.* (2011) reported the antitumor effect of wheat bran arabinoxylans in S180 mice by promoting cell mediated immunity with peripheral leukocytosis and increased haemopoiesis. Among these cereals wheat is an important

Table 1. Overview of the anticoccidial effect of botanicals against avian coccidiosis

Botanical and English names	Active ingredients	Dose	Mode of action	Species studied	Affected parameters	Sources
<i>Aegle marmelos</i> (Bael)	Unknown	Orally @ 2 mL for 5 consecutive days	Unknown	Mixed infection	OC↓, FC↑, WG↑	Khan <i>et al.</i> , 2008
<i>Ageratum conyzoides</i> (Ageratum)	Flavonoids	Orally 500-1000 mg/kg b.w.	Oxidative stress	E.t	OC↓, WG↑, PCV↑, RBC↑, OC↑	Nweze and Obiwulu, 2009
<i>Carica papaya</i> (Papaw)	Papaine	Dry leaf powder 15% of feed	Sporozoites digestion in the caeca	E.t	-	Al-Fifi, 2007
<i>Cyamopsis tetragonoloba</i> (Guar)	Glactomannans and saponins	5% of feed	Binding with sterol molecules present on protozoal cell membrane surfaces	E.t	OC↓, BD↓	Hassan <i>et al.</i> , 2008
<i>Eclipta alba</i> (Bhringaraj)	Coumestans	120 pp in feed	Unknown	E.t	OC↓, FC↑, WG↑	Michels <i>et al.</i> , 2011
<i>Linum usitatissimum</i> (Flaxseed)	N-3 fatty acids	15% of feed	Oxidative stress	E.t	LS↓, degree of parasitization↓	Allen <i>et al.</i> , 1997
<i>Lentinus edodes</i> and <i>Tremella fuciformis</i> (Mushrooms)	Polysaccharide extracts	1 g/kg feed	Immune stimulation	E.t	WG↑	Guo <i>et al.</i> , 2004; 2005
<i>Musa paradisiacal</i> (Banana)	Unknown	Methanolic extract @ 1,000 mg/kg b.w.	Unknown	E.t	OC↓, CS↓, PCV↑	Anosa and Okoro, 2011
<i>Olea europaea</i> (Olive tree)	Maslinic acid (2- α , 3- β -dihydroxiolean-12-en-28-oic acid)	90 ppm of maslinic acid in feed	Anti-inflammatory & antioxidant properties	E.t	OC↓, LS↓, WG↑	De Pablos <i>et al.</i> , 2010
<i>Pinus radiata</i> (Monterey pine)	35% condensed tannins	Oocysts exposed to 500-1000 mg pine bark/mL	Damage of cytoplasm (sporont)	E.t; E.m; E.a	Sporulation↓	Molan <i>et al.</i> , 2009
<i>Passum sativum</i> (Pea plant)	Antibody fragments	-	Inhibition of sporozoites reproduction	E.t	Sporozoite infectivity and reproduction↓	Khalafalla and, Dausgschies 2010
<i>Sophora flavescens aiton</i> (Sophora)	Unknown	6-30 g/L Drinking water	Unknown	E.t	M↓, LS↓, OC↓, WG↑	Youn and Noh, 2001
<i>Tulbaghia violacea</i> (Society garlic, sweet garlic)	Antioxidant compounds (S-(methylthiomethyl) Cysteine sulphoxide (marasmine), bisl((methylthio) methylsulfide and various derivatives)	Aqueous extract 35 mg/kg feed	Oxidative stress	Mixed infection	FCR↑, OC↓	Naidoo <i>et al.</i> , 2008
<i>Vitis vinifera</i> (Grape seed)	Tannins	10-20 mg/kg Feed	Oxidative stress	E.t	M↓, LS↓, WG↑	Wang <i>et al.</i> , 2008
<i>Vernonia amygdalina</i> (Vernonia tree)	Vernoside	Dry leaf powder @ 15% of feed	Oxidative stress	E.t	OC↓	Al-Fifi, 2007

↑ = improvement/increase/higher; ↓ = decrease/lower; E.t = *Eimeria tenella*; E.a = *Eimeria acerulina*; E.m = *Eimeria maxima*; E.b = *Eimeria brunetti*; E.n = *Eimeria necatrix*; E.miv = *Eimeria mivati*; WG = body weight gain; FC = feed consumption; FCR = feed conversion ratio; LS = lesion scores; OC = oocyst count; BD = bloody diarrhea; M = mortality; PCV = packed cell volume; RBC = red blood cells; CS = clinical signs.

Table 2. Overview of the anticoccidial effect of herbal complexes against avian coccidiosis

Herbal complex	Composition	Dose	Mode of action	Species studied	Affected parameters	Sources
Herbal complex	<i>Uncariae ramulus cum Uncis, Agrimoniae herba, Sanguisorbae radix, Eclipta prostrata herba, Pulsatillae radix, Sophorae feed flavescens radix, Rehmanniae radix, Glycyrrhizae radix</i>	2 g/mL drinking water & 10 g/kg	Unknown	E.t WG↑	LS↓	Du and Hu, 2004
<i>Muscadine pomace</i>	By-product of the production of wine and juice from <i>Vitis rotundifolia</i>	0.5-2.0% of feed	Unknown	E.a; E.m; E.t	M↓, LS↓, WG↑	McDougald <i>et al.</i> , 2008
Herbal complex	<i>Solanum nigrum</i> (35%), <i>Aloe vera</i> (15%), <i>Moringa indica</i> (35%) and <i>Mentha arvensis</i> (15%)	10% in feed for 7 days continuously	Unknown	E.t	LS↓, WG↑, FCR↑	Chandrakesan <i>et al.</i> , 2009
Herbal complex	<i>Allium sativum</i> 4 g, <i>Zingiber officinale</i> 6 g, <i>Azadirachta indica</i> 3 g and <i>Berberis lyceum</i> 10 g mixed per liter drinking water	Treated water for 14 days	Unknown	Mixed infection	OC↓	Nidaullah <i>et al.</i> , 2010
Herbal complex	<i>Azadirachta indica</i> , <i>Nicotiana tabacum</i> , <i>Calotropis procera</i> and <i>Trachyspermum ammi</i>	Orally (2-6 g once a day) for 7 Days	Unknown	E.t	M↓, LS↓, WG↑, FCR↑, OC↓	Zaman <i>et al.</i> , 2011

LS = lesion score; WG = weight gain; FCR = food consumption ratio; OC = oocyst count; M = mortality.

Table 3. Some natural products commercially available for prevention and treatment of coccidiosis

Product	Ingredients	Supplier
Avihicox	Clove and <i>Bocconia cordata</i> extract	Centaur
Nutrimin	Apple cider vinegar	Chicken lickin
Kocci Free	Olive leaf, mustard seed, black seed, cloves, grapefruit seed extract	Amber Technology
Oil of oregan	Oregan extra virgin olive oil (80% carvacrol)	Natural factors
Oilis	Natural vegetal extracts	Engormix
Oreganico	Oregan oil and essential oils	Flyte so fancy
Garlic granules	Garlic	Flyte so fancy
Poultry Provita	Probiotics and prebiotic inulin	Vets Plus
CitriStim	Mannan oligosaccharides and beta glucans	ADM
Orego Stim	Carvacrol (82%) and Thymol (2.4%)	Saife vetmed
Herban	Etheric oils, soya oils, oregan oils	Uncle Ted Organics Ltd
Herb 'n' thrive	Concentrated blend of herbs and essential oils	Chicken lickin
Eimericox	Several essential oils	Phytosynthese/Trouw Nutrition
Natustat	Several essential oils and yeast cell walls	Alltech
Enteroguard	Garlic and cinnamon	Orffa
Xtract Immunocox	Spanish pepper and turmeric	Pancosma
Coxynil	<i>Allium sativum</i> Linn 15%, <i>Cinnamomum camphora</i> Nees & Eberum 15%, <i>Elephantopus scaber</i> Linn 15%, <i>Valeriana walliegii</i> DC 15%, Sulphur dioxide 25% and NaCl 15%.	Growell India
Ropadiar solution	Oregan oil (on diatomite)	Ropapharm

immuno-modulator against various diseases. Singh *et al.* (2015) described the immunomodulation of potent prebiotic, xylooligosacchrides (XOS) resulting from

hydrolysis of agricultural byproducts. These XOS improved gut epithelial health for microflora and regulated antioxidant activity. Akhtar *et al.* (2012) evaluated the

immuno-stimulatory and anticoccidial potentials of wheat (*Triticum aestivum*) bran derived arabinoxylans (AXs) in chickens. These showed an improved daily weight gain, organ body weight ratio for thymus and cecal tonsils with lower oocyst count and lesion scores and higher antibody titers against sheep red blood cells.

Fungal extracts. Fungal, *Sclerotinia sclerotiorum* derived beta glucans are used to treat many disease conditions due to their therapeutic effects. Suzuki *et al.* (1989) conducted a study in mice and found that fungal derived β -glucans were responsible to modulate immune system. Higher spleen cell proliferation was noted in response to concanavalin A (T-cell mitogen) and lipopolysaccharide (B-cell mitogen) with comparison to control group of mice. Moreover, oral administration of *S. sclerotiorum* glucans also improved the function of NK (natural killer) cells and lysosomal enzyme that actively fight back against numerous pathogens. In addition to these, antitumor activity was also observed.

This study suggests that *S. sclerotiorum* derived beta glucans can be used to enhance immune system. *Saccharomyces cerevisiae* is an important fungus that may have immunostimulatory effect by increasing different interleukins and cytokines production. In a study, Pelizon *et al.* (2005) investigated that *S. cerevisiae* derived β -glucans were responsible for increasing the fungicidal and natural killer cell activity. Moreover, increased cytokine production, IL-12 and TNF- α was also observed. Among body's complex system one is the immune system that is broadly categorized into adaptive and innate immune system. It is proved experimentally that both these system can be modulated by β -glucans. Chan *et al.* (2009b), suggested that these polysaccharides initiated their response through immune receptors. These receptors included CR3 (complement receptor), TLR-2/6, Dectin-1 and activated a set of immune cells including dendritic cells, monocytes, neutrophils, NK cells and macrophages. These polysaccharides with specific linear backbone 1 \rightarrow 3 beta-glycosidic chain could not be digested orally. Some beta glucans were initially internalized by macrophages and then fragmented inside the cells. After that these fragmented β -glucans were released and eventually picked up by other immune cells. Moreover, β -glucans with variable branching patterns and sizes had different immune potency.

In recent years, an experiment was performed by Mahdi and Al-Abass (2012), and they concluded that *S. cerevisiae* derived β -glucans had immunomodulatory effect in broilers. Results of their study showed that administered group had faster clearance rate of carbon particles than untreated control group. The fast clearance rate might be due to increased phagocytic activity. Moreover, it was also observed that β -glucans administered group had improved their body weight gain than control group. Conclusions of their study suggested that β -glucans can be used to improve weight gain in broilers.

Conclusion

Over a time, anticoccidial drugs development has increased in response to the urgent need to control avian coccidiosis. Today, we have many strategies available, many of which currently widely used in chickens farms. Moreover, new alternatives are emerging, as is the case with anticoccidial is obtained from plants, fungal or microorganisms. One of advantages of using natural extracts is the lower risks of developing resistance, such as that observed with chemical drugs. It is widely known that availability of raw materials and cost of production could be high in the development of natural extracts alternatives. However, the cost is well worth it if we consider that these alternatives are friendly to the environment, producers and consumers.

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