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Review

Role of Herbal Immunomodulators in Control of Coccidiosis Disease

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Abstract. Herbal plants and their derivatives have been utilized since antiquity in the control and management of poultry coccidiosis. The best known herbal plants in use against coccidiosis are corn, wheat bran, rice bran, polysaccharides, soya bean, barley, oat, extracts of grape seed, *Dictamnus dasycarpus* Turcz, *Pulsatilla koreana*, *Sinomenium acutum*, *Ulmus macrocarpa*, *Dichroafe brifuga* and other botanical antioxidants which contain many active compounds. These compounds have been found to possess antiprotozoal, anti-parasitic, anti-inflammatory and antioxidant properties. Currently demand and utilization of these aforesaid herbs has increased because these have been proved successful and effective in control of coccidiosis, eco-friendly and economical. The effective potential of these herbals and derivatives to have been reviewed overcome coccidiosis effectively in a better way than other synthetic products against which resistance has been developed.

Keywords: coccidiosis, immunomodulators, herbal plants, poultry

Introduction

Poultry, the domesticated species of birds including chicken, geese, duck and guinea fowl, are reared for meat and eggs. Poultry industry is a flourishing industry of livestock which contributes 2% in national GDP of Pakistan. It plays main role in the stability of mutton and beef prices. Commercial poultry in Pakistan was started in 1963 (Mohsin *et al*., 2008) and Chicken meat production increased by 58.48% in the world from 2000-2012 (Bogosavljevic *et al*., 2010).

Avian Coccidiosis, a protozoal infectious highly fatal, economical and most prevalent disease is caused by *Eimeria* species in poultry. As a result of it, a massive destruction of intestinal epithelium is seen leading to bloody diarrhoea, poor weight gain, low FCR and high mortality (Razzaq *et al*., 2011). It is endemic disease in tropical and subtropical zones of the world where environmental and managemental conditions favour the onset, development and propagation of the disease (Obasi *et al*., 2006). Over 1000 species of *Eimeria* are discovered out of which seven species of genus *Eimeria* are recognized in coccidiosis infections affecting poultry and each species has characteristic virulence, pathogenicity, site of infection and immunogenicity (Williams, 1998).

Seven pathogenic species of genus *Eimeria* in poultry are *E. tenella, E. mitis, E. praecox, E. maxima, E. acervulina, E. necatrix* and *E. brunetti*. *Eimeria acervulina* predilection site is duodenum, *E.tenella* develops in ceacum, *E.brunetti* in ceacum and rectum, *E.necatrix* in small intestine, *E. mitis* and *E. maxima* predilection site is, mid of small intestine while *E. preacox* infects anterior gut. The pathogenicity of *Eimeria* specie depends upon bird's immune status and number of *Eimeria* oocytes ingested by the bird (Shah *et al.*, 2009). Eimeria life cycle is quite complex comprising of endogenous stage (gametogony and schizogony) and exogenous stage (sporogony). Birds excrete unsporulated oocytes which undergo sporulation and converted into sporulated (infective) oocyst consisting of four of sporocysts and two sporozoites (McDougald, 2003). Infections occur after viable oocyst ingestion from contaminated water, food or dust. Followed by oocytes swallowing, these are exposed to

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enzymatic actions in intestine and grinding in gizzard thus leading to liberation of sporozoites termed as excystation. Then sporozytes penetrate epithelial tissues of small intestine, transported by macrophages to depth of intestinal glands where advanced development start over (Jeurissen and Veldman, 2002). In un-sporulated form oocyte is non-infective which can survive upto 7 months in cecal tissues; it becomes infective on sporulation (Reid, 1990).

Coccidiosis is found in three forms in birds based on disease severity and pathogenicity; (1) mild infection in which no adverse effects are exhibited, (2) subclinical form in which reduction in feed utilization and weight gain is seen and (3) clinical coccidiosis; which is the most serious form with high morbidity and mortality (William, 2005). Spread of disease occurs by fecal-oral route whereby unsporulated oocytes are voided in feaces from intestinal mucosa. These oocytes sporulate and get infective (Kheysin, 1972). Clinical manifestation of disease are; malabsorption, poor FCR, intestinal hemorrhages, diarrhoea, unproductive feed utilization, impaired growth in broilers while in layers, egg production is also declined (Lillehoj and Lillehoj, 2000).

For chemoprophylaxis anticoccidial drugs were used as feed additives which overcome the disease but complications have been started by emerging drug resistance and hazardous effects of such drugs on bird's health (Abbas *et al*., 2011). Anticoccidials are categorized into two groups; ionophores that interfere passage of ions through cell membrane of parasite and cause its death and synthetic drugs or chemicals which inhibit various biochemical pathways of parasite (Chapman *et al*., 2010).Attenuated vaccines were developed but these were expensive to be produced. Its substitute option was birds' vaccination by live *Eimeria* oocytes, but poor management may induce severe reactions which may decline the performance of broiler flocks (Chapman *et al*., 2000). Alternative strategies being sought for safer and effective control of *Eimeria* are: use of botanicals and herbals. These are natural products and consist of new therapeutic ingredients against which resistance has not accomplished yet (Abbas *et al*., 2012).

Review of literature. One of the methods of controlling coccidiosis is immuno-stimulation (immunomodulation) in which efficiency and functionality of immune system is enhanced against infections of coccidiosis. These substances termed as immunomodulators enable the birds to combat the disease (Chasity and Rami, 2010).

Immunomodulatory effects of *Oryza sativa* (Rice bran). The mechanical strength of gizzard helps in breaking oocytes walls. Higher pancreatic secretions especially chymotrypsin causes excystation of sporocysts for hydrolysing Stieda body. Rice bran and its related derivatives have the capability of immunomodulation. Arabinoxylans extracted from rice bran augment in secretion of IFN-α and TNF-α from lymphocytes in human beings and also augment phagocytic activities of macrophages and monocytes (Ghoneum and Jewett, 2000). Immunopotentiating effects of *Oryza sativa* were studied against the inhibition of human leukemic cells U937 with mononuclear cell conditioned medium (MNC-CM). This MNC-CM induced maturation of monocytes and macrophages and enhanced their phagocytic activity. Amount of interferons and tumour necrosis factor (TNF-α) were significantly increased (Liao *et al*., 2006).

Therapeutic and immunomodulatory effect of wheat bran. Arabinoxylans (AXs) derived from *Triticum aestivum* (wheat) were analysed for immunomodulation in broilers and its efficacy against coccidiosis and were administered with arabinoxylans. Chicks showed best performance with highest antibody titers and showed maximum protective efficacy against coccidiosis. Oocysts per gram were evaluated from day 3-12 post challenge and results showed marked reduction in OPG. Furthermore, chicks treated with AXs showed better water and feed intake, improved weight gain and signs of coccidiosis were lessened (Akhtar *et al*., 2012a). Immuno-stimulatory evaluation of arabinoxylans derived from wheat bran and its anticoccidial potential showed improved weight gain, lowest oocyst count and higher antibody titre against sheep erythrocytes (Akhtar *et al*., 2012b).

Role of antioxidants in coccidiosis control. 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 ceacal lesions. Fats decreased parasitic infestation and provided immunity against *Eimeria* (Allen *et al*., 2000).

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). Cercumin extracted from *Cercuma longa* reduced significantly the severity of infections of small intestine (upper and middle) resulted by

E. acervulina and *E. maxima*, respectively (Allen *et al*., 1998). Artemisinin extracted from *Artemisia annua* when fed at 2.5 mg/kg, has the potential of decreasing development and shedding of Eimerial oocytes (Arab *et al*., 2006). Many of the diseases are concerned with oxidative stress which is merged with formation of free radical. For this, interest has been developed in antioxidants for enhancing immunity, so antioxidant and immunological effects of polysaccharides are under consideration (Rao and Muralikrishna, 2006). The effect of *Nigella sativa* has significant effect against *Eimeria* infection in chicken and can be utilized in coccidial control (Deyab and Laji, 2007). 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 react with free redicals existing in cytosol and blood plasma (Surai., 2007).

Proanthocyanidine extracted from grape seed (polyphenolic antioxidant) showed significant decline in mortality rate and improved performance in bird. Proanthocyanidine had the potential to inhibit chemokine pro-inflammatory cytokines responses brought by lipopolysaccharides (Wang *et al*., 2008).Utilization 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). *Artimesia annua* acted as botanical coccidiostat in affected broilers. Broilers fed with *A. annua*containing ration showed marked inhibition in parasitic growth and trophozites development while weight gain was also improved. *A. annua* could be used as commercial coccidiostat and could serve as potential source of nourishment and medication (Brisibe *et al*., 2008). Day old chicks when with lyophilized derived from plums exhibited increased immune response (Lee *et al*., 2008). *Galla rhois* extracts had strong antimicrobial effects. Its constituents included 4-galloyl-gallic acid, methyl gallate and phenolic compounds, due to which extracts had antibacterial and antiviral properties (Hong *et al*., 2008). It has been investigated that dietary supplementation of alpha tocopherol has reduced the incidence of coccidiosis. Dietary supplementation of alpha tocopherols at 90 mg/kg enhanced weight gain and reduced lesions of *Eimeria*. 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). Owing to anticoccidial drugs resistance new strategies for control of coccidiosis should be developed. Efforts should be done in finding in herbal compounds and natural antioxidants; their use to counteract oxidative stress associated with pathogenesis of various diseases incorporating coccidiosis (Masood *et al*., 2013).

Herbals anticoccidial effects. The effect of grinded seeds of *Nigella sativa* and curumin against *E.tenella* has been studied earlier. Chicks were classified in six groups receiving different concentrations of *Nigella sativa* and curumin. Chicks were infected with sporulated oocytes at 28th day; results exhibited proved that group of birds treated with 1000 ppm of *Nigella sativa* had lowest oocyst and lesions score (Fetouh and Naji, 2007). Herbal formulation were comprising of four plants; *Calotropis procera, Nicotiana tabacum, Azadirachta indica* and *Trachyspermum ammi.* The results showed increased weight gain of medicated birds than non-medicated control group. Extent of bloody diarrhoea was reduced and there was lowest oocyst and lesions score (Zaman *et al*., 2011). Effect of *Galla rhois* extracts against coccidial infections was analysed utilizing two parameters; fecal oocyst count and weight gain of birds. Chickens infected with coccidiosis when fed with *Galla rhois* showed the least oocyst per gram of feces than infected chicks fed on standard diet and also weight gain of birds was improved. A number of herbal and botanical complexes have been reported to have anticoccidial effect. For example; *Aloe excelsa, Artemisia annua, Yucca schidigera, Azadirachta indica (Neem), Triticum aestivum, Beta vulgaris, Curcuma longa, Echinacea purpure, Agele marmelos, Origanum vulgare, Saccharum officinarum,* and *Eclipta alba.* These botanicals offer novel approach for control of coccidiosis effectively and also meet the urgent needs of new solutions against widespread emerging drug resistant *Eimeria* strains. Bird's innate immune defense is enhanced and the requirement of synthetic drug therapy is eliminated (Abbas *et al*., 2012).

Immunomodulatory and therapeutic effect of arabinoxylans. Arabinoxylans derived from corn husk, increased production of cytokines and exaggerate activity of natural killer cells thus possessed immuno-stimulation effect in broilers (Zhang *et al*., 2004). Arabinoxylans effect extracted from corn husk hydrolysed these arabinoxylans partially and utilized these for immunomodulation. Arabinoxylans extracted from wheat showed immuno-stimulatory and shielding effect against *Eimeria* infections (Akhtar *et al*., 2012a).

Immunomodulatory and therapeutic effect of β-glucans. Fungal origin β-glucans and its immunomodulatory activities have been studied by Maeda *et al*. *(*1988) when administered intraperitonially or intravenously. But via parenteral routes certain hazardous effects were seen including pain, granuloma formation, micro-embolization and inflammation.The combination of enzymes like β-glucanase, pectinase, cellulase, amylase, and xylanase extracted from corn, barley, oat etc. decreased the risk of coccidiosis and necrotic enteritis and improved digestion of non-soluble polysaccharides (Elwinger and Teglof, 1991).

β-glucans are potential non-specific immunomodulators (Propagermanium), radio-protective and anti tumour agents. These possessed wide applications in immune system as immuno-adjuvants. By stimulating host immunity against various diseases of viruses, bacteria, fungi and parasites, β-glucans have valuable effect to stimulate the immune system and are categorized as biological response modifiers (Sandula *et al.,* 1999). They stimulate host immunity and exert beneficial effects of on variety of viral, protozoal, bacterial and fungal diseases. β-glucans administered intraperitonially or intravenously exhibited strong immuno-stimulatory effects but owing to their adverse effects by said routes these were administered orally. In order to improve the potential of β-glucans various derivation protocols used are; sulphonation, carboxymethylation, phosphation etc. β-glucans are found in cell wall, polysaccharides excreted, cytosol and its components. Therapeutic belongings of glucans are owing to their chemical nature, structure and spatial arrangements of their molecules. Slight variations in structure yield peculiar features with new applications in biotechnology (Chakraborty *et al.,* 2004). β-glucans, heterogeneous polysaccharides comprising of D-glucose monomers attached by glycosidic linkage, are essential cell wall structural elements. β-glucans have the capability of modulation the immune system. Effect of β-glucans derived from yeast was studied against *Eimeria* infections in broilers. Severity of gross lesion scores in intestines (duodenum and jejunum) was reduced significantly in birds fed with diet supplemented with β-glucans (Cox *et al.,* 2010a; 2010b). Glucans extracted from mushrooms presented pharmacological and biological properties including; antioxidant, hepatoprotective, anti-inflammatory and immunomodulatory activities. Glucans are bioactive products and are well known for their pharmacological effects. β-glucans as well as arabinoxylans; both are water soluble non-starch polysaccharides producing viscous solution. They inhibit the passage of chyme through gut, hampering stomach discharges, decline the absorption of sterols and glucose in intestines and reduce blood cholesterol and glucose level. Also these cannot be fermented in large intestines (Havrlentova *et al*., 2011).

Immunomodulatory effect of corn. The severity of disease was declined in poultry fed by raw soya bean meal of corn. Roundtable On Sustainable Biomaterials (RSB) and pancreatic enzymes significantly inhibited *Eimeria* infections (Mcdougald and Reid, 1991). Conducted experiments on diet influence on enteritis and coccidiosis presented that corn, barley and wheat had potential to control necrotic enteritis as well as coccidiosis. Corn also reduced oocyst count and enhanced weight gain compared to wheat and barley. Corn feeding diminished coccidial lesions (Ridell *et al*.,1983). Hydroxycinnamates such as ferulic acid can successfully be liberated from corn fibre by using enzymes; ferulic acid esterases procured from *Humicola insolens* and *Aspergillus niger* and exhibit significant antioxidant properties (Benoit *et al*., 2006). Corn fibre extraction with isopropanol and methanol yielded products which comprised of low quantity of hydroxylcinnamates and showed distinct activity against oxidation of lipids (Bauer *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 hydroxylcinnamates like *p*-coumaric acid and ferulic acid (Bauer *et al*., 2013).

Immunomodulatory potential of barley and oat. Poultry diet influenced the severity and pathological changes in coccidiosis. Feeding chickens by low protein diet showed marked reduction in coccidiosis morbidity rate. It was related to stimulus suppression for release of pancreatic enzymes. Because pancreatic enzymes were essential for excystation of sporozoites from sporocysts. Soya beans consist of proteins that inhibit pancreatic enzymes specifically trypsin thus inhibited coccidial infections (Mathis *et al*., 2011). Barley is well-known for its immuno-stimulatory potential against certain diseases. Therapeutic significance of β-glucans extracted from oat and barley was analysed against metabolic syndrome and obesity in humans for maintenance of enteric wellbeing in humans (Khoury *et al*., 2012).

Conclusion

Anticoccidials were added to poultry feed as chemoprophylactic agents to overcome coccidiosis but the strategy failed due to arising complications of drug resistance and mal effects of these drugs on health and production of birds because drug residues offer accumulation of toxic compounds in the meat. Vaccines have also been developed for control and prevention of coccidiosis but owing to variations in species and strains of *Eimeria*, vaccines were also failed. Then safer and efficient alternative strategies were sought to overcome the disease and hence herbals, their derivatives and other botanicals were found to be the most suitable alternatives to synthetic drugs and vaccines. These herbals are eco-friendly and natural products comprising of therapeutic ingredients to which still no resistance has built. A novel approach in control of coccidiosis has been provided by these herbals. Herbals enhance immunity of birds and act as immuno-stimulants or immunomodulators and diminish the needs of synthetic drugs. Ingredients contained in these herbals have the potential of immuno-stimulation and eliminating the disease more effectively than other products. Moreover, these herbals are economical, cost effective and no hazardous effects are seen regarding the health and production quality of the birds. In short, to overcome and control coccidiosis the most efficient approach is the utilization of herbals and botanicals at scientific levels as substituent of antiparasitic drugs and other synthetic products.

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