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REVIEW

Towards identifying novel anti-*Eimeria* agents: trace elements, vitamins, and plant-based natural products

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Abstract Eimeriosis, a widespread infectious disease of livestock, is caused by coccidian protozoans of the genus *Eimeria*. These obligate intracellular parasites strike the digestive tract of their hosts and give rise to enormous economic losses, particularly in poultry, ruminants including cattle, and rabbit farming. Vaccination, though a rational prophylactic measure, has not yet been as successful as initially thought. Numerous broad-spectrum anti-coccidial drugs are currently in use for treatment and prophylactic control of eimeriosis. However, increasing concerns about parasite resistance, consumer health, and environmental safety of the commercial drugs warrant efforts to search for novel agents with anti-*Eimeria* activity. This review summarizes current approaches to prevent and treat eimeriosis such as vaccination and commercial drugs, as well as recent attempts to use dietary antioxidants as novel anti-*Eimeria* agents. In particular, the trace elements selenium and zinc, the vitamins A and E, and natural products extracted from garlic, barberry, pomegranate, sweet wormwood, and other plants are discussed. Several of these novel anti-*Eimeria* agents exhibit a protective role against oxidative stress that occurs not only in the intestine of *Eimeria*-infected animals, but also in their non-parasitized tissues, in particular, in the first-pass organ liver. Currently, it appears to be promising to identify safe combinations of low-cost natural products with high anti-*Eimeria* efficacy for a potential use as feed supplementation in animal farming.

Keywords *Eimeria* · Eimeriosis · Anti-coccidial agents · Selenium · Garlic · Berberine · Artemisinin

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Introduction

Coccidiosis or, more specifically, eimeriosis is an economically important infectious disease of livestock including cattle, rabbits, sheep, goats, and, particularly, poultry. This disease is caused by protozoans of the coccidian genus *Eimeria*, striking the digestive tract of their hosts (Daugschies and Najdrowski 2005; Blake and Tomley 2014; Chapman 2014; Mehlhorn 2014). It is characterized by oxidative stress, inflammation, malabsorption of nutrients, diarrhea, fluid loss, dehydration, as well as increased susceptibility to bacterial pathogens, as, e.g., necrotic enteritis in chicken (Dkhil et al. 2013a; Alnassan et al. 2014). If not treated, mortality may be up to 80 %, depending on the *Eimeria* species (Fossum et al. 2009). Reduced body weight gain and death of infected animals cause enormous economic losses. Worldwide, the costs for control measures of coccidiosis only in cattle and poultry are estimated to exceed about 2 billion dollars annually (Williams 1999; Shirley et al. 2005; Dalloul and Lillehoj 2006; Blake and Tomley 2014).

Eimeriosis

More than 800 different species are ascribed to the coccidian genus *Eimeria* (Mehlhorn 2014). These obligate intracellular parasites infect vertebrates in a host-specific manner and exhibit a monoxenous life cycle. The development of sexual and asexual stages of parasites is restricted to specific parts of the intestinal tract of a single host (Daugschies and Najdrowski 2005; Blake and Tomley 2014; Chapman 2014; Mehlhorn 2014).

Infections begin by oral uptake of sporulated *Eimeria* oocysts. Excystment of oocysts in the intestine usually releases four sporocysts and eight sporozoites, respectively (Seemann et al. 2012), and the sporozoites in turn invade intestinal epithelial cells. Different parts of the host's intestine can be infested by different *Eimeria* species. For instance, the cecum is the final target site of *Eimeria tenella* in chicken and *Eimeria coecicola* in rabbits, whereas *Eimeria papillata* dwells in the jejunum of mice. The intracellular stages of parasites rapidly multiply in asexual schizogonic cycles, before oocysts are formed from the sexual micro- and macrogamont stages containing the two-type wall-forming bodies (Frölich et al. 2013). The oocysts are finally released with the feces to the environment, and these oocysts in the environment are highly infectious. The fast reproduction cycle of *Eimeria* parasites and the close contact of animals in industrial farming favor the spread of the disease, especially among young animals, when primarily infected (Ryley and Robinson 1976; Pakandl 2005).

Oxidative stress in *Eimeria* infections

Oxidative stress is a critical initial event in eimeriosis. Upon invasion by parasites, epithelial host cells activate membrane-bound NAD(P)H oxidases to form superoxide anion radicals and, upon dismutation, hydrogen peroxide. Moreover, oxidative stress is amplified by neutrophils and macrophages recruited to the invasion sites of parasites, since the activation of these phagocytes also leads to the production of high amounts of superoxide by NADPH oxidases inside the phagosome, as well as the formation of nitric oxide (NO) by NO synthases in the cytoplasm. NO may diffuse into the phagocytic vacuole, where the superoxide and the nitric oxide radicals react to form peroxynitrite. The reactive oxygen/nitrogen species (ROS/RNS) serve to counteract and to paralyze the invading parasites. However, over-production of ROS/RNS results in host cell damage and, together with the released lysosomal enzymes, in tissue lesions (Puertollano et al. 2011; Nathan and Cunningham-Bussel 2013; Prolo et al. 2014).

The concept of oxidative stress describes damage of biomolecules such as DNA, lipids, proteins, and carbohydrates (Sies 1986), and it was extended to take into account the emerging role of biologically generated oxidants in redox signaling (Jones and Sies 2007): "Oxidative stress is an imbalance between oxidants and antioxidants in favour of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage." The multiple biological oxidants are matched by multiple layers of antioxidant defense systems, and there are several strategies of antioxidant defense (Sies 1993). These include control of the prooxidant enzyme systems, e.g., NADPH oxidases and the mitochondrial respiratory chain, as well as the biosynthesis and activity of antioxidant enzymes, e.g., catalase, superoxide dismutases, glutathione peroxidases, the thioredoxin system, and the peroxiredoxins (Nathan and Cunningham-Bussel 2013; Prolo et al. 2014; Sies 2014).

While the digestive tract is the target site of *Eimeria* parasites, the infection also affects other tissues, in particular, the first-pass organ liver, which are not targeted by the disease-causing intracellular stages of the parasites. In *E. coecicola*-infected rabbits, for example, oxidative stress and associated inflammation, pathological changes, and organ-specific changes of gene expression do not only occur in the cecum as the target site of the parasites, but also in the non-parasitized organs as the liver and spleen (Al-Quraishy et al. 2012; Dkhil et al. 2012, 2013b). This evolution of the disease is presumably caused by both parasite antigens and host factors such as cytokines systemically transferred to other tissues. Intraepithelial lymphocytes in the cecum of chickens infected with *E. tenella* have been described to produce the interleukins IL-1β, IL-6, and IL-17 (Zhang et al. 2013). Large amounts of IL-6 mRNA have also been measured in the cecum of *E. coecicola*-infected rabbits, suggesting a critical role of IL-6 during these infections (Dkhil et al. 2012). Possibly, IL-6 *trans*-signaling is a parasite-induced host mechanism that contributes to spread the disease process to other organs, including organ-specific changes in gene expression (Dkhil et al. 2013b). Indeed, IL-6 binds to the soluble IL-6 receptor α, and this complex can signal through GP130 receptors expressed in plasma membranes of all other host cells (Drucker et al. 2010; Wunderlich et al. 2012).

Anti-*Eimeria* vaccination

Vaccines are rational measures for prophylactic control of infectious diseases including eimeriosis, as reviewed elsewhere in detail (Williams 2002; Shirley et al. 2005; Dalloul and Lillehoj 2006; Blake and Tomley 2014; Chapman 2014). The 'ideal' anti-*Eimeria* vaccine (a) should prevent intestinal infection, for example, by inhibiting oocyst excystment and/or sporozoite invasion of intestinal host cells, (b) should induce solid host immunity, and (c) should be affordable to farmers worldwide and practically feasible, particularly in animal farm housing. To date, however, such a vaccine has not yet been realized, though it is now more than 50 years ago that the first vaccine, Coccivac^{R}, was commercially introduced (Williams 2002). Other first-generation vaccines such as ImmunoCox^{R} followed and, later, second-generation vaccines (ParaCox^{R}, Livacox^{R}), which are all *live* vaccines based in principle on weakly virulent and/or attenuated lines of *Eimeria* species and strains. Even a first subunit vaccine (CoxAbic) has been developed, acting against *E. maxima*, based on transmission-blocking antigens of the sexual parasite stages (Wallach et al. 1992, 2008; Frölich et al. 2012). Currently, a series of other antigen candidates has been described, and these are being tested with the aim to develop third-generation subunit vaccines and even DNA vaccines against *Eimeria* (Blake and Tomley 2014; Chapman 2014). However, as recently stated by Blake and Tomley (2014), "the reasons why none of these approaches have reached field testing or commercialization remain obscure, but clearly indicate a lack of reproducible, efficacious vaccine protection."

Commercial anti-*Eimeria* drugs

Acute eimeriosis can be only treated with anti-coccidial drugs, which are also used, at least in part, for prophylaxis. A series of effective drugs is available, classified according to their apparent mechanisms of action (Greif et al. 2001). One class of anti-coccidial drugs is comprised of substances described to presumably destroy membrane integrity, as, e.g., polyethers such as monensin, maduramicin, salinomycin, narasin, semduramycin, and lasalocid. Another class encompasses substances supposed to inhibit protein synthesis, as, e.g., clindymacin, spiramycin, clarithromycin, and paronomycin. A third class describes drugs which ultimately lead to inhibition of DNA synthesis such as decoquinate, methylbenzoquate, clopidol, robenidin, sulfonamides, nicarbazin, ethopabate, pyrimethamine, diaveridine, ormothroprim, epiroprim, and amprolium.

Furthermore, the symmetric triazinone derivative toltrazuril is a very effective broad-spectrum drug to control eimeriosis in poultry (Harder and Haberkorn 1989; Greif et al. 2001; Mathis et al. 2004; Alnassan et al. 2013). It is also used against porcine neonatal isosporosis (Mundt et al. 2007) and against coccidiosis in calves (Mundt et al. 2003) and lambs (Mundt et al. 2009) in many countries. Toltrazuril has been described to target all intracellular stages of coccidian parasites (Mehlhorn et al. 1984). Different protein targets for toltrazuril have been proposed to date, e.g., several enzymes of the respiratory chain, dihydrofolate reductase, dihydroorotate cytochrome-c-reductase (Haberkorn et al. 2001), and D1 protein of the rudimental photo system II of apicomplexan protozoans (Hackstein et al. 1995). Furthermore, toltrazuril has been reported to induce swelling of mitochondria and endoplasmic reticulum, as well as damage of the wall-forming bodies II in macrogamonts and perturbations of the nuclear division of parasites as revealed in cell cultures of *Neospora caninum*- and *E. tenella*-infected ceca by light- and electron-microscopic studies (Mehlhorn et al. 1984; Darius et al. 2004).

The *E. tenella*-specific novel ABH-like cyclophilin *Et*Cyp21 has been identified as another target for toltrazuril (Bierbaum 2009). Cyclophilins are ubiquitous peptidyl-prolyl-*cis*/*trans*-isomerases among archea, prokaryotes, and eukaryotes (Maruyama et al. 2000; Barik 2006), and they are known to be very heterogeneous, even in a given species, with respect to molecular mass ranging from 18 to 100 kDa (Hosse et al. 2008), abundance, cellular localization, and functions (Schneider et al. 1994; Yao et al. 2005; Barik 2006; Bell et al. 2006). Recombinant *Et*Cyp21 exhibits peptidyl-prolyl-*cis*/*trans*-isomerase activity and RNase T1 refolding capacity (Bierbaum 2009). Toltrazuril inhibited these activities of recombinant *Et*Cyp21 but not those of recombinant *Et*Cyp19, another novel recombinant cyclophilin of *E. tenella* (Bierbaum 2009). The action of toltrazuril on recombinant *Et*Cyp21 differs from that of cyclosporin A, which is known as an inhibitor of cyclophilins (Wang and Heitmann 2005). A series of circumstantial evidences supports the view that *Et*Cyp21 is not only an in vitro, but also an in vivo target for toltrazuril in *E. tenella* (Bierbaum 2009).

Searching for novel anti-*Eimeria* treatments

The advantage of drug medication, in comparison to vaccination, is its wide action spectrum, i.e., drugs are widely applicable against many different *Eimeria* species in different hosts. A major disadvantage, however, is drug resistance as an ever-existing and widely occurring problem. To counteract the development of drug resistance, the rotation of two and even three drugs with different modes of action is practiced in poultry farming (Chapman 2001). Moreover, there are increasing concerns about the impact of widely used drugs on the food chain and environment, all the more as accessible information hereof is scarce. Thus, there is an urgent need to search for novel active agents characterized by lower risks for consumer health and by more environmental compatibility and sustainability.

As mentioned above, oxidative stress occurs both in target organs of parasites and in non-parasitized organs of infected animals upon invasion by parasites. Dietary antioxidants such as the essential trace elements selenium (Se) and zinc (Zn), the vitamins A and E, and plant-derived natural products have been shown to fulfill a protective role in infections by parasites (Puertollano et al. 2011). Several compounds counteracting oxidative stress have been examined in different animal models for their potential use as anti-*Eimeria* medications. In addition, it is important to note that there are effects of these and other redox-active compounds beyond 'simple' antioxidant functions. These relate predominantly to the regulation of master switches of gene expression, including the NFκB and Nrf2/Keap1 systems.

Trace elements with anti-*Eimeria* activity

Selenium

Se occurs predominantly as selenomethionine and Se-methylselenocysteine in plant sources and as selenocysteine in meat. Dietary supplements may contain sodium selenite and selenate, as well as selenomethionine (Rayman 2012). Se is important for the proper regulation of the immune system in inflammation and infection. The Se status influences activation, differentiation, and proliferation of immune cells including T and B cells and macrophages (Huang et al. 2012; Rayman 2012). Se is present as the rare amino acid selenocysteine in the active center of selenoenzymes. Key antioxidant selenoproteins are glutathione peroxidases, thioredoxin reductases, and selenoprotein P, which are involved in protection of cells and cellular macromolecules from oxidative damage (Steinbrenner and Sies 2009) and highly expressed in the intestine in both epithelial and immune cells (Huang et al. 2012; Speckmann and Steinbrenner 2014). The role of Se and selenoproteins in inflammatory bowel diseases and experimental colitis has been reviewed recently (Speckmann and Steinbrenner 2014). Intestinal epithelial cells use dietary Se compounds for the biosynthesis of selenoprotein P, which is secreted and might support the intestinal immune system by providing Se to antibody-producing plasma cells (Speckmann et al. 2014).

The effect of dietary Se supplementation was investigated in *E. papillata*-infected mice (Dkhil et al. 2014). In comparison to a Se-adequate diet containing 0.15 ppm Se, male mice fed a high-Se diet (1 ppm Se) revealed a dramatic lowering of maximal output of oocysts on day 5 post-infection. All developmental stages of the parasites were affected, as meronts, micro- and macrogamonts, and developing oocysts were increased in intestinal tissue in comparison with mice fed the Se-adequate diet. At a high Se-diet, the number of parasite stages in the jejunum was higher than in animals kept on a Se-deficient diet, and the histological injuries substantially decreased. It still remains to be investigated whether Se exerts its beneficial effects directly by affecting the intracellular parasites or indirectly by protecting the host cells against infection-induced oxidative damage.

Regarding *Eimeria* infections of livestock, protective actions of Se have been explored for poultry. It has long been known that chickens infected with *E. tenella* exhibit better weight gain and lower mortality when fed a diet supplemented with adequate Se (0.25 ppm Se). Dietary Se supplementation enhanced immune responses of chickens against *Eimeria* (Colnago et al. 1984). More recently, *E. tenella* infections in chickens have been reported to be associated with decreased Se levels (Gabrashanska et al. 2009). In broiler chickens infected with *Eimeria acervulina*, dietary Se improved the antioxidant capacity and increased body performance of the treated chickens (Georgieva et al. 2011a). Injection of selenite (10 and 20 μg Se/egg) into developing eggs enhanced the immune response following oral infection of the hatched chicken with sporulated *E. maxima* oocysts and also resulted in better weight gain (Lee et al. 2014).

Incidentally, the EFSA (European Food safety Authority) has recently stated that Se in the form of DL-selenomethionine is "safe for chickens for fattening provided total dietary Se does not exceed 0.5 mg/kg complete feed"; this conclusion is extended to all animal species (EFSA 2014). Highlighting the narrow 'therapeutic window' of Se, it is also worthwhile to mention that selenomethionine in eggs of several species of aquatic birds at levels above 3 ppm (on a wet weight basis) was associated with reduced hatchability and the occurrence of deformed embryos (Spallholz and Hoffmann 2002).

Zinc

Zn is fundamentally important for a balanced redox state, for the immune system, as well as for growth and development. Zn ions are essential for proper functioning of many transcription factors by stabilizing their so-called zinc finger domains, as well as for the activity of Zn-dependent enzymes including the Cu/Zn-dependent superoxide dismutase SOD1. Sufficient Zn supply depends on the amount and the bioavailability of Zn in the food. Major sources of Zn are cereals, legumes, and meat. The bioavailability of Zn is lowered if feed contains high amounts of phytate, calcium, or soy proteins. For example, requirements for growing chicken will increase from 20 to 35 mg Zn/kg dry weight to 40–50 ppm when feeding a corn–soy diet (Bafundo et al. 1984; Nielsen 2012).

There is long-standing evidence for a protective role of dietary Zn supplementation in chicken suffering from eimeriosis. An early study reported time-dependent changes in the intestinal absorption rate of Zn after infection of chickens with *Eimeria necatrix* (Turk and Stephens 1966). Mild intestinal damage with slight inflammation increased Zn absorption 1 day after infection, whereas severe damage and hemorrhage decreased or even inhibited Zn absorption by the third day post-infection. Dietary supplementation with 50 ppm Zn increased Zn absorption in chicken infected with *E. acervulina*, resulting in higher hepatic Zn levels and improvements in rate and efficiency of weight gain (Bafundo et al. 1984). These results have recently been confirmed and extended: Zn, given as Zn–Cu–salt, exerted an ameliorating antioxidative effect in *E. acervulina*-infected chicken (Georgieva et al. 2011b).

Vitamins with anti-*Eimeria* activity

Vitamin A

The provitamin ß-carotene and the retinoids are the major constituents of the fat-soluble A-vitamins, which may act as antioxidants as well. A wide variety of plants, e.g., broccoli, spinach, carrot, pumpkin, papaya, mango, tomato, sweet potatoes, pea, and apricot, contain ß-carotene and other carotenoids, which are fundamentally important for several vital functions, in particular for both humoral and cell-mediated immune responses (Dalloul and Lillehoj 2005) and for maintaining the mucosal integrity in *Eimeria*-infected hosts (Chew 1995). Vitamin A deficiency has been shown to dampen local intestinal immune responses including a diminution of intraepithelial CD4$^+$-T cells. Susceptibility to *E. acervulina* infections was increased in vitamin A-deficient broilers, as evidenced by increased oocysts output and an impaired capacity of spleen cells to respond to mitogens (Dalloul et al. 2002, 2003; Chew and Park 2004; Masood et al. 2013).

Vitamin E

The group of the fat-soluble E-vitamins consists of four tocopherols and four tocotrienoles with α-tocopherol being the major and most active compound. Tocols are synthesized only by plants; vegetable oils, cereal grains, and nuts are good dietary sources. Vitamin A protects lipids against oxidative damage, acting as radical scavenger, which breaks ROS-induced chain reactions of lipid peroxidation. Besides its antioxidant properties, α-tocopherol affects the activity of enzymes such as proteinkinase C and phospholipase (Traber and Sies 1996).

α-Tocopherol is already used as feed supplementation in poultry. Indeed, dietary tocopherol has been shown to increase weight gain and to decrease intestinal lesions in *E. tenella*-infected chicken (Colnago et al. 1984), which has been ascribed to lowered lipid peroxidation and improved membrane integrity in broilers (Jafari et al. 2012).

Plant-based natural products with anti-*Eimeria* activity

Currently, plant-based natural products are promising sources for novel anti-*Eimeria* candidate agents. These products do not necessarily target only the parasites, but may also have organ-protective properties in the *Eimeria*-infected hosts. A recent review (Masood et al. 2013) has summarized the anti-*Eimeria* activity of diverse secondary plant metabolites such as polyphenols, flavonoids, tannins, saponins, and aromatic herbs. Even artemisinin, which is currently used as first-choice medication against the malaria parasite *Plasmodium* has been found to be effective against *Eimeria*. Though there are some in vitro studies available, as, e.g., curcumin effects on *E. tenella* sporozoites (Khalafalla et al. 2011), this review focuses on those plant-based natural products more recently investigated in different experimental systems with respect to anti-*Eimeria* activity, and antioxidant and anti-inflammatory properties.

Garlic (***Allium sativum***)

A. sativum has a long tradition for preventing and treating a variety of diseases. It exhibits antimicrobial activity (Chowdury et al. 1991; Yoshida et al. 1998; Fleischauer et al. 2000), antitumor activity (Sundaram and Milner 1996; Karasaki et al. 2001), as well as antithrombic, antiarthritic, hypolipidemic, and hypoglycemic activities (Duraka et al. 2002; Kumar et al. 2003a, b). Garlic is also effective against diverse parasitic protozoans such as amoebae (Peyghan et al. 2008), *Leishmania* (Ghazanfari et al. 2006), *Trypanosoma* (Nok et al. 1996), and *Cryptosporidium* (Wahba 2003). One of the major protective functions of garlic is to decrease oxidative damage. The antioxidative properties of garlic are presumably due to four major chemical components, i.e., allinin, allyl cysteine, allyl disulfide, and allicin (Chung 2006).

In *E. papillata* infections of mice, garlic has been found to have both anti-*Eimeria* activity and anti-inflammatory and protective effects on the host. Garlic significantly decreased the fecal output of oocysts and counter-acted the infection-induced loss of glutathione and the activities of catalase and superoxide dismutase in the liver (Al-Quraishy et al. 2011). Moreover, the anti-*Eimeria* activity of garlic was associated with specific changes in the miRNA signature of the mouse jejunum, the target site of *E. papillata* in mice (Al-Quraishy et al. 2011). Possibly, specific miRNAs are involved in garlic-activated pathways to decrease and/or to repair infection-induced tissue injury. Incidentally, there is evidence that miRNAs are transferred to other cells by exosome vesicles, suggesting an involvement of disease spreading (Bala et al. 2012; Kawai and Akira 2011). Moreover, miRNAs are ligands for Toll-like receptors (TLRs) (Fabbri et al. 2012). A series of synthetic TLR agonists and antagonists is currently available and patented (Savva and Roger 2013; Hussein et al. 2014), which might be therefore also considered as candidate agents for the treatment of *Eimeria* infections.

Barberry (***Berberis***)

The isoquinoline alkaloid berberine occurs predominantly in roots and stem-bark of plants of the genus *Berberis*, as well as in other medically important plants (Dkhil 2014). Berberine-based formulations are widely used in traditional Chinese medicine and Ayurveda. Berberine has anti-hypersensitive, anti-inflammatory, antioxidant, antidepressant, anticancer, anti-diarrheal, cholagogue, and hepatoprotective activities

(Wongbutde 2008; Vuddanda et al. 2010). Also, berberine possesses antimicrobial activities against a variety of infectious agents, including viruses, bacteria, fungi, parasitic protozoans, and helminths (Dkhil 2014).

In *E. papillata*-infected mice, berberine has been reported to ameliorate pathological changes in nutrient homeostasis, decreasing elevated blood glucose and lipid levels, as well as restoring jejunal carbohydrate content (Al-Quraishy et al. 2014).

Chinese galls (***Galla rhois***)

Extracts of Chinese galls, induced by the plant-louse *Melaphis chinensis*, have strong antiviral and antibiotic effects (Hong et al. 2008; Lee et al. 2008a, b). The major constituents of *G. rhois* extracts are methyl gallate, 3-galloyl-gallic acid, 4-galloyl-gallic acid isomers, 1,2,3,4,6-penta-*O*-galloyl-b-D-glucose, and two inactive phenolic compounds, gallic acid methyl ester and gallic acid (An et al. 2005).

When administered as 0.5 % feed supplementation to chicken heavily infected with *E. tenella*, the *G. rhois* extract significantly decreased oocysts shedding and improved body weight gain (Lee et al. 2012).

Sweet wormwood (***Artemisia annua***)

This plant belongs to the Asteraceae, and its dried leaves have been used in traditional Chinese medicine for more than 2,000 years. Artemisinin is the main bioactive sesquiterpene lactone of *A. annua*, and this is active against malaria (Weathers et al. 2014), against babesiosis in donkeys (Kumar et al. 2003a), against cutaneous leishmaniasis (Yang and Liew 1993), and against trypanosomiasis (Mishina et al. 2007). Moreover, it is active against *Schistosoma japonicum* and *Fasciola hepatica* in vitro (Ferreira et al. 2011).

A. annua leaf powder was tested at 1.5 % in daily diet post-infection against heavily *E. tenella*-infected chicken (Drăgan et al. 2014). This contained on average 0.75 % artemisinin, 0.18 % dihydroartemisinic acid, and 0.03 % artemisinic acid and had approximately the same effect against *E. tenella* as lasalocid in terms of lowered oocysts shedding and a lower lesion score, and better weight gain for chickens.

Pomegranate (***Punica granatum***)

The pomegranate is used in traditional medicine for treatment of various diseases (Abdel-Moneim 2012). It has strong antioxidant and anti-inflammatory activity. It has been described to act against cestodes and nematodes (Pradhan et al. 1992; Korayem et al. 1993; Fernandes et al. 2004a, b; Abdel-Ghaffar et al. 2010), as well as against protozoan parasites (Calzada et al. 2006; Dell'Agli et al. 2009; Al-Mathal and Alsalem 2012).

One of the present co-authors studied the effect of peel extracts from the pomegranate in *E. papillata*-infected mice (Dkhil 2014), which were applied by daily oral gavage at a dose of 300 mg/kg body weight. Pomegranate extracts were found to exert anti-*Eimeria* activity, lowering oocyst shedding and decreasing the number of *Eimeria* parasites in the intestine host cells by about 40 %. Also, the antioxidant activities manifested themselves as increased nitric oxide metabolites and glutathione, as well as decreased malondialdehyde in jejunum of infected mice.

Neem (***Azadirachta indica***)

Neem is known for its agricultural and medical applications in India for more than thousand years. It has been reported to exert insecticidal, pesticidal, and agrochemical features, and it is used for treatment of different infectious, metabolic, and cancer diseases (Ezz-Din et al. 2011). Also, it possesses antibacterial (Alzoreky and Nakahara 2003), hypoglycemic (Kar et al. 2003), anti-ulcer (Raji et al. 2004), and chemotherapeutic properties (Elavarasu et al. 2012).

Methanolic extracts from neem leaves at a dose of 500 mg/kg body weight were shown to exhibit anti-*Eimeria* activity in *E. papillata*-infected mice, as evidenced as decreased fecal shedding of oocysts (Dkhil et al. 2012). Also, it exhibited anti-inflammatory and hepatoprotective effects in host mice. The neem extract lowered the infection-induced increase in serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin levels, and it counter-acted the increase in malondialdehyde and the decrease in glutathione levels in the jejunum of infected mice. In addition, the neem extract diminished body weight loss (Dkhil et al. 2012).

Date palm (***Phoenix dactylifera***)

The date palm is one of the oldest cultivated trees in the world (Al-Taher 2008). Date fruits are an integral part of the Arabian diet (Baliga et al. 2011). Palm extracts were shown to have strong hepatoprotective effects against various harmful toxicants (Saafi et al. 2011). Metwaly et al. (2012a, b) revealed in *E. papillata*-infected mice that methanolic palm extracts significantly decreased the fecal output of *E. papillata* oocysts and decreased the damage induced by the infection in intestinal tissue and liver. Also, palm pollen grains exhibit anti-*Eimeria*, anti-inflammatory, and anti-apoptotic activities in this animal model.

Oregano (***Origanum vulgare***)

O. vulgare is a member of the Lamiaceae and contains as essential oil constituents carvacrol, thymol, g-terpine, and p-cymene (Szaboova et al. 2012). Oregano extracts are known for their antimicrobial (Lambert et al. 2001) and antioxidant activities (Sarac et al. 2009). Recently, oregano has been shown also to exert anti-*Eimeria* activity: It diminishes fecal shedding of oocysts in rabbits and lowers oxidative stress (Szaboova et al. 2012).

Herbal extracts

Apacox is a commercial preparation of herbal extracts from *Agrimonia eupatoria*, *Echinacea angustifolia*, *Ribes nigrum*, and *Cinchona succrubra*. It has been shown to exert coccidiostatic effects on *E. tenella*-infected broiler chicken (Christaki et al. 2004). However, the effect was less than that of the anti-coccidial drug lasalocid.

Concluding remarks

A number of drugs are commercially available for the treatment of eimeriosis. However, their efficacy is being increasingly impaired due to emerging parasite resistance. This urgently requires the implementation of novel anti-*Eimeria* agents with a focus on low-cost medications. Trace elements such as selenium and zinc, the vitamins A and E, and a series of plant-based natural products have been found to possess anti-*Eimeria* activity in various animal models. Even though these substances are not capable of curing eimeriosis completely and only a few of them reach efficacies similar to currently available anti-*Eimeria* drugs, they might become useful in future as affordable feed supplementation to diminish the dosage regimen of commercial drugs for cure and prophylactic prevention of *Eimeria* infections. This prospect should encourage present efforts to invest more in basic research with the aim to identify the effective anti-*Eimeria* compounds in the diverse plant extracts and to improve our still scarce understanding of the mode of molecular action of these compounds and their metabolism in the treated animals to evaluate their potential noxious risks for consumer health. A new aspect in the combat against *Eimeria* might also derive from the observation that the anti-*Eimeria* activity of garlic is associated with changes in the intestinal miRNA pattern, as miRNAs in exosomes may induce inflammatory responses, not only at the parasite target sites, through Toll-like receptors.

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