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REVIEW ARTICLE

Phenolics of Botanical Origin for the Control of Coccidiosis in Poultry

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ABSTRACT

Eimeria are the absolute intestinal parasites belonging to phylum Apicomplexa, causing the intestinal disease known as coccidiosis. It is a lethal disease that affects a large variety of animals and birds including cattle, camel, goats, sheep, poultry, etc. causing severe devastation and mortalities. Controlling poultry coccidiosis by the means of preventive and prophylactic use of chemical drugs is currently being practiced on a commercial scale. Regardless of a history of successful use of these drugs, resistance and public health concerns demand their alternatives. Several alternatives including vaccination, organic acids and botanicals, are being suggested. Several preparations of botanicals have been experimented and found useful, but exact compound identification is a question of interest for scientists. Phenolic compounds are among the most abundant phytochemicals found in diverse structural forms comprising mainly phenolic acids, tannins, flavonoids, and others. Research states that they have the potential to control coccidiosis because of their direct and indirect anticoccidial activities. Phenolics have been reported to control coccidiosis by targeting *Eimeria* species directly and reducing the damages by antioxidant, immunomodulatory, and anti-inflammatory properties. Phenolics kill *Eimeria* by engulfing schizonts, rupturing the cell membrane of sporozoites, and inhibiting growth by stopping ATP synthesis mechanisms and other pathways depending on their chemical nature and the subgroup of phenolic compounds. Because of the high potential of being oxidized; they capture the reactive species produced because of cell rupture during rapid schizogony and immune invasion. Phenolics give negative feedback to several inflammatory mediators and reduce the inflammatory destruction of the gut, hence minimizing the loss. Regardless of these activities, phenolics have some drawbacks i.e., they reduce nutrient uptake, disturb carbohydrate disturbance, have cytotoxic effects, and undefined long-term response. Extensive research is needed to investigate the proper anticoccidial compound and reduce the side effects of phenolics to manage coccidiosis in an accurate, rapid, and safe way.

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INTRODUCTION

Coccidiosis is a disease of parasitic origin that affects a wide variety of organisms (Mesa-Pineda *et al.*, 2021). Coccidiosis is a globally prevalent disease that is widespread because of its high prevalence, direct life cycle, and acute nature of spread (Abebe and Gugsa, 2018). The members of the *Eimeria*, the obligate intestinal protozoan parasites cause poultry coccidiosis. Coccidiosis is widely prevalent and regardless of strict biosecurity measures, it is the major factor reducing poultry production and economic feasibility of the poultry industry. Coccidiosis is the only disease that needs the persistent addition of anticoccidial substances in the feed because of its prevalent nature. It causes high economic losses and mortalities in industries and there may be a persistent loss of production in breeders and parent stocks owing to this disease at an early age (Akalu, 2017).

Etiological agents of coccidiosis are apicomplexan of the genus *Eimeria* (Reid *et al.*, 2014). Several species of *Eimeria* have been discovered in the various parts of the intestine of the chicken and turkey (El-Sherry *et al.*, 2019). Members of the genus *Eimeria* are highly host-specific and site-specific. *Eimeria* species have a direct life cycle that involves no vector or carrier for their transmission (Abbas *et al.*, 2023). The control of coccidiosis strictly adheres to understanding of life cycle and the reasons for its site and host specificities. *Eimeria* has a biphasic life cycle and it consists of reproductive and nonreproductive methods of replication (Mohsin *et al.*, 2021). The environmental part

of the *Eimeria* life cycle consists of a thick-walled oocyst that is initially unsporulated and later, with the provision of humidity and temperature it turns into a sporulated oocyst (Abbas *et al.*, 2023). The sporulated oocysts are the infective stage of *Eimeria*, which contains four sporulated oocysts each having two sporozoites. The sporozoites are vegetative forms of *Eimeria* and they replicate inside the cell. Sporozoites are released after stomach and post-stomach digestion of the Eimeria's oocyst wall and reach the intestine's predilection site. The pathogenic part of Eimeria's life cycle starts after the sporozoites enter the intestinal epithelial cells (Dubey *et al.*, 2022).

Sporozoite of *Eimeria* releases its immunogenic proteins which diagnose their site of replication (Olajide *et al.*, 2022). The poultry infectious *Eimeria* can be categorized into three major groups which are small intestinal, mid-intestinal, and large intestinal pathogens (Kimminau, 2015). In the intestinal cells, *Eimeria* replicates asexually and makes an intracellular structure called meront or schizont through a specialized process called merogony (Bangoura and Daugschies, 2018). The merozoites rupture to give rise to merozoites which enter the cells again, repeating the cycle. After an unpredictable number of cycles of merogony, reasons are still unknown, the merozoites undergo differentiation into micro and macrogamete, which form an oocyst on sexual reproduction. These oocysts are released into the environment, which initiates another cycle (King and Monis, 2007).

Life cycle events and associated risk factors of *Eimeria* help to understand the points of controlling coccidiosis (Rehman *et al*., 2011; Mesa-Pineda *et al.*, 2021). The most important parts in the life cycle include 1) the entry of *Eimeria* inside the host cell and 2) the rupture of schizont and the release of merozoites. Because the entry of *Eimeria* inside the cell and schizogony and rupture of the schizont lead to the destruction of the epithelium and immune system activation, these processes lead to inflammation and the production of reactive oxygen species, which lead to the production of lesions and the problems of coccidiosis (López-Osorio *et al.*, 2020). Control of coccidiosis depends upon the control of pathogenic lesions by reducing the production of reactive oxygen species and lowering the inflammatory changes in the body (Nahed *et al.*, 2022).

Synthetic chemical drugs used as anticoccidial work on the mechanisms and they are designed for coccidiosis by directly controlling the cellular processes of *Eimeria* either by stopping its reproduction (coccidiostat) and limiting the number of *Eimeria* oocysts or by destructing the cell structure of *Eimeria* by targeting the vital processes of *Eimeria* species (Coccidioides) (Chapman, 2018). These anticoccidial drugs are routinely used as prophylactic and therapeutic drugs effectively in commercial farms (Noack *et al.*, 2019). However, in the current era, multiple drugs have been restricted from being used because of their public health issues or reports of resistance (Martins *et al.*, 2022). Resistance to chemical drugs leads to the demand for the development of alternatives for the effective control of parasites including Eimeria (Abbas *et al*., 2011a; Chapman and Rathinam, 2022; Al-Saeed *et al*., 2023; Velázquez-Antunez *et al*., 2023).

Several alternatives have been suggested by scientists for the control of coccidiosis, including vaccination, organic acids, and botanical compounds (Abbas *et al*., 2010, 2011b, 2011c, 2012; Hussain *et al*., 2023; Saeed and Alkheraije, 2023). Botanicals are the most prominent alternatives being researched, and multiple researchers have reported their anticoccidial activity (Abbas *et al*., 2010, 2012; Ghaniei *et al.*, 2022; Abbas and Alkheraije, 2023; Al-Hoshani *et al.*, 2023). Multiple forms of botanical compounds are effective in controlling coccidiosis, but the issue is that these botanical products are mixtures of compounds and proper control of coccidiosis needs to identify the main active compounds. Phenolics are the major phytochemicals present in various forms and are known for their potency and efficacy against several infectious diseases, including coccidiosis (Lillehoj *et al.*, 2018). This review overviews the phenolics of plants and their mechanisms of action against coccidiosis.

Phenolics and derivatives: Phenolics the organic compounds containing a phenol ring (Benzene with a single hydroxyl) group in their structure, and they are among the most prominent medicinal compounds found in plants (Marchiosi *et al.*, 2020; Al Mamari, 2021). Phenolic compounds are widely present naturally, especially in plants (Kumar *et al.*, 2020). Phenolics are present in various forms and various plant parts, including fruits, seeds, flowers, roots, etc. (Al-Snafi, 2020). They have diverse sizes and chemical properties depending on their functional groups and structural isomerization. However, the presence of a hydroxyl (-OH) group in their structure, they have polarity in their nature, making them hydrophilic substances (Kim *et al.*, 2021). Phenolics are organic substances and are readily soluble in organic solvents too (Alara *et al.*, 2021). This makes phenolics the best to be extracted from most of the solvents (Alara *et al.*, 2021). Because of their organic nature phenolics can easily cross the cellular membranes and have high intracellular activities (Nourbakhsh *et al.*, 2022).

Phenolics derivatives can easily be divided into two main groups i.e., simple phenolics and polyphenolics (Albuquerque *et al.*, 2021). Simple phenolic compounds have single phenolic rings, while polyphenolic compounds contain two or more phenolic rings in their chemical structure (Al Mamari, 2021). While polyphenolics have multiple phenolic rings in their chemical structure and increase in ring ensures increased hydroxyl groups per molecule. These divisions are categorized into phenolic acids, flavonoids, tannins, lignin, lignans, etc. (Fig. 1). They have multiple differences in their chemical composition, reactivities, and medicinal properties. However, all the phenolics share some major chemical properties which are because of their phenolic ring and these properties have a lot of relationship with their medicinal use, including anticoccidial activities (Al Mamari, 2021).

Phenolic compounds possess polar behavior and exhibit hydrogen bonding in the aqueous solution, which is the strongest polar intermolecular force in covalently bonded molecules (Wang *et al.*, 2020). This makes them highly reactive in aqueous environments. Phenolic compounds can donate their hydroxyl group and show ionic behavior in aqueous environments and biological systems (Zhong *et al.*, 2020). Phenolics and their derivatives are highly oxidizable so oxidizing substances (e.g. free radicals) easily react with them, get neutralized, and cannot destroy the cells nearby (Wu and Kozlowski, 2022).

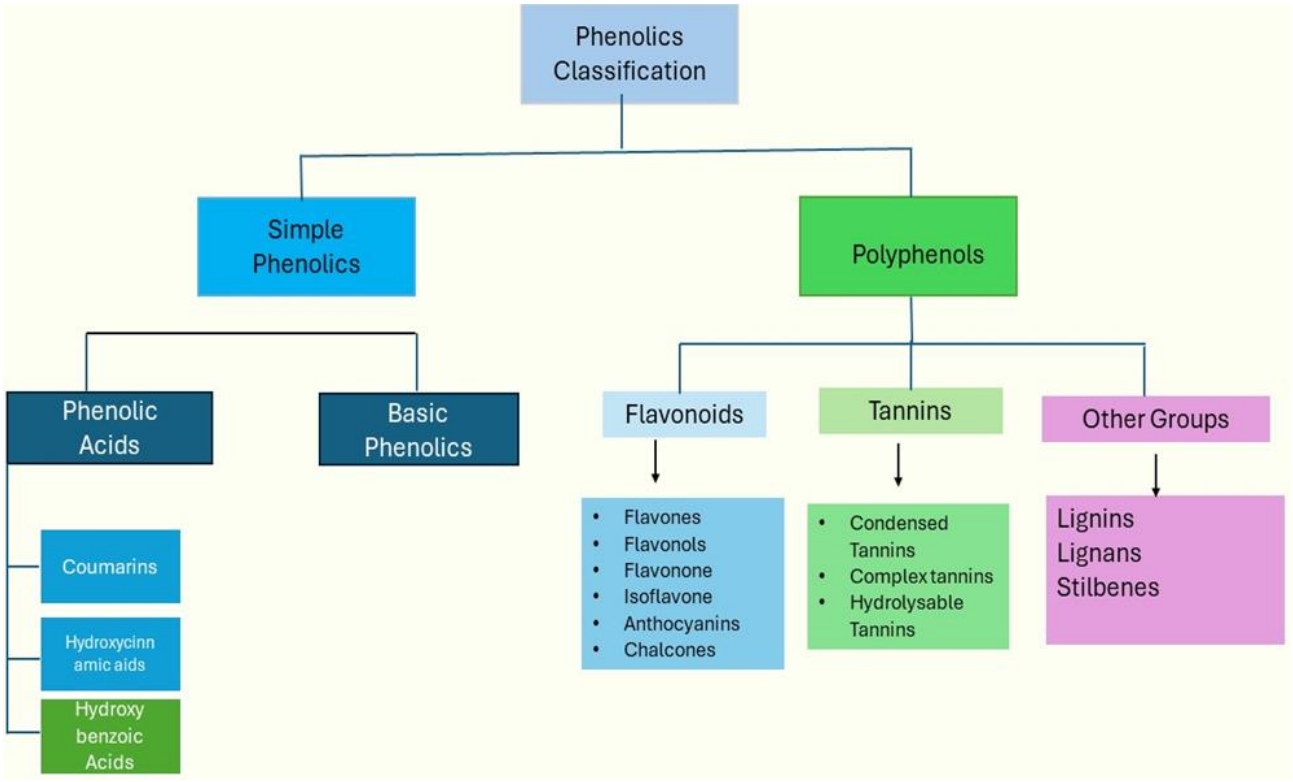

Fig. 1: Classification of Phenolic compounds of plants.

Phenolic compounds can penetrate biological membranes, can be extracted in various solvents, and can easily capture the oxidizing substances which makes them an efficient candidate to be evaluated for medicinal properties (Losada-Barreiro *et al.*, 2022). These properties of phenolic compounds make them strong antioxidant and anti-inflammatory agents because of their capacity to react to multiple oxidizing agents.

Anticoccidial mechanisms of actions of phenolics: Phenolic compounds have been used in experiments for several years and it has been proven that they have anticoccidial activities. Several research experiments state that plant extracts containing phenolics have been effective in controlling coccidiosis (Table 1). Although there is great diversity in phenolic compounds and they exhibit a variety of activities depending upon their chemical structure, these can be summarized into two major categories i.e., direct, and indirect anticoccidial activities. Below in the paragraph is an overview of these activities and mechanisms of actions of phenolics given to estimate their use for anticoccidial product development.

Direct anticoccidial activities: Phytochemical compounds, including phenolics, are known for their indirect actions, but research states that phenolic compounds can target several microbes, including *Eimeria* spp., and can arrest the life cycle (Nahed *et al*., 2022). Phenolic compounds damage the oocyst structure of Eimeria by acting in various ways depending upon their structure and stage of the life cycle of *Eimeria* spp.

Simple phenolic compounds having a single phenolic ring in their structure have been found to target the cellular process of the sporozoite of *Eimeria* spp (Lahlou *et al.*, 2021). Some simple phenolics have been reported to cause a disturbance in the cell permeability of the sporozoite (Anthony, 2008). phenolics disturb the ion transport channel of sodium and potassium ions, leading to an imbalanced ionic environment in the cells (Idris *et al.*, 2017). This leads to the loss of cell functionality, pH, osmolarity, and ion transport inside the cell. The cell functions are lost, and the cell membrane gets ruptured, leading to cell death. Some phenolics also interact with the energy production mitochondrial process of *Eimeria* (Song *et al.*, 2023). Phenolics like carvacrol disturb the ATP synthesis of the *Eimeria* and lead to cessation of the cell functionality of the *Eimeria* (Gholami-Ahangaran *et al.*, 2022). Single phenolic ring-containing compounds also destroy the mature cells of the intestinal lining, leading to the removal of schizont-containing and reducing the replication of *Eimeria* (Nahed *et al.*, 2022). These phenolic compounds are hydrophobic and act on the overgrown cells because of the high aqueous cytoplasmic content in them leading to their necrosis. This process is helpful for intestinal renewal along with premature necrosis of schizont-containing cells (Wu *et al.*, 2021). Tannins are an important group of phenolic compounds and they have been found to destroy the cell structure of the cell of *Eimeria.* The mechanism of action of tannins against the parasite is that they damage the cytoplasm, disturb the cell cycle-related changes of the cell of *Eimeria*, and cause disruption of cell structure and cell division leading to control of coccidiosis (Saeed and Alkheraije, 2023). Flavonoids are also important phytochemicals, and they may cause a disturbance in the host-parasite interaction of *Eimeria* by inhibiting the entry of *Eimeria* inside the cell and stopping the coccidiosis signs and symptoms. Multiple other phenolic compounds have been associated with the direct anticoccidial mechanisms by *in vitro* sporulation inhibition of the oocyst of *Eimeria*, reduction in oocyst

Table 1: Various groups of phenolic compounds from the botanicals and their mechanisms of actions against various specie species of *Eimeria*

Sr No	Group of Phenolic Compounds	Example of Compounds	Mechanism of Action	Plant Species	Target Species	Reference(s)
1.	Simple phenols	Carvacrol and thymol	Alteration in selective permeability if cell mebrane by alterin Na^+/K^+ transport channels	*Origanum vulgare*	*E. maxima, E. tenella, E. acervulina*	(Tsinas *et al*., 2011; Sidiropoulou *et al*., 2020)
2.		-do-	*In vitro* sporulation inhibition. Destroy the structure of sporulated oocyst	*Trachyspermum ammi*	*E. tenella, E. brunetti, E. maxima*	(Abbas *et al*., 2019)
3.		-do- and cineol	Decrease the oocyst count	Mixture of Phenolics from different plants	Multiple species of *Eimeria*	(Remmal *et al*., 2013)
4.		Eugenol, cineol, carveol	-do-	Mixture of botanical phenolics	Multiple species of *Eimeria*	(Bozkurt *et al*., 2016)
5.	Flavonoids		Cell entry blockage	*Aloe* spp.	*Eimeria maxima, E. necatrix*	(Akhtar *et al*., 2012; Musa, 2021)
6.			Antioxidant activities	*Artemisia annua*	*E. tenella*	
7.			Increase in specific antibodies. Cellular and humoral immune respocnes improved	*Astragalus membranaceus*	-do-	(Abdel-Tawab *et al*., 2020)
8.			-do-	*Barberis lycium*	-do-	(Nguyen *et al*., 2021)
9.			Concentration dependent inhibition of sporulation	*Emblica officinalis*	*E. acrvulina, E. maxima, E. tenella*	(Kaleem *et al*., 2014)
10.			Antioxidant activities	*Moringa oliefera*		(Ola-Fadunsin and Ademola, 2013)
11.	Tannins		Nonspecific anticoccidial activity	*Azadirachta indica, Trachyspermum ammi* and other plants	*E. tenella*	(Zaman *et al*., 2012)
12.			Sporulation inhibition	*Psidium guajava*	-do-	(Langerudi *et al*., 2022)
13.			Cytoplasm destruction. Inactivation of sporulation related enzymes	*Pinus radiata*	*E. acervuline, E. maxima, E. tenella*	(Abbas *et al*., 2017)
14.			-do-	*Commiphora swynnertonii*	*E. tenella, e. mitis, E. maxima*	(Bakari *et al*., 2013)
15.			Immunomodulatory response by increasing specific immunoglobulins	*Astragalus membranaceus*	*E. tenella*	(Guo *et al*., 2004)
16.	Phenolic acids	Hydroxycinnamic acid, Sinapic acids	*In vitro* sporulation inhibition	*Saccharum ofiicinarum*	*E. tenella, E. mitis, E. necatrix, E. brunetti*	(Awais and Masood Akhtar, 2012)
17.			Antioxidant activities	*Vitis vinifera*	*E. tenella, e. mitis, E. maxima, E. brunetti*	(Abbas *et al*., 2020)
18.	Alkaloids	Casiarin emodine	Antioxidant activities	*Senna siamea*	*E. tenella*	(Dakpogan *et al*., 2019)
19.			Stop replication of *Eimeria* in intestinal tissue	*Salvadora persica*	*E. tenella, E. maxima, E. maxima, E.*	(Aljedaie and Al-Malki, 2020)
20.		Isorhncophyline, ryncopyline	*In vitro* sporulation inhibition	*Uncariac ramulus*	*Eimeria tenella*	(Du and Hu, 2004)
21.		Sophoridine, matrine, isomatrine	-do-	*Saphora falvescence,*	-do-	(Youn and Noh, 2001)

count of *Eimeria,* and multiple other mechanisms (Fatemi *et al.*, 2015; Toah *et al.*, 2021). However, the data justify that the phenolic compounds can control coccidiosis efficiently because of their diverse modes of action.

Antioxidants: Coccidiosis is marked by intestinal lesions produced by the production of reactive oxygen and nitrogen species (Abbas *et al*., 2013) when *Eimeria* invade the intestinal cells as well as at the time of the schizonts rupture and release of merozoites (Allen, 1997). Cellular membranes and intracellular contents release reactive species that oxidize the nearby cells and rupture them hence enhancing the extent of damage (Blokhina *et al*., 2003). They may lead to the intestinal blood supply, leading to the production of pathognomonic signs of coccidiosis i.e., bloody diarrhea and intestinal blood engorgement. Phenolic compounds are highly oxidizable, and their oxidization depends on the number of hydroxybenzene (phenolic rings) (Foti, 2007; Collado *et al.*, 2011). Because of the more phenolic rings, the more available hydroxyl (-OH) groups will be there. These hydroxyl groups release their proton in the aqueous environment hence these reactive species and free radicals can easily oxidize them. Phenolics are proven to be strong antioxidants in various *in vitro* and *in vivo* experiments.

Anti-inflammatory: Phenolic compounds are among the potent anti-inflammatory agents. Researchers have stated that plant-based phenolics can control coccidiosis because of their anti-inflammatory properties (Wunderlich *et al*., 2014). Anti-inflammatory properties of the phenolic compound depend on their chemical structure especially Carbon to Carbon bonding, reaction capacity, and the extent of antioxidant capacity (Sobhani *et al*., 2021).

In coccidiosis, the schizogony of *Eimeria* and the invasion of the immune system lead to the initiation of inflammatory responses (Del Cacho *et al.*, 2014; López-Osorio *et al.*, 2020). Multiple inflammatory markers, including interleukins 1b, 2, 3, 4, 6, etc., tumor necrosis factor, interferon-gamma, and multiple other cytokines are released in coccidiosis (Ovington *et al.*, 1995). They start inflammatory reactions and try to destroy the *Eimeria* by altering the gut environment (Jeurissen and Veldman, 2002; Macdonald *et al.*, 2017). Although these are beneficial to an extent for the control of coccidiosis, their overexpression leads to great damage in the gut and destruction of epithelial cells along with other factors, which leads to heavy mortalities and persistent lesions on the gut (Grenier *et al.*, 2016).

Phenolic acid derivatives, including flavonoids, etc. have been reported to have anti-inflammatory effects (Moschona *et al.*, 2017). In several research experiments, researchers have proved that phenolics have efficiency in controlling inflammatory cytokines and can control inflammatory reactions (Costa *et al.*, 2012). Flavonoids have been reported to control inflammatory cytokines, interleukins, and interferon-gamma, and can stop inflammation (Adefegha *et al.*, 2020). In multiple studies, phenolics of various classes have been reported to show anti-inflammatory effects in coccidiosis research.

Limitations and future perspectives: Phenolic compounds are among the most suitable compounds to be used for the control of coccidiosis (Nahed *et al.*, 2022). They can directly and indirectly control coccidiosis by their direct antiprotozoal, antioxidant, anti-inflammatory, immunomodulatory, and cytotoxic effects. Despite these properties of phenolic compounds, several constraints need to be resolved before their clinical trials (Rahman *et al.*, 2021). First, phenolics are cytotoxic compounds (Perveen and Al-Taweel, 2017). Cytotoxicity of phenolic compounds is helpful for the eradication of *Eimeria* by killing the vegetative forms of the parasite and removing schizonts, but they can also destroy normal cells of the intestine (Ibrahim, 2016). The research states that the phenolic compounds can be dangerous for intestinal lining too because in some previous intestinal diseases or any injury to the intestine may lead to exposure of phenolic compounds to interior layers of the gut causing erosions and toxicities (Rahman *et al.*, 2021). Some phenolics, e.g., tannins are also anti-nutritional substances and cause reduced appetite and nutrient uptake from the gut, which also may adversely affect the productive performance of the birds. (Abbas, 2020) Multiple groups of phenolic compounds have been reported to act as anti-nutritional substances i.e., tannins reduce the protein digestibility while phenolic acids and flavonoids are inhibitory factors for the alpha-amylase and alpha glycosidase; two enzymes involved in carbohydrate metabolism (Li *et al.*, 2018). The anti-nutritional effect of phenolics is minor when given in therapeutic doses, but long-term studies are rare (Salim *et al.*, 2023), so no final inference can be drawn on whether their use is beneficial in terms of cost-to-benefit analysis or not.

Phenolics used as anticoccidials in the future need toxicity analysis and long-term studies to compare the beneficial effects and the expected hazards. The chemical substitution with other compounds to improve pharmacological properties of the phenolics can also be practiced.

Conclusion: According to the findings presented in this review article, phenolic substances are characterized as aromatic compounds that possess a phenolic ring in their structure. These compounds exhibit quick antioxidant activity and can be found in many plant species, making them widely distributed. These compounds are diverse and can have single or multiple phenolic rings, which are the defining factors for their medicinal properties. Because of their structure, they can attach to multiple organelles of *Eimeria* including cell membranes, mitochondria, etc., and can cause their destruction. They are also strong antioxidants and reduce the oxidative damage caused by the reactive oxygen species in the environment. These properties make them ideal substances to be used for the control of coccidiosis, but a few concerns are there that demand further research to make them practically suitable to be administered. Phenolics have some minor problems like cytotoxicity and antinutritive effects which need to be studied so that side effects may be avoided.

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REFERENCES

Abbas RZ, Iqbal Z, Khan MN, *et al*., 2010. Anticoccidial activity of *Curcuma longa* L. in Broiler Chickens. Braz Arch Biol Technol 53: 63-67.

Abbas A and Alkheraije KA, 2023. Immunomodulatory Effects of Carica papaya extract against Experimentally Induced Coccidiosis in broiler chickens. Pak Vet J 43(3): 628-632.

Abbas RZ, Iqbal Z, Blake D, *et al*., 2011a. Anticoccidial drug resistance in Fowl Coccidia: The state of play revisited. Worlds Poult Sci J 67: 337-350.

Abbas RZ, Munawar SH, Manzoor Z, *et al*., 2011b. Anticoccidial effects of acetic acid on performance and pathogenic parameters in broiler chickens challenged with *Eimeria tenella.* Pesq Vet Brasil 31: 99-103.

Abbas RZ, Munawar SH, Manzoor Z, *et al*., 2011c. Anticoccidial activity of hydrochloric acid (HCl) against *Eimeria tenella* in broiler chickens. Pesq Vet Brasil 31: 425-429.

Abbas RZ, Colwell D and Gilleard J, 2012. Botanicals: an alternative approach for the control of avian coccidiosis. Worlds Poult Sci J 68: 203-215.

Abbas R, Iqbal Z, Mansoor M, *et al*., 2013. Role of natural antioxidants for the control of coccidiosis in poultry. Pak Vet J 33(4):401-407.

Abbas A, Iqbal Z, Abbas RZ, *et al*., 2017. Immunomodulatory activity of *Pinus radiata* extract against coccidiosis in broiler chicken. Pak Vet J 37:145-149.

Abbas A, Abbas RZ, Khan MK, *et al*., 2019. Anticoccidial effects of *Trachyspermum ammi* (Ajwain) in broiler chickens. Pak Vet J 39(2):301-304.

Abbas RZ, Abbas A, Iqbal Z, *et al*., 2020. In vitro anticoccidial activity of *Vitis vinifera* extract on oocysts of different Eimeria species of broiler chicken. J Hellen Vet Med Soc 71(3):2267-2272.

Abbas G, 2020. An augmented review about anti-nutrients and toxins of feed stuff and their control strategies, a step toward sustainable resource utilization. Int J Agric Innov Res 8(4):361-377.

Abbas RZ, Saeed Z, Bosco A, *et al*., 2023. Botanical control of coccidiosis in ruminants. Pak J Agric Sci 60(4): 473-485.

Abdel-Tawab H, Abdel-Baki AS, El-Mallah AM, *et al*., 2020. In vivo and in vitro anticoccidial efficacy of Astragalus membranaceus against Eimeria papillata infection. J King Saud Univ Sci 32(3):2269-2275.

Abebe E and Gugsa G, 2018. A review on poultry coccidiosis. Abyss J Sci Tech 3(1):1-12.

Adefegha SA, Bottari NB, Leal DB, *et al*., 2020. Interferon gamma/interleukin-4 modulation, anti-inflammatory and antioxidant effects of hesperidin in complete Freund's adjuvant (CFA)-induced arthritis model of rats. Immunophamrmacol Immunotoxicol 42(5):509-520.

Akalu A, 2017. Status of poultry coccidiosis on private farm in Addis Ababa City, Ethiopia. Braz Poult Sci 6(3):80-86.

Akhtar M, Hai A, Awais MM, *et al*., 2012. Immunostimulatory and protective effects of *Aloe vera* against coccidiosis in industrial broiler chickens. Vet Parasitol 186(3-4):170-177.

Al-Hoshani N, Syaad KMA, Saeed Z, *et al*., 2023. Anticoccidial activity of star anise (Illicium verum) essential oil in broiler chicks. Pak Vet J 43(3): 553-558.

Al-Saeed FA, Bamarni SSI, Iqbal KJ, *et al*., 2023. In vitro anthelmintic efficacy of Haloxylon salicornicum leaves extract using adult Heamonchus contortus worms. Pak Vet J 43(1): 91-96.

Al-Snafi AE, 2020. Phenolics and flavonoids contents of medicinal plants, as natural ingredients for many therapeutic purposes-A review. IOSR J Phatrmacol 10(7):42-81.

Al Mamari HH, 2021. Phenolic compounds: Classification, chemistry, and updated techniques of analysis and synthesis. Phenolic Compounds: Chemistry, Synthesis, Diversity, Non-Conventional Industrial, Pharmaceutical and Therapeutic Applications pp.73-94.

Alara OR, Abdurahman NH and Ukaegbu CI, 2021. Extraction of phenolic compounds: A review. Curr Res Food Sci 4:200-214.

Albuquerque BR, Heleno SA, Oliveira MBPP, *et al*., 2021. Phenolic compounds: Current industrial applications, limitations and future challenges. Food Funct 12(1):14-29.

Aljedaie MM and Al-Malki ES, 2020. Anticoccidial activities of Salvadora persica (arak), Zingiber officinale (ginger) and Curcuma longa (turmeric) extracts on the control of chicken coccidiosis. J King Saud Univ Sci 32(6):2810-2817.

Allen PC, 1997. Production of free radical species during Eimeria maxima infections in chickens. Poult Sci 76(6):814-821.

Anthony JP, 2008. The inhibitory properties and mode of action of plant essential oils and fruit extracts on protozoan parasites. PhD Thesis, Queen Margaret University.

Awais MM and Masood Akhtar MA, 2012. Evaluation of some sugarcane (*Saccharum officinarum* L.) extracts for immunostimulatory and growth promoting effects in industrial broiler chickens. Pak Vet J 32(3): 389-402.

Bakari GG, Max RA, Mdegela RH, *et al*., 2013. Effect of resinous extract from *Commiphora swynnertonii* (Burrt) on experimental coccidial infection in chickens. Trop Anim Health Prod 45:455-459.

Bangoura B and Daugschies A, 2018. Eimeria. Parasitic protozoa of farm animals and pets:55-101.

Blokhina O, Virolainen E and Fagerstedt KV, 2003. Antioxidants, oxidative damage and oxygen deprivation stress: a review. Annal Botany 91(2):179-194.

Bozkurt M, Ege G, Aysul N, *et al*., 2016. Effect of anticoccidial monensin with oregano essential oil on broilers experimentally challenged with mixed Eimeria spp. Poult Sci 95(8):1858-1868.

Chapman HD, 2018. Applied strategies for the control of coccidiosis in poultry. CABI Reviews (2018):1-11.

Chapman HD and Rathinam T, 2022. Focused review: the role of drug combinations for the control of coccidiosis in commercially reared chickens. Int J Parasitolo Drug Drug Resist 18:32-42.

Collado S, Laca A and Diaz M, 2011. Effect of the carboxylic substituent on the reactivity of the aromatic ring during the wet oxidation of phenolic acids. Chemic Engg J 166(3):940-946.

Costa G, Francisco VC, Lopes M, *et al*., 2012. Intracellular signaling pathways modulated by phenolic compounds: application for new anti-inflammatory drugs discovery. Current Med Chem 19(18): 2876-2900.

Dakpogan HB, Gandaho CS, Houndonougbo PV, *et al*., 2019. Anticoccidial activity of Khaya senegalensis, Senna siamea and Chamaecrista rotundifolia in chicken (Gallus gallus). Int J Biol Chem Sci 13(4):2121-2128.

Del Cacho E, Gallego M, Lillehoj HS, *et al*., 2014. IL-17A regulates Eimeria tenella schizont maturation and migration in avian coccidiosis. Vet Res 45:1-9.

Du A and Hu S, 2004. Effects of a herbal complex against Eimeria tenella infection in chickens. J Vet Med B 51(4):194-197.

Dubey JP, Khan A and Rosenthal BM, 2022. Life cycle and transmission of Cyclospora cayetanensis: Knowns and unknowns. Microorganisms 10(1):118.

El-Sherry S, Ogedengbe ME, Hafeez MA, *et al*., 2019. Cecal coccidiosis in turkeys: Comparative biology of Eimeria species in the lower intestinal tract of turkeys using genetically typed, single oocyst–derived lines. Parasitol Res 118:583-598.

Fatemi A, Razavi SM, Asasi K, *et al*., 2015. Effects of Artemisia annua extracts on sporulation of Eimeria oocysts. Parasitolo Res 114:1207-1211.

Foti MC, 2007. Antioxidant properties of phenols. J Pharmacy Pharmacol 59(12):1673-1685.

Ghaniei A, Tohidi E and Vafaei A, 2022. Efficacy of a commercial mixed botanical formula in treatment and control of coccidiosis in poultry. Veterinarski Arhiv 92(6):723-734.

Gholami-Ahangaran M, Ahmadi-Dastgerdi A, Azizi S, *et al*., 2022. Thymol and carvacrol supplementation in poultry health and performance Vet Med Sci 8(1):267-288.

Grenier B, Dohnal I, Shanmugasundaram R, *et al*., 2016. Susceptibility of broiler chickens to coccidiosis when fed subclinical doses of deoxynivalenol and fumonisins—special emphasis on the immunological response and the mycotoxin interaction. Toxins 8(8):231.

Guo FC, Kwakkel RP, Williams BA, *et al*., 2004. Effects of mushroom and herb polysaccharides on cellular and humoral immune responses of Eimeria tenella-infected chickens. Poult Sci 83(7):1124-1132.

Hussain K, Abbas A, Alanazi HAH, *et al*., 2023. Immunomodulatory effects of Artemisia brevifolia extract against experimentally induced coccidiosis in broiler chicken. Pak Vet J 43(2): 333-338.

Ibrahim B, 2016. An evaluation of the anticoccidial potency of some ethnomedicinal plants used in the treatment of poultry diseases in Zaria, Nigeria. Ahmadu Bello University, Nigeria,

Idris M, Abbas RZ, Masood S, *et al*., 2017. The potential of antioxidant rich essential oils against avian coccidiosis. World Poult Sci J 73(1):89-104.

Jeurissen SHM and Veldman B, 2002. The interactions between feed (components) and Eimeria infections in poultry health. Nutrition and Health of the Gastrointestinal Tract. MC Blok, HA Vahl, L. de Braak, G. Hemke, and M. Hessing, eds. Wageningen Academic Publisher, Wageningen, The Netherlands:159-182.

Kaleem QM, Akhtar M, Awais MM, *et al*., 2014. Studies on Emblica officinalis derived tannins for their immunostimulatory and protective activities against coccidiosis in industrial broiler chickens. Scient World J 2014

Kim D, Kang M, Ha H, *et al*., 2021. Multiple functional groups in metal–organic frameworks and their positional regioisomerism. Coordinat Chem Rev 438:213892.

Kimminau E, 2015. Eimeria species in commercial broiler complexes in the United States.

King BJ and Monis PT, 2007. Critical processes affecting Cryptosporidium oocyst survival in the environment. Parasitol 134(3):309-323.

Kumar S, Abedin MM, Singh AK, *et al*., 2020. Role of phenolic compounds in plant-defensive mechanisms. Plant Phenol Sustaine Agric 1:517-532.

Lahlou RA, Bounechada M, Mohammedi A, *et al*., 2021. Dietary use of Rosmarinus officinalis and Thymus vulgaris as anticoccidial alternatives in poultry. Anim Feed Saci Tech 273:114826.

Langerudi MT, Youssefi MR and Tabari MA, 2022. Ameliorative effect of Psidium guajava essential oil supplemented feed on chicken experimental coccidiosis. Trop Anim Health Prod 54(2):120.

Li K, Yao F, Du J, *et al*., 2018. Persimmon tannin decreased the glycemic response through decreasing the digestibility of starch and inhibiting α-amylase, α-glucosidase, and intestinal glucose uptake. J Agri Food Chem 66(7):1629-1637.

Lillehoj H, Liu Y, Calsamiglia S, *et al*., 2018. Phytochemicals as antibiotic alternatives to promote growth and enhance host health. Vet Res 49(1):1-18.

López-Osorio S, Chaparro-Gutiérrez JJ and Gómez-Osorio LM, 2020. Overview of poultry Eimeria life cycle and host-parasite interactions. Frontiers Vet Sci 7:384.

Losada-Barreiro S, Sezgin-Bayindir Z, Paiva-Martins F, *et al*., 2022. Biochemistry of antioxidants: Mechanisms and pharmaceutical applications. Biomedicines 10(12):3051.

Macdonald SE, Nolan MJ, Harman K, *et al*., 2017. Effects of Eimeria tenella infection on chicken caecal microbiome diversity, exploring variation associated with severity of pathology. PLoS One 12(9):e0184890.

Marchiosi R, dos Santos WD, Constantin RP, *et al*., 2020. Biosynthesis and metabolic actions of simple phenolic acids in plants. Phytochem Rev 19:865-906.

Martins RR, Silva LJG, Pereira AMPT, *et al*., 2022. Coccidiostats and poultry: A comprehensive review and current legislation. Foods 11(18):2738.

Mesa-Pineda C, Navarro-Ruíz JL, López-Osorio S, *et al*., 2021. Chicken coccidiosis: from the parasite lifecycle to control of the disease. Front Vet Sci 8:787653.

Mohsin M, Abbas RZ, Yin G, *et al*., 2021. Probiotics as therapeutic, antioxidant and immunomodulatory agents against poultry coccidiosis. World Poult Sci J 77(2):331-345.

Moschona A, Kyriakidis KD, Kleontas AD, *et al*., 2017. Comparative study of natural phenolic acids and flavonols as antiplatelet and anti-inflammatory agents. Grant Med J 2(4):057-066.

Musa H, 2021. the efficacy of a commercial herbal formulation in the prevention of coccidiosis under natural exposure to Eimeria species. PhD Thesis. Federal University of Minna, Nigeria.

Nahed A, Abd El-Hack ME, Albaqami NM, *et al*., 2022. Phytochemical control of poultry coccidiosis: a review. Poults Sci 101(1):101542.

Nguyen BT, Flores RA, Cammayo PLT, *et al*., 2021. Anticoccidial activity of berberine against Eimeria-infected chickens. Korean J Parasitol 59(4):403.

Noack S, Chapman HD and Selzer PM, 2019. Anticoccidial drugs of the livestock industry. Parasitolo Res 118:2009-2026.

Nourbakhsh F, Lotfalizadeh M, Badpeyma M, *et al*., 2022. From plants to antimicrobials: Natural products against bacterial membranes. Phytotherapy Research, 36(1):33-52.

Ola-Fadunsin SD and Ademola IO, 2013. Direct effects of Moringa oleifera Lam (Moringaceae) acetone leaf extract on broiler chickens naturally infected with Eimeria species. Trop Anim Helath Prod 45:1423-1428.

Olajide JS, Qu Z, Yang S, *et al*., 2022. Eimeria proteins: order amidst disorder. Parasite Vector 15(1):1-16.

Ovington KS, Alleva LM and Kerr EA, 1995. Cytokines and immunological control of Eimeria spp. Int J Parasitol 25(11):1331-1351.

Perveen S and Al-Taweel AM, 2017. Phenolic compounds from the natural sources and their cytotoxicity. Phenolic Compounds-Natural Sources, Importance and Application pp. 29-60.

Rahman MM, Rahaman MS, Islam MR, *et al*., 2021. Role of phenolic compounds in human disease: current knowledge and future prospects. Molecules 27(1):233.

Rehman TU, Khan MN, Sajid MS, *et al*., 2011. Epidemiology of Eimeria and associated risk factors in cattle of district Toba Tek Singh, Pakistan. Parasitol Res 108: 1171-1177.

Reid AJ, Blake DP, Ansari HR, *et al*., 2014. Genomic analysis of the causative agents of coccidiosis in domestic chickens. Genome Research 24(10):1676-1685.

Remmal A, Achahbar S, Bouddine L, *et al*., 2013. Oocysticidal effect of essential oil components against chicken Eimeria oocysts. Int J Vet Med 2:133-139.

Saeed Z and Alkheraije KA, 2023. Botanicals: A promising approach for controlling cecal coccidiosis in poultry. Front Vet Sci 10:1157633.

Salim R, Nehvi IB, Mir RA, *et al*., 2023. A review on anti-nutritional factors: Unraveling the natural gateways to human health. Front Nutr 10.

Sidiropoulou E, Skoufos I, Marugan-Hernandez V, *et al*., 2020. In vitro anticoccidial study of oregano and garlic essential oils and effects on growth performance, fecal oocyst output and intestinal microbiota in vivo. Front Vet Sci 7:420.

Sobhani M, Farzaei MH, Kiani S, *et al*., 2021. Immunomodulatory; anti-inflammatory/antioxidant effects of polyphenols: A comparative review on the parental compounds and their metabolites. Food Rev Int 37(8):759-811.

Song H-Y, Deng M-L, Yang J-F, *et al*., 2023. Transcriptomic, 16S ribosomal ribonucleic acid and network pharmacology analyses shed light on the anticoccidial mechanism of green tea polyphenols against Eimeria tenella infection in Wuliangshan black-boned chickens. Parasite Vect 16(1):330.

Toah ET, Payne VK, Cedric Y, *et al*., 2021. In vitro oocysticidal sporulation inhibition of Eimeria tenella and antioxidant efficacy of ethanolic and aqueous extracts of Conyza aegyptiaca. J Anim Sci Vet Med 6(1):30-40.

Tsinas A, Giannenas I, Voidarou C, *et al*., 2011. Effects of an oregano based dietary supplement on performance of broiler chickens experimentally infected with Eimeria acervulina and Eimeria maxima. J Poult Sci 48(3):194-200.

Velázquez-Antunez J, Olivares-Perez J, Olmedo-Juárez A, *et al*., 2023. Biological activity of the secondary compounds of Guazuma ulmifolia leaves to inhibit the hatching of eggs of Haemonchus contortus. Pak Vet J 43(1): 55-60

Wang X, del Mar Contreras M, Xu D, *et al*., 2020. Different distribution of free and bound phenolic compounds affects the oxidative stability of tea seed oil: A novel perspective on lipid antioxidation. LWT 129:109389.

Wu J and Kozlowski MC, 2022. Catalytic oxidative coupling of phenols and related compounds. ACS Catalysis 12(11):6532-6549.

Wu M, Luo Q, Nie R, *et al*., 2021. Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiotaCriti Rev Food Nutr 61(13):2175-2193.

Wunderlich F, Al-Quraishy S, Steinbrenner H, *et al*., 2014. Towards identifying novel anti-Eimeria agents: trace elements, vitamins and plant-based natural products. Parasitol Res 113:3547-3556.

Youn HJ and Noh JW, 2001. Screening of the anticoccidial effects of herb extracts against Eimeria tenella. Vet Parasitol 96(4):257-263.

Zaman MA, Iqbal Z, Abbas RZ, *et al*., 2012. Anticoccidial activity of herbal complex in broiler chickens challenged with Eimeria tenella. Parasitol 139(2):237-243.

Zhong Y, Chen Y, Feng X, *et al*., 2020. Hydrogen-bond facilitated intramolecular proton transfer in excited state and fluorescence quenching mechanism of flavonoid compounds in aqueous solution. J Mol Liquid 302:112562.