



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 Gugsu, 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 Dauschies, 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 (Abbas *et al.*, 2011a; Chapman and Rathinam, 2022).

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; 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; 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 (Al Mamari, 2021; Marchiosi *et al.*, 2020). 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 Kozłowski, 2022).

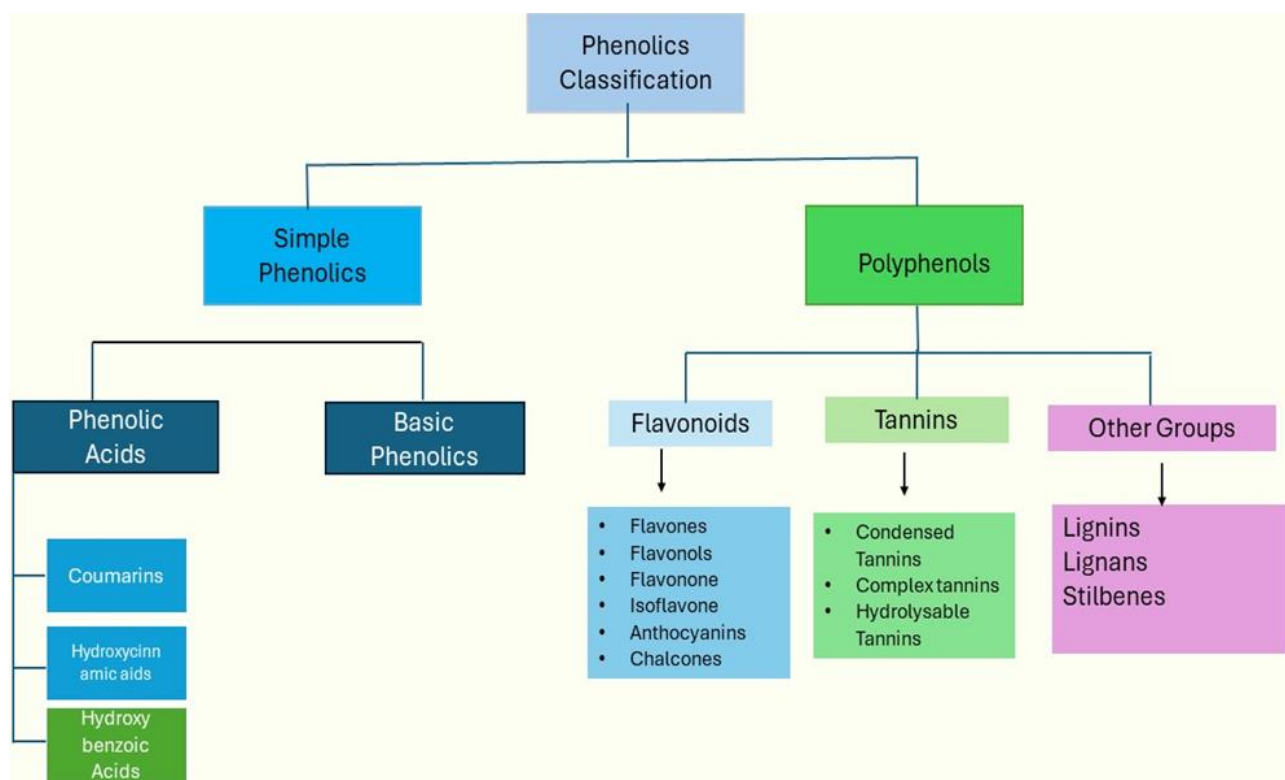


Fig. 1: Classification of Phenolic compounds of plants.

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	<i>Origanum vulgare</i>	<i>E. maxima</i> , <i>E. tenella</i> , <i>E. acervulina</i>	(Tsinas <i>et al.</i> , 2011; Sidiropoulou <i>et al.</i> , 2020)
2.	-do-	-do-	<i>In vitro</i> sporulation inhibition. Destroy the structure of sporulated oocyst	<i>Trachyspermum ammi</i>	<i>E. tenella</i> , <i>E. brunetti</i> , <i>E. maxima</i>	(Abbas <i>et al.</i> , 2019)
3.	-do- and	cincol	Decrease the oocyst count	Mixture of Phenolics from different plants	Multiple species of <i>Eimeria</i>	(Remmal <i>et al.</i> , 2013)
4.	-do-	Eugenol, cineol, carveol	-do-	Mixture of botanical phenolics	Multiple species of <i>Eimeria</i>	(Bozkurt <i>et al.</i> , 2016)
5.	Flavonoids	-do-	Cell entry blockage	<i>Aloe spp.</i>	<i>Eimeria maxima</i> , <i>E. necatrix</i>	(Akhtar <i>et al.</i> , 2012; Musa, 2021)
6.	-do-	-do-	Antioxidant activities	<i>Artemisia annua</i>	<i>E. tenella</i>	-do-
7.	-do-	-do-	Increase in specific antibodies. Cellular and humoral immune respocnes improved	<i>Astragalus membranaceus</i>	-do-	(Abdel-Tawab <i>et al.</i> , 2020)
8.	-do-	-do-	-do-	<i>Barberis lycium</i>	-do-	(Nguyen <i>et al.</i> , 2021)
9.	-do-	-do-	Concentration dependent inhibition of sporulation	<i>Emblica officinalis</i>	<i>E. acervulina</i> , <i>E. maxima</i> , <i>E. tenella</i>	(Kaleem <i>et al.</i> , 2014)
10.	-do-	-do-	Antioxidant activities	<i>Moringa oliefera</i>	-do-	(Ola-Fadunsin and Ademola, 2013)
11.	Tannins	-do-	Nonspecific anticoccidial activity	<i>Azadirachta indica</i> , <i>Trachyspermum ammi</i> and other plants	<i>E. tenella</i>	(Zaman <i>et al.</i> , 2012)
12.	-do-	-do-	Sporulation inhibition	<i>Psidium guajava</i>	-do-	(Langerudi <i>et al.</i> , 2022)
13.	-do-	-do-	Cytoplasm destruction. Inactivation of sporulation related enzymes	<i>Pinus radiata</i>	<i>E. acervuline</i> , <i>E. maxima</i> , <i>E. tenella</i>	(Abbas <i>et al.</i> , 2017)
14.	-do-	-do-	-do-	<i>Commiphora swynnertonii</i>	<i>E. tenella</i> , <i>e. mitis</i> , <i>E. maxima</i>	(Bakari <i>et al.</i> , 2013)
15.	-do-	-do-	Immunomodulatory response by increasing specific immunoglobulins	<i>Astragalus membranaceus</i>	<i>E. tenella</i>	(Guo <i>et al.</i> , 2004)
16.	Phenolic acids	Hydroxycinnamic acid, Sinapic acids	<i>In vitro</i> sporulation inhibition	<i>Saccharum officinarum</i>	<i>E. tenella</i> , <i>E. mitis</i> , <i>E. necatrix</i> , <i>E. brunetti</i>	(Awais and Masood Akhtar, 2012)
17.	-do-	-do-	Antioxidant activities	<i>Vitis vinifera</i>	<i>E. tenella</i> , <i>e. mitis</i> , <i>E. maxima</i> , <i>E. brunetti</i>	(Abbas <i>et al.</i> , 2020)
18.	Alkaloids	Casiarin emodine	Antioxidant activities	<i>Senna siamea</i>	<i>E. tenella</i>	(Dakpogan <i>et al.</i> , 2019)
19.	-do-	-do-	Stop replication of <i>Eimeria</i> in intestinal tissue	<i>Salvadora persica</i>	<i>E. tenella</i> , <i>E. maxima</i> , <i>E. maxima</i> , <i>E. tenella</i>	(Aljedaie and Al-Malki, 2020)
20.	-do-	Isorhncophyline, ryncopyline	<i>In vitro</i> sporulation inhibition	<i>Uncariac ramulus</i>	<i>Eimeria tenella</i>	(Du and Hu, 2004)
21.	-do-	Sophoridine, matrine, isomatrine	-do-	<i>Saphora falvescence</i>	-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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