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PHYTOCHEMICALS AS ALTERNATIVE ANTHELMINTICS AGAINST POULTRY PARASITES: A REVIEW

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ABSTRACT

Parasitic diseases causing considerable losses are one of the most common infections in humans, animals, and birds. This review emphasizes the devastation of the poultry industry by parasites and the use of bioactive components of plants as an alternative to control the damage. Synthetic medicines that are used in poultry as anthelmintic lead to the emergence of resistance in helminths as well as adversely affect birds and reduce their production. Different compounds are extracted from plants that show effective anthelmintic activity. Steroidal saponin alters the membrane permeability and inhibits mitochondrial activity resulting in worm death. Condensed tannins cause the death or paralysis of helminths. Flavonoids' mode of action involves the inhibition of several enzymes like phosphodiesterase and Ca-ATPase. Both flavonoids and tannins act synergistically and have the same function as praziquantel. Isoflavones inhibit energy generation and calcium utilization causing the death of worms. Isoquinoline alkaloids are neurotoxic to the different helminths. Phytochemicals have an important role in improving growth, enhancing immunity, increasing nutrient absorption, and maintaining gut integrity. Phytochemicals are added to poultry feed as an additive, antibiotic, growth promoter, and anthelmintic. Plant products are cheap, easily available, and have the least tendency for resistance to be developed. Therefore, they could be proved beneficial against helminths. But there are some limitations such as the lack of proper research on phytochemicals, their efficacy, toxicity, dosage, and mechanism of action of phytochemicals. As an alternative strategy, phytochemicals have shown good results against the resistant species of helminths, but the reason behind the effectiveness of phytochemicals against anthelmintic-resistant parasites needs further studies. In developing countries, the use of plant-based anthelmintics is limited. So, there is a need for proper studies and research on different plant sources having anthelmintic activity. This could save the poultry industry from huge economic losses due to parasitic infections.

***Keywords*:** Parasites, Poultry, Resistance, Alternative Anthelmintics, Phytochemicals

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1. INTRODUCTION

Poultry is the largest business all over the world and also an important part of the economy in developing countries and plays a vital role in the eradication of poverty (Abebe and Gugsa 2018). In the food industry, poultry fulfills the egg and meat demand all over the world (Belova et al. 2012). Poultry eggs and meat are widely used all over the world and meat is the second largest source of food at the global level including poultry meat (FAOSTAT 2016). All over the world, total poultry egg production is up to 73 million tons and total poultry meat production is up to 100 million tons. The contribution of broilers, backyard, and layers in overall poultry meat production is 92, 2, and 6% respectively (Gleam 2016). Among the total poultry production of the world, most of the production occurs in Asian countries. In recent years, in the poultry market Asia has dominated other continents (Tucker et al. 2007; Kandeel et al. 2022). Annually 42 billion broilers are produced all over the world (Jamil et al. 2022). Commercial

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poultry farming is working in Pakistan since the 1960s and is playing an important role in fulfilling the gap between the supply and demand of protein. Infectious diseases such as parasitic infestations are important health problems that cause economic losses and severe illness (Alvi et al 2020; Sharif et al. 2021; Alvi et al. 2021; Du et al 2022; Alvi et al. 2022a). In poultry, major losses are due to parasitic infections (Hunduma et al. 2010). Parasites adversely affect the health of birds by interfering with the metabolism and immunity of birds (Khater 1993; Abbas et al. 2015). Nematodes, Cestodes, and *Eimeria* species are those internal parasites that cause major economic losses in poultry production (Puttalakshmamma et al. 2008). *Eimeria* species cause coccidiosis, an important parasitic infection in poultry (Dalloul et al. 2006). Coccidia causes more than 20% of deaths of birds (Al-Fifi 2007). Coccidiosis provides a suitable environment for the growth of *Clostridium perfringens* which causes necrotic enteritis. There is an estimated loss of US$ 6 billion due to this disease due to low growth in broilers (Wade et al. 2015). Helminth infections decrease the efficiency of feed utilization and hence results in poor performance and weight gain of birds (Belete et al. 2016). *Histomonas meleagridis* is a parasite of the lower digestive tract and causes enterohepatitis mostly in turkeys but also in chickens and is commonly known as “Black Head”. Tan-yellow sulfur dropping is a common clinical sign (Huber *et al.* 2005). In poultry, parasitic diseases are the main problems that cause extensive economic losses on commercial levels and small backyard flocks (Ohaeri and Okwum 2013). Among nematodes, one of the most common roundworms of poultry is *Ascradia* galli and the adult stage resides in the small intestine and causes major damage by absorbing nutrients (Zaman et al. 2020). Ascaridiasis causes large economic loss through the reduction of egg production and growth rate. They cause mortality in severe infections by interfering with the normal functions of the small intestine (Islam et al. 2008; Adang et al. 2012; Salam 2015). In poultry different types of parasites, e.g., cestodes, nematodes, trematodes, and ectoparasites cause different diseases. In poultry important nematodes include *Ascaridia galli* (ascaridiasis), *Hetarakis gallinarum* (histomonosis), *Heterakis isolonche* (heterakidosis), *Capillaria caudinflata (*capillariasis). Important cestodes of poultry include *Hymenolepis cantaniana* (hymenolepisas), *Raillientina tetragona* (nodular tapeworm disease) while trematodes include *Prosthogonimus anatinus* (prosthogonimiasis), *Echinostoma cinetorchis* (echinostomiasis), *Zygocotyle lunata* (paramphistomiasis), and *Echinoparyphium recurvatum* (echinostomiasis). *Histomonas* (Blackhead disease), *Trichmonas* (trichomoniasis), *Plasmodium relictum* (avian malaria), and *Coccidia* (coccidiosis) are protozoal parasites which adversely affect poultry and reduce their production. External parasites include Fleas, lice, Ticks, and Mites (Ola-Fadunsin et al. 2019). For controlling parasites different treatment methods are used including the use of anthelmintics, nanoparticles, and phytochemicals (Tucker et al. 2007; Zaman et al. 2019; Rafay et al. 2021; Kandeel et al. 2022; Jamil et al. 2022; Adoho et al. 2022; Nahed et al. 2022; Batool et al. 2023). But here only phytochemicals as an alternative treatment method for poultry parasites will be discussed. These chemicals were also used in traditional medicines. For instance, salicin was obtained from the bark of a white willow tree which possesses analgesic and anti-inflammatory properties. Aspirin is the synthetic form of salicin (Sneader 2000; Landau 2010). The phytochemical paclitaxel was extracted from the plant named the English yew tree. This chemical is directly toxic to animals and humans but later on it is used successfully in cancer patients (Molyneux et al. 2007). In the previous year, the use of aromatic medicinal plants and their essential oils enhanced therapeutic industries (Kebede and Hayelom 2008; Kejlová et al. 2010). According to a WHO report in 1985, 80% 0f the world’s population is dependent on herbal medicines as a primary healthcare need, and the remaining 20% of the population lives in developing countries where 50% of all drugs are originated from plants (Balandrin et al. 1993; Farnsworth 1994; Kinghorn et al. 2003). In developing countries, 30 to 40% of all doctors rely on herbal preparations (Ullah and Khan 2016). In 3000 BC, the people of China and Egypt used herbal medicines for the treatment of various human and animal diseases (Withington 2010). About 2000 years ago, in India, herbal medicine composition was started to be saved in handwritten form. The actual discovery of pharmacy and herbal medicines started with Hippocrates. Hippocrates is called the “father of medicine”. Those people collected nearly 400 samples for medical purposes and strongly believed that nature and the environment influenced the health of both humans and animals. One of the best quotes of Hippocrates was that “let food be our medicine and medicine be our food” (Finlayson 1934; Barros and Casey 2020). Greeks especially Dioscordies reported the most important herbal medicines in his book “De Materia Medica” (Withington et al. 2010). In 1597, the English Master-surgeon John Gerard wrote a book on herbal medicine named “The Dark Age”. In this book, he discussed 3500 plants that have a role in medicine (Walsh and Schwartz-Bloom 2004). The great Muslim physician and philosopher Bu-Ali-Sina wrote a book “Qanun fi al Tibb” which is the principles of medicine. In the book, he discussed 700 herbal drugs (Walsh 1940; Cortez et al. 2008). In India, the history of herbal medicines wrote in the two most famous books “Rigvedas” and “Ayurveda”. In Ayurveda, 700 medicinal plants are discussed (Ullah and Khan 2016). Overall, the world, there are 25 best-selling pharmaceutical agents among them 12 are plant derivatives (O'Neill and Lewis 1993; Degla et al. 2022). In the United States pharmacopeia, more than 600 phytomedicines were discovered and are extensively used in Europe and some of them are banned (Tyler and Mitchell 1994; Madhuri et al. 2012).

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1.1. Phytochemicals

From ancient times to the present, plant parts and various chemicals extracted from them have been used for improving the health status of humans and animals. Humans have developed different methodologies and techniques to know the properties of chemicals that are extracted from plants and play vital roles in controlling internal parasites (Alvi et al. 2022b). Phytochemistry is defined as the study of compounds extracted from plants (Dreyfuss and Chapela 1994; Sasidharan et al. 2011). Phytochemicals are compounds that originate from plants and are produced through primary or secondary mechanisms (Harborne et al. 1999; Saxena et al. 2013). Phytochemicals play an important role in growth and defense against pathogens and are also used for treating infections in animals as well as humans (Jarić et al. 2015). These compounds furnish plants with color, odor, and taste (Molyneux et al. 2007). Classification of phytochemicals is shown in the following flowchart (Fig.1).

The inclusion of phytobiotics in animal feeds, speeds up growth, improves immunity, increases nutrient absorption, and maintains gut integrity and as well as decreases diarrheal syndrome (Zdunczyk et al. 2010; Gong et al. 2013; Zeng et al. 2015). Phytochemicals that contain one substituted phenolic ring are called the simplest bioactive phytochemicals. Phenylpropane-derived compounds are composed of cinnamic and caffeic acids which have the highest oxidation state. The tarragon and thyme herbs contain high caffeic acid which has proved to be beneficial against viruses, bacteria, and fungi (Geissman 1963; Brantner and Grein 1994; Klančnik et al. 2010). Catechol and pyrogallol are categorized as hydroxylated phenols that are toxic to different microorganisms (Thomson 1978; Al-Marzoqi et al. 2015). The phenolic structure of flavones consists of only one carbonyl group. Flavonol is made by the addition of three hydroxyl groups in the structure of flavones (Duke 1985; Panda 2004). Catechins are reduced forms of flavonol compounds that are extensively found in green tea and have antimicrobial activity (Kazmi et al. 1994; Dave and Ledwani 2012). Flavonoids are widely present in plants and have more than one benzene ring. Flavonoids are frequently used as antioxidants and free radical scavengers. Among them, there are more than 4000 flavonoids pigmented. Common flavonoids include quercetin, kaempferol, etc. which are found in nearly 70% of plants (Kar et al. 2007; Singla et al. 2019). The phytochemicals, e.g. terpenes, phenolics, and alkaloids have antiparasitic and antimicrobial properties (Hocquemiller et al. 1991; Kayser et al. 2003; Crozier et al. 2009; Lacombe et al. 2013; Rahman et al. 2021). Condensed tannins show anthelmintic characteristics in three different ways by lowering egg production in adults, hinders metamorphosis from egg to larval stage (L3) and inhibits abnormal development of L3 (Hoste et al. 2015; Qamar et al. 2022).

1.2. Reasons for Anthelmintic Resistance

Macrocyclic lactones like ivermectin are agonists to the inhibitory chlorides that are activated by glutamic acid (Geary et al. 2012; Wolstenholme et al. 2012). In previous studies, it is reported that the main reason behind the emergence of resistance of macrolides is genetically determined (Gill et al. 1998; Le Jambre et al. 2000; Prichard 2009). Resistance develops in helminths when mutations occur in more than three genes that code for the glutamate-gated chloride channels (GluCl) mostly of alpha subunits (Wang et al. 2010). It is also possible that mutations in those genes that do not code for GluCl can also lead to resistance (Holden et al. 2006). All these mutations lead to the change in the pharyngeal muscle (Keane et al. 2003) and result in changing the ivermectin receptors. Levamisole resistance is also related to the mutations in the nicotine cholinergic receptors in those nematodes that are resistant to anthelmintics (Kaplan and Vidyashankar, 2012). These mutations are in the nicotine Acetylcholine receptors (nAchRs) encoding for those genes that are responsible for the resistance of Levamisole

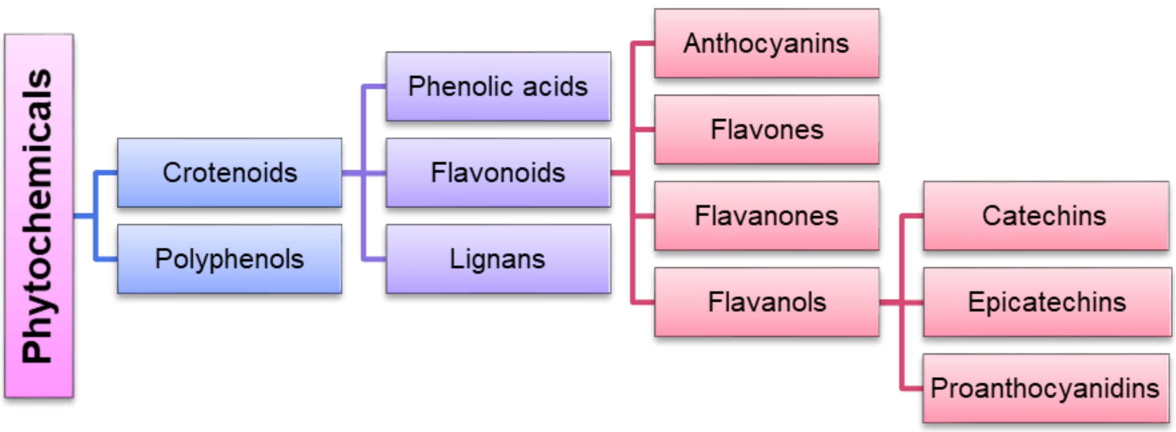

Fig. 1: Classification of phytochemicals.

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(Jabbar et al. 2006). Research done on nAchRs has been done by different techniques like patch- clamp that showed the difference in the AchR activity and resistance in the nematodes (Martin et al. 2012; Choudhary et al. 2022). Levamisole receptors have been observed to be deactivated in the resistant strains of nematodes (Qian et al. 2008) resulting in shifting in properties towards the resistant strains of parasites (Kotze *et al.* 2014). Benzimidazole resistance is also due to the mutation in β-tubulin genes that involves the precise substitutions of only specific amino acids that form the receptor protein (Roos 1997; Watkins 2003; Beech et al. 2011). Resistance is mostly seen in those cases when benzimidazoles are administrated when there were low numbers of eggs and larvae in the environment (Köhler 2001; Fissiha and Kinde 2021). Such situations lead to cross-resistance and change in gene expression (Von Samson et al. 2005). *Ascradia galli* is completely susceptible to benzimidazoles (Tarbiat 2018) but some selected species of this helminth have shown resistance. Change in β-tubulin genes leads to either the deactivation of receptors or decrease in affinity of receptors to bind with the benzimidazoles (Lubega et al. 1990; Keri et al. 2015).

Poultry is affected by anthelmintic resistance due to many direct or indirect losses. It has also been noted that the increasing global warming results in increasing the chances of anthelmintic resistance (Yazwinski et al. 2013). Phytochemicals have proved to be a better alternative to synthetic anthelmintics that have no effect on resistant strains of parasites (Mahdi et al. 2019; Aslam et al. 2021). For example, terpenoids encapsulated within yeast have proved to be effective against albendazole-resistant helminths (Mirza et al. 2020). The reason for the effectiveness of phytochemicals behind the resistant strains of parasites is still unknown, but it is noted that some composites of phytochemicals have the same mechanism of action as that of synthetic anthelmintics. For example, the action of saponins is similar to that of praziquantel (Wang et al. 2010). So, phytochemicals are effective against synthetic anthelmintic-resistant parasites.

1.3. The Demand of Phytochemicals as Anthelmintic

One reason for using phytochemicals as anthelmintics is the emergence of resistance in parasites against drugs present in the market. Resistance is the phenomenon in which parasites are unable to respond to those chemicals that are lethal to them (Von samson et al. 2005; Beech et al. 2011). Many cases of anthelmintic resistance have been reported from different parts of the world (Giri et al. 2015; Tarbiat 2018). Resistance against anthelmintics is common because of the modification in helminths due to frequent exposure of parasites to a particular anthelmintic (Kaplan et al. 2012; Whittaker et al. 2017). Anthelmintics are being used in huge amounts without any restrictions in some countries due to the lack of proper checks and balances and biomedical policies (Lalthanpuii et al. 2020).

1.4. Anthelmintic Activity of Phytochemicals

For the first days, the anthelmintic activity of medicinal plants was determined by observing their harmful effects on earthworms (Ali and Mehta 1970; Dixit and Varma 1975; Ferreira et al. 2018). The essential oils of *Gardenia lucida* (*Rubiaceae*), *Cyperus rotendus* (*Cyperaceae*), *Inula racemosa* (*Compositae*), *Psitacia integrrima* (*Anacardiaceae*), *Litsea chinensis* (*Lauraceae) and Randia dumetorum* (*Rubiaceae*) seeds have been reported to have anthelmintic activity against tapeworm and earthworm (Girgune et al. 1979; Mishra and Gupta 1979; Jaradat et al. 2016). The efficacy of plants having anthelmintic activity was determined by the expulsion of worms or decrease in egg per gram in the feces of infected host (Desta 1995; Demma et al. 2007). Some researchers have used a modified egg hatch assay to determine the anthelmintic activity against *Haemonchus contortus* (Coles et al. 2006). In some other research in vivo studies have used larval motility assay or larval development assay have been used to check the anthelmintic resistant (Assis et al. 2003, Lateef et al. 2003). The essential oils of several plants namely, *Callistemon viminalis* (*Myrtaceae*), *Anacardium occidentale* (*Anacardiaceae*), *Buddlea asiatica* (*Loganiaceae*), *Chloroxylon swientenia* (*Rutaceae*) and *oleo-gum* resin of *Commiphora mukul* (*Buberaceae*) have been reported to have anthelmintic property against hookworms and tapeworms and efficacy of all these compounds have been compared with piperazine phosphate and hexylresorcinol (Dengre 1982; Fokou et al. 2020). Important medicinal plants that are effective against internal parasites along with their composites and extracts are given below in Table 1.

1.5. Mechanism of action of various phytochemicals

Mechanism of action (MOA) of different composites is briefly discussed in Fig. 2 given below. In above figure MOA of different types of phytochemicals involve following pathways: 1) Phenolic acid effect the gene expression and also interfere in cell signaling pathway leading to death of the worm, 2) Isoquinoline alkaloid damage the neurons of the helminths that causes death of the helminths, 3) Flavonoids affect the calcium pump and ATPase that leads to the death of the worm, 4) Saponins alter the membrane permeability of helminths and also affect the mitochondrial action leading to death of helminths, and 5) Tannic acid or condensed tannins causes the paralysis and death of the worm.

Table 1: Plants with anthelmintic efficacy against poultry parasites

Family name	Scientific name	Common name	Part used	Method of preparation	Composition	Poultry parasite	References
Fabaceae	*Sophora flavescens*	Shrubby sophora	Bark	Decoction	Flavonoids and Phenols	*Eimeria tenella*	Qaid et al. (2021)
Piperaceae *Rosaceae*	*P. nigrum and U. dioica*	Black paper and nettle	Leaves	Ethanolic extract	Phenols, Flavonoids, Alkaloids, Saponins, Carbohydrates	*Coccidial species*	Muthamilselvan et al. (2016); Wajiha and Qureshi (2021)
Fagaceae *Rosaceae* *Combraetaceae*	*Q. infectoria, R. chinensis, and T. Chebula*	Aleppo oak, Chinese rose, black/chebulic myrobalan	Ground powder	N/A	Gallic acid, gallotannins and hydrolysable tannins	*E. tenella, E. acervulina, E. Maxima*	Thangavel et al. (2020)
Caricaceae	*Carica papaya L.*	Pawpaw	Seeds	Infusion	Alkaloids, Proteolytic enzymes, Benzyl isothiocyanate (BITC	*Ascraridia galli*	Stepek et al. (2004); Adu et al. (2009); Nghonjuyi et al. (2020)
Arecaceae	*Areca catechu L.*	Betel Nut	Fruit	Water extract	Alkaloids	*Ascraridia galli*	Ozaraga et al. (2017); Mubarokah et al. (2019)
Lythraceae	*Punica granatum L.*	Pomegranate	Peels	Methanol extract	Ellagitannins, Anthrocyanis ,Polyphenols	*Ascaridia galli*	Madrigal et al. (2009); Uddin et al. (2018)
Cucurbitaceae	*Momordica chorantia L.*	Bitter melon	Fruit	Alcohol extract	Charantin, Tannins, Phenolics, Terpenoids	*Ascraridia galli*	Grover et al. (2004); Alam et al. (2014); Poolperm et al. (2017)
Gunneraceae	*Gunnera perpensa L*	River pumpkin	Leaves	Water extract	Ellagic acids Flavonoids Phenols Proanthocyanidins, tannins, Alkaloids	*Heterakis gallinarum*	Mwale et al. (2015); Maroyi and A (2016)
Asphodelacae	*Aloe secundiflora Engl.*	Aloe	Leaves, Stem Bark	Methanol Extract	Tannins, Phenoles	*Ascraridia galli*	Kaingu et al. (2013); Raza et al. (2016)
Asparagaceae	*Agave sisalana prrine*	Sisal hemp	Leaves	Water extract of waste from decortication machine	Terpenoids	*Heterakis gallinarum*	Mwale et al. (2015)
N/A	*Aloe ferox Mill.*	Alligator jaw aloe	Leaves	Water Extract	Anthraquinone	*Heterakis gallinarum*	Mwale et al. (2015)
Mimosaceae	*Mimosa pudica L.*	Shame plant	Leaves	Ethanol extract	Steroids Flavonoids Phenols Alkaloids	*Ascaridia galli*	Tamilarasi et al. (2012); Nghonjuyi et al. (2015)
Fabaceae	*Flemingia vestita L.*	Sohphlang	Root tuber	Spirit extract of dried root peels	Genistein	*Earthworm Ascaridia galli Heterakis gallinarum*	Tandon et al. (1997); Shailajan et al. (2014)
Fabaceae	*Sesbania grandiflora (L.) Poir*	Vegetable hummingbird	Flowers	Water extracts	proteins Flavonoids Alkaloids Saponins	*Ascaridia galli*	Sable et al. (2013); Karumari et al. (2014)
Fabaceae	*Senna occidentalis (L.*	Coffee senna	Stem barks	Methanol extracts	Tannins Alkaloids Flavonoids	*Heterakis gallinarum, Ascaridia galli*	Kateregga et al. (2014); Suleiman et al. (2014)
Lamiaceae	*Mentha longifolia (L.) L.*	Wild mint	Leaves	Aqueous and HCL extract	Piiperitone oxide, Pipertenone oxide	*Ascaridia galli*	Ghoulami et al. (2001); Ali et al. (2013)
Meliaceae	*Azadirachta indica A.Juss.*	Neem	Stem barks Leaves	Pound and mixed with feeds	Glycosides Terpenoids Tannins Flavonoids, Alkaloids	*Ascaridia galli*	Pande et al. (2007); Susmitha et al. (2013)
Rosaceae	*Rubus fruticosus L.*	Black berry	Leaves Fruits	Methanol extract	Flavonoids Sesquiterpenes Saponins Tannins	*Ascaridia galli*	Lans et al. (2011); Ali et al. (2013)
Cucurbitaceae	*Cucurbita Moschanta Duchesne*	Pumpkin	Seeds	Methanol extract of ground seeds	Terpenoids, Cucurbitin, Saponin	*Ascraridia galli*	Marie et al. (2011)
Amaryllidaceae	*Allium sativum L.*	Garlic	Cloves	Decoctions or Macerates in water	Ajoenes	*Ascraridia galli*	Velkers et al. (2010)
Asteraceae	*Gymnanthemum amygdalinum*	Bitter leaves	Leaves	Infusion	Tannin, Saponin, Alkaloid	*Ascraridia galli*	Siamba et al. (2007)
Leguminosae	*Tephrosia vogelli Hook.f.*	Fish poison bean	Leaves Stems	Soxhlet method, maceration of ethanolic extracts	Alkaloids Anthocyanins Rotenoids Tannins	*Ascaridia galli*	Siamba et al. (2007)
Dryopteridaceae	*Dryopteris filix-mas (L.) Schott*	Male fern	Leaves, Stems	Ether Extract	Flavaspidic acid, Aspidinol	*Ascaridia galli, Trichostrongylus spp*	Blakemore et al. (1964); Githiori et al. (2004)
Lamiaceae	*Coleus scutellarioides (L.) Benth.*	Coleus	Leaves	Juice of leaves	Tannins Saponins Flavonoids	*Chicken tapeworm*	Satrija et al. (2001b)
Cucurbitaceae	*Cucurbita Moschanta*	Pumpkin	Seeds	Methanol extract of ground seeds	Saponins	*Ascraridia galli*	Blancard et al. (1991)

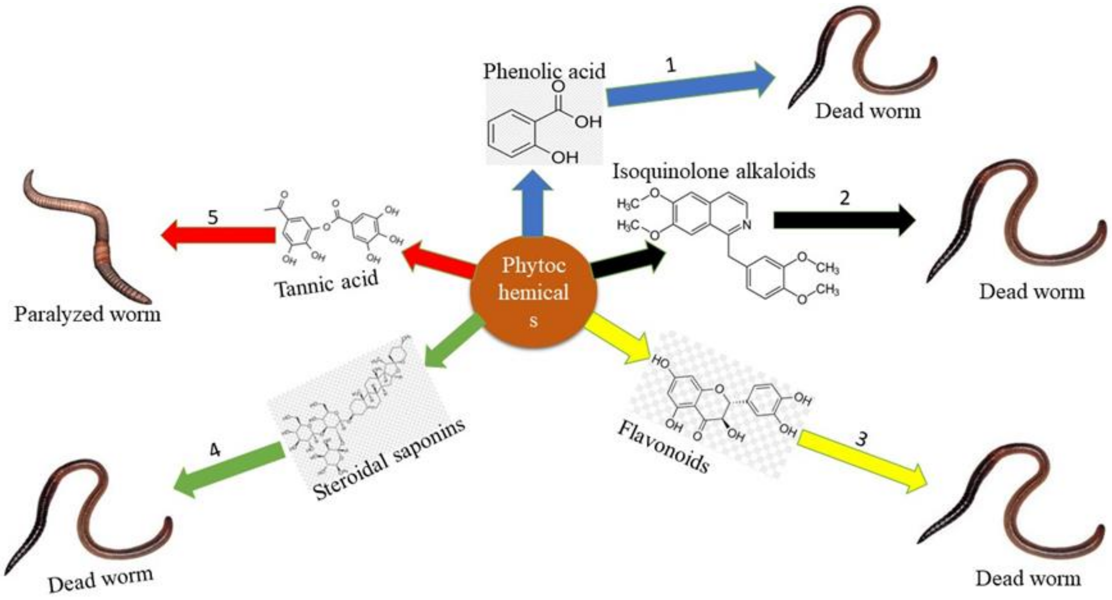

Fig. 2: Mode of action (MOA) of different phytochemicals

2. Conclusion

Ethnomedicines have been used by humans since long ago for the treatment of many parasitic diseases. But recently, development of resistance has been observed due to their excessive and non-specific use. As with every other medicine used as chemotherapeutic agents, the resistance develops. Therefore, the treatment of such diseases for which allopathic drugs are not showing their therapeutic effect involves the herbal medicines. In poultry due to the emergence of resistance against anthelmintic, phytochemicals have been used which showed good therapeutic results. Plant products are cheap, easily available and have least tendency for resistance to be developed. Therefore, they could be proved beneficial against helminths. But there are some limitations such as the lack of proper research on phytochemicals, their efficacy, toxicity, dosage, and mechanism of action of phytochemicals. So, there is need of proper studies and research on different plant sources having anthelmintic activity. This could save poultry industry from huge economic losses due to parasitic infections.

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