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Alternative Therapeutic Strategies for Histomonosis: A Review

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ABSTRACT

Histomonosis is a protozoan disease of poultry that can cause severe mortalities in turkeys and production losses in the chicken. It is a fastidious disease with pathological lesions in the liver and ceca of infected birds. The disease has been known for more than 100 years when in vitro and in vivo experiments started to understand histomonosis, causative agent and its treatment. The traditional antiprotozoal medicines are being used for control, but public health concerns and resistance are limiting their use. Herbal products, nutraceuticals, vaccines and managemental measures are among the alternatives being investigated. Herbal products with antihistomonal activities also have been launched with limited advantages, feed additives are also showing many beneficial effects have been mentioned. The vaccines are also being investigated which can provide protective immunity in the near future. All of possible treatments their effects and limitations along with preventions have been mentioned in this article. There is a need to work on these substances tirelessly to manage the problem of histomonosis in Poultry.

Key words: Blackhead, Herbal, Vaccines, Poultry, Turkey, Potent; Histomonosis

INTRODUCTION

Histomonosis, also known as blackhead or infectious enterohepatitis, is caused by the protozoan *Heterakis meleagridis* (Smith, 1895). Histomonosis was first time reported by Cushman in 1893 while working on turkeys (Mitra et al., 2018). Histomonosis was ranked 22nd important disease among 36 diseases in 2006, in a survey conducted by American veterinarians, and later it was ranked 13th and 9th important diseases of turkeys in 2015 and 2016 respectively (Clark & Kimminau, 2017). Number of reported cases of Histomonosis in turkeys were 55 while in 2016 it increased to 101 in 2016 in turkey farms (Clark & Kimminau, 2017).

Turkey fowl (*Maleagris* spp.) is the most common host of *H. meleagridis* but other gallinaceous birds like layers, broilers, game birds etc. are also infected with *H. meleagridis* (Lund et al., 1975; Clarke et al., 2017; Jajere et al., 2018). *H. meleagridis* can be transmitted either directly or through embryonated eggs of *Heterakis gallinarum* (Daş et al., 2021). *H. meleagridis* is antigenically linked to *Dientameoba fragilis*, an intestinal parasite with a wide host range in animals, including humans, and is also known as the "neglected parasite (Dwyer, 1972; Stark et al., 2016). It has been observed that chickens are less susceptible to histomonosis with lower mortality rates in outbreaks, so they are most of the time serving as reservoir hosts of *H. meleagridis*. Turkeys are the most susceptible to *H. maleagridis*, where mortality rate may be as higher as 70-100% (Dolka et al., 2015; Nguyen et al., 2015). Histomonosis causes inflammation of the ceca and thickening of the cecal wall with necrotic foci on liver seen in infected birds. It causes severe cecal and liver damage in turkeys, while it causes mild liver lesions and cecal lesions in chickens (Smith and Graybill, 1920). However, it has been shown in investigations that fatal histomonosis in young chickens as well in laying hens has been observed (Esquenet et al., 2003; Zahoor et al., 2011; Liebhart et al., 2013). Histomonosis infection in laying hens is more common in those with alternative housing (Grafl et al., 2011).

Traditional Control of Histomonosis

Several useful arsenic-containing compounds are being used to cure Histomonosis in birds all around the world throughout the years. Multiple researchers stated that the trivalent arsenical compounds and pentavalent arsenic compounds are routinely being used for the control of histomonosis. Trivalent arsenical compounds are less effective while pentavalent arsenical compounds are more effective for the control of (Tyzzer, 1923; McDougald, 1979, 2005). There are many other drugs

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which remained in practice for control of coccidiosis but public health issues and resistance of parasite lead to ban on their use.

Many drugs of various groups have been banned till today among which Enheptain-T was among the first drugs to be banned. It was an efficient against histomonosis in turkeys; however, it caused weight reduction (Seeger et al., 1950). Paromomycin was successful as a preventative measure against histomonosis, and its 200-400 ppm dose also reduced *Clostridium perfringens*, however, it was effective as a preventative measure but failed as a therapeutic measure against histomonosis since it was unable to reduce the mortality in turkey flocks (Hafez & Shehata, 2021; Lin, 2021). Nitroimidazole compounds were effective against *H. meleagridis* both in vivo and in vitro, but they were toxic at high doses (Lindquist, 1962; McGuire et al., 1964; Mitrovic et al., 1969; Doneley, 2004; Hu et al., 2004; Lin, 2021). Nitroimidazole was banned in 1987 while nitrofurans were banned in the United States in 1991 (Liebhart et al., 2010). Nitrosone was the last preservative to be banned in the US in 2015 due to its carcinogenic effects on consumers (Grabensteiner et al., 2008; Regmi et al., 2016; Clark & Kimminau, 2017; Hafez & Shehata, 2021). Multiple drugs have been banned to be used in the birds due to their harmful effects (Table 1)

Another issue with these drugs was that some compounds performed well in vitro but did not perform well in vivo (Grabensteiner et al., 2008; Thøfner et al., 2012). Sodium nitrate, sodium chloride, and boric acid are just a few of the many chemicals that have lately been studied and found to be more effective in vitro against *H. meleagridis* but have no therapeutic effects in vivo (Barros et al., 2020; Beer et al., 2020a; Beer et al., 2020b). *H. meleagridis* has developed resistance against dome of drugs i.e., some of its isolates showed resistance to nitrozone and metronidazole. Resistance, public health concerns and failure of drugs forced the researchers to investigate new substances.

Alternative therapeutic strategies for histomonosis

Failure of anthelmintic drugs due to resistance and public health issue has led the researchers to investigate the alternatives for the treatment of histomonosis. There was need of solution that may have s effect against the resistant strains of *H. meleagridis* (Hess & McDougald, 2013; Abraham et al., 2014; Umar et al., 2016). When no effective treatment was available, various techniques, such as bird protection, were used to prevent *H. meleagridis* infection (McDougald, 2005) by limiting direct exposure of birds to *H. meleagridis* and by treating other protozoans and their hosts such as earthworms. It is also possible to prevent the disease by reducing the spread of mechanical vectors such as rodents and insects (Tyzzer and Collier, 1925; Hu & McDougald, 2003; Hu et al., 2006).

Herbal Treatment for Histomonosis

Herbal compounds i.e., plant parts, extracts sand essential oils, have antibacterial and antiprotozoal action (Zenner et al., 2003; Hauck & Hafez, 2007). Some herbal preparations exhibit in vitro and in vivo effects against *H. meleagridis* activity (Arshad et al., 2008; Van Der Heijden & Landman, 2008b). The in vitro methods are immediate and economical techniques for assessing ability of product with anti-histomonosis activity. Many products showed the anthelmintic activity against *H. meleagridis* while other products did not have direct antihistomonal activity but showed effect on the cecal bacteria in culture that are required for *H. meleagridis* multiplication (McDougald, 2005). Some plant extracts having anthelmintic activity against blackhead have been mentioned in table 2.

Some essential oils derived from plants like lemon, rosemary, cinnamon, thyme, and garlic were tested, and they showed their activity against *H. meleagridis* (Zenner et al., 2003; Hauck & Hafez, 2007; van der Heijden & Landman, 2008a). Some commercially available plant derived products have been available in the market like protophyte®, Natustat®, Enteroguard™ and Protophyte® (Available in two forms, Protophyte® B dissolved in water and Protophyte® SP feed formulation). Protophyte® B and Protophyte® SP are made from the essential oils extracted from garlic, rosemary, cinnamon, and lemon. Protophyte ® B and Protophyte® SP were used and they reduced mortalities in histomonosis effected flocks but Protophyte ® B showed antihistomonal activity while Protophyte® SP showed no effect against *H. meleagridis* in vitro (Tyzzer, 1923). Both products reduced mortality from 50-20% but did not eliminate the liver and caecal lesions (Hafez & Hauck, 2006). In another experiment, Protophyte® showed no effect on birds and they showed 100% mortality like other birds of the control group who were not provided with any medicine (Van Der Heijden & Landman, 2008b). In field cases, it showed a decrease in mortality (Popp et al., 2011).

Natustat® is an herbal preparation which has unspecified extracts from plants and was described that it has antihistomonal activity (Duffy et al., 2004, 2005). Other commercial products like enteroguard™ and Aromabiotic did not show any antihistomonal activity, however Enteroguard™ showed in vitro effect against *H. meleagridis* (van der Heijden & Landman, 2008a, b). Water and ethanol extract from certain plants like *Thymus vulgaris*, *Vitis vinifera*, *Olea europaea*, *Peganum harmala*, *Ginkgo biloba*, and *Aesculus hippocastanum* were taken and experimented with in vitro in turkey. Ethanol extracts showed some antihistomonal effects, but water extracts did not show any appreciable activity against *H. meleagridis* (Arshad et al., 2008; Grabensteiner et al., 2008). Extracts from the *Artemisia Annua* also inhibited the growth of *H. meleagridis* in the culture media but did not decrease the mortality when added to feed or water of chicken and turkey (Thøfner et al., 2012).

From all these studies we concluded that herbal method of treatment against histomonosis is less effective and is not as efficacious as was chemotherapy method of treatment. We need more studies on plant extracts to find a better source of treatment. It is need of the hour to find an alternative, efficacious and safe source of treatment against the blackhead.

Table 1: Some of the banned or withdrawn drugs used for control of histomonosis.

Parent formula	Generic name	Brand name	Status	References
Nitrofurans	Furazolidone	Furox, Smith-kalin	It was banned by FDA in 1991.	(Gottschall & Wang, 1995)
	Sulfuride	Nifursol, Solvey	It was banned by the European Union (EU) from 2002-2003	(Li et al., 2010; Jones et al., 2020)
Nitroimidazole	Dimetridazole	Emtryl, solvey	It was banned by FDA in 1987 and by the EU in 1995 and 2001.	(Bleyen et al., 2009; Jones et al., 2020)
	Ipronidazole	Ipropran, Hoffman-La Roche	It was banned by FDA or withdrawn from the market in 1989.	(Kassem et al., 2016)
Arsenic (Pentavalent)	Carbarsone	Whitmyor to Alpharma, Carb-O-Sep	It was not marketed	(Clark & Kimminau, 2017)
	Nitrasone	Histostat-50, Alpharma to solvey to zoetis	It was withdrawn from the market on January 1, 2016.	(Clark & Kimminau, 2017)

Vaccination

Several studies on histomonosis have begun from the beginning of the last century. These studies range from the experiments on the difference in the virulence factors to the recent well-developed model of vaccination. In the first attempt to make the vaccine, it was found that the parasite lost its virulence factors during its cultivation during in vivo application (Tyzzer, 1923). After some time, researchers described certain immunization experiments that gave information on certain protective effects of the in vitro attenuated *H. meleagridis* in chicken and turkey, and there was no uniformity of duration of cultivation between different strains of *H. meleagridis* (Tyzzer, 1936). It was discovered that pathogenicity in chicken and turkey cannot be restored by serial passage (Tyzzer, 1936; Dwyer, 1972). These studies suggested that live attenuated vaccines can prevent disease more effectively (Nguyen et al., 2015).

In another study by Lund, it was found that when birds were inoculated with a non-pathogenic strain of *Histomonas* like *H. wenrichi* and virulent strains did not show any disease (Lund, 1959, 1963). After that, theses researchers observed the immunization properties (in vitro) and hypothesized that the difference in the virulence was due to the different strains of Histomonas present in the material that was used at the time of cultivation (Lund et al., 1966). But that hypothesis was later rejected by long-term cultivation and cloning (Hess et al., 2008). However, it was observed that long-term attenuation up to 1000 passages results in loss of immunogenicity (Lund et al., 1967). As it has been mentioned above that the chemotherapy was available and effective against the blackhead since the middle of the last century. It was observed that the birds that recovered from infection were resistant to histomonosis which supported the idea of vaccination (Brackett & Bliznick, 1949; Sautter and Pomeroy, 1950; Kendall, 1957). It was further confirmed by Clarkson that precipitating antibodies did not protect turkey against histomonosis, and he concluded that immunity against histomonosis was provided by the local immunity of the ceca, serum factors, or leukocytes (Clarkson, 1963). After that investigation was made by Hess et al. (2008) to check the efficacy of the vaccine to protect the turkey against histomonosis. In this experiment, both inactivated and attenuated vaccines were used. Inactivated vaccines were made by freezing and thawing process and addition of formol to the culture of *H. meleagridis*. While the attenuated vaccine was developed by passing the parasites for 2 years in only 2-3 days and then used in experiments. In his experiment (Hess et al., 2008), They administered 0.5ml of inactivated vaccine via the intramuscular route to the birds while on other hands attenuated vaccine was administered cloacally. Then the birds were given infection of 10,000 parasites per bird. The turkey that was administered with the attenuated vaccine did not show any signs and symptoms as no DNA of *H. meleagridis* was observed in the liver of birds, but the turkey that was injected with the inactivated vaccine showed signs and symptoms of the disease and died soon. Hence attenuated vaccine was proved successful in protecting turkey against histomoniasis.

Another study was done by Bleyen et al. (2009) based on active and passive immunity in the protection of birds against Blackheads. Active immunization was done by directly administrating the antigen of *H. meleagridis* via cloacal or intramuscular way. On the other hand, in passive immunity antisera from recovered birds was injected via the peritoneal cavity. These antisera can fight against the *H. meleagridis* as they developed resistance in previous birds. The experiment proved that a strong antiparasitic serum antibody reaction was observed in the case of active immunity. On the other hand, birds while experimented for passive immunization did not show immunity against 3×10^5 histomonads. This proved that passive immunizations did not develop any immunity in turkey against the Blackhead (Bleyen et al., 2009). One of the scientists named Liebhart experimented and evaluated the efficacy of oral vaccination in turkey. He also assessed some negative effects of the prototype on the performance of the birds. He used five different groups vaccinated, but not challenged, non-vaccinated and not challenged, cloacally challenged two weeks after oral vaccination, cloacally challenged four weeks after oral vaccination, and inoculum challenged but non-vaccinated. All the non-vaccinated birds were not challenged and 71.4% of birds in group two weeks of the cloacally challenged after oral vaccination got disease even after vaccination (Liebhart et al., 2010). These experiments gave us the idea for the first time that vaccines can be administrated orally also and support the idea of Hess (Hess et al., 2008).

Liebhart et al. (2010) also experimented with the effects of virulent and attenuated *H. meleagridis* both on chicken and turkey. The virulent Histomonads were obtained after 21 passages of colonial culture while attenuated Histomonads were obtained after 295 passages. The turkey and chicken were subjected to histomonads with a dose rate of 10^4 via the oral route, but the chicken

Table 2: Some plant extracts having activity against *H. meleagridis*

Herbal extract	Plant/commercial name	Ingredients	Experiment Type	References
Water extract	*Thymus vulgaris*	Benzene, phenol, terpene	In vitro	(Grabensteiner et al., 2008)
	Crataegus oxyacantha	Flavonoid, oligomeric phenolic acid, proanthocyanidin, tannin	In vitro	(Grabensteiner et al., 2008)
	Lycopersicon esculenstum	Alkaloid, flavonoid, phenolic acid, terpene	In vitro	(Grabensteiner et al., 2008)
	Helianthus annus	Fatty acid	In vitro	(Grabensteiner et al., 2008)
	Olea europaea	Fatty acid, flavonoid, phenolic acid	In vitro	(Grabensteiner et al., 2008)
	Mangifera indica	Benzole, flavonoid, phenolic, terpene	In vitro	(Grabensteiner et al., 2008)
	Linum usitatissimum	Fatty acid, glycoside and phenol	In vitro	(Grabensteiner et al., 2008)
	Aesculus hippocastanum	Saponin	In vitro	(Grabensteiner et al., 2008)
	Ginko Biloba	Flavonoid, terpene	In vitro	(Grabensteiner et al., 2008)
	Daucus carota	Polyacetylene	In vitro	(Grabensteiner et al., 2008)
	Vaccinium myrtillus	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
	Cynara scolymus	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
	Cucurbita pepo	Amino acid, sterol, tocopherol	In vitro	(Grabensteiner et al., 2008)
	Vitis vinifera	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
	Serenoa repens	Fatty acid, flavonoid, sterol	In vitro	(Grabensteiner et al., 2008)
Ethanol Extract	*Thymus Vulgaris*	Benzene, phenol, terpene	In vitro	(Grabensteiner et al., 2008)
	Dacus Carota	Polyacetylene	In vitro	(Grabensteiner et al., 2008)
	Echinacea purpurea	Hydroxycinnamic acid	In vitro	(Grabensteiner et al., 2008)
	Linum usitassimum	Fatty acid, glycoside, phenols	In vitro	(Grabensteiner et al., 2008)
	Mangifera indica	Benzole, flavonoid, phenolic, terpene	In vitro	(Grabensteiner et al., 2008)
	Olea europaea	Fatty acid, flavonoid, phenolic acid	In vitro	(Grabensteiner et al., 2008)
	Salix alba	Glycoside	In vitro	(Grabensteiner et al., 2008)
	Helianthus annuus	Fatty acid	In vitro	(Grabensteiner et al., 2008)
	Lycopersicum esculentum	Alkaloid, flavonoid, phenolic acid, terpene	In vitro	(Grabensteiner et al., 2008)
	Crataegus oxyacantha	Flavonoid, oligomeric proanthocyanidin phenolic acid, tannin	In vitro	(Grabensteiner et al., 2008)
	Primula veris, Gentiana lutea, Rumex species	Fatty acid, glycoside, flavonoid, saponin, tannin, terpene	In vitro	(Grabensteiner et al., 2008)
	Panganum harmala	Alkaloid	In vitro	(Arshad et al., 2008)
	Serenoa repens	Fatty acid, flavonoid, sterol	In vitro	(Grabensteiner et al., 2008)
	Vitis vinifera	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
	Cucurbita pepo	Amino acid, sterol, tocopherol	In vitro	(Grabensteiner et al., 2008)
	Cynara scolymus	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
	Vaccinium myrtillus	Flavonoid, phenol, tannin	In vitro	(Grabensteiner et al., 2008)
Essential oils	*Citrus lemon pericarps*	Terpene	In vitro	(Zenner et al., 2003)
	Organum vulgari, capsicum annum, thymus Vulgaris, citrus Limon (Repaxol)	Alkaloid, benzene, cinnamaldehyde, phenol, terpene	In vitro	(Hauck and Hafez, 2007)
	Rosmarinus officinalis, Citrus limon, Allium sativum, Cinnamomum aromaticum (Protophyte)	Cinnamaldehyde, hydroxycinnamic acid, terpene, diallyl tri-and disulfide	In vivo Orally	(van der Heijden and Landman, 2008a, b)
	Thymus vulgaris, Rosmarinus Officinalis (unspecified)	Benzene, phenol, terpene, hydroxycinnamic acid	In vitro	(Grabensteiner et al., 2007)
	Cinnamomum aromaticum	cinnamaldehyde	In vitro	(Zenner et al., 2003; Grabensteiner et al., 2007)
	Natustat (unspecified)	Unspecified active components of plants, yeast-derived mannanoligosaccharide, organic mineral nutrients	In vivo in the feed	(Duffy et al., 2004, 2005)
	Citrus x Aurantium	Alkaloid, glycoside	In vitro	(Hauck and Hafez, 2007)
B-carboline alkaloid	*Penganum harmala*	Harmane, harmalol hydrocholoride dehydrate, Harmaline	In vitro	(Arshad et al., 2008)
Plant material	*A. annua*	Artemisinin	In vitro	(Thøfner et al., 2012)
Steroidal glycoalkaloid	*Q. Saponaria*	Saponins	In vitro	(Grabensteiner et al., 2007)
Lyophilisate	Allium sativum, Cinnamomum aromaticum (Enteroguard)	Cinnemaldehyde, diallyl tri- and disulfide	In vitro in feed	(van der Heijden and Landman, 2008a, b)

was administrated with some additional cloacal dose. The lesions were observed both in the liver and caeca in chicken as well as turkey in which the virulent parasite was given while the birds in which attenuated parasite was given did not show any lesions at any site. Additionally, it was seen that virulent parasites were present in different organs while attenuated parasites were present only in caeca in a PCR test. This was one of those few studies that focused on the vaccination of this parasite. It could also be helpful for other scientists in the future for the vaccine development against *H. meleagridis* (Liebhart et al., 2010). One thing that was not satisfactory in this experiment was the dose rate of 10^4 which was less than the dose rate used by other scientists by 1.4×10^5 to 10^6 (Zenner et al., 2003; Hu et al., 2004; Hafez and Hauck, 2006). This could be one of the reasons why attenuated parasites did not show any signs and symptoms in the birds. Further studies are required for this experiment for the development of satisfactory results and an effective vaccine.

Other researchers (Nguyen et al., 2015) experimented with the lower virulence of *H. meleagridis* in turkey as a protective function against the blackhead. The low virulence of *H. meleagridis* was obtained by the back passages via intracloacal. The back passage was obtained by the intracloacal inoculation of *H. meleagridis* in three-week-old turkey birds. After 13 days of infection, these birds were used to obtain the parasites to inoculate in new birds. It was seen that in last three passages birds did not show any lesions and signs of the blackhead disease. So, the back passage 10 was used to test the protective capacity against histomoniasis. The birds vaccinated with this low virulence back passage parasite showed lower signs and lesions against the disease than that unvaccinated birds and no mortality in those birds that were vaccinated as compared to the 71% in unvaccinated birds (Nguyen et al., 2015). Therefore, we come to know that low virulence back passage can also be used as a vaccine against the blackhead disease. Some other studies showed that vaccines act as a single inoculum that does not affect attenuation and efficacy (Ganas et al., 2012). In some experiments, it was shown that the layer birds in which live vaccine was used did not show any egg drops when inoculated with *H. meleagridis* (Liebhart et al., 2013). Most recently cross-protection was also demonstrated using genetically different strains of *H. meleagridis* (Sulejmanovic et al., 2016).

From all the above-mentioned data about vaccination against blackhead, we could say that there is a need for some more studies on vaccination against this disease. As there are not 100% results of any vaccine in all studies obtained and there is no commercial vaccine in the market. So, the gap between experimental studies and products in the market must be bridged. We can expect that soon we will obtain an effective commercial product of vaccination against histomonosis. There is still doubt and debate in some of the past studies on vaccination. But Nguyen et al. (Nguyen et al., 2015) studies gave satisfactory results against blackhead. These studies suggest that the vaccines have the potential to control histomonosis but there is a dire need to work on the practical vaccine to develop the commercial vaccine.

Nutraceuticals

As it has been seen that not any single product is available in the market that can be used as a treatment for blackhead. Researchers suggest the use of combination therapy including nutraceuticals for the control of this havoc on farms. A lot of research was done in mid of the 1900s on the interrelationship of diet and medicine used in poultry to prevent different diseases (Roberts et al., 2015). It was seen that when vitamin E was added to any antihistomonal medicine like ipronidazole it improved the efficacy of the drug and reduced the mortality and morbidity of the birds to the great extent (Schildknecht & Squibb, 1979). It gave new revolutionary ideas of using some of the vitamins in the diet as well as drugs to prevent diseases and to enhance the immunity of the birds. Copper sulfate was used in the diets of the chicken and turkey due to its antibacterial and growth promoter properties (Smith, 1969; Pesti & Bakalli, 1996; Miles et al., 1998). Some farmers have used copper sulphate for the treatment of *Trichomonas gallinarum*, a parasite related to *H. meleagridis*, but the results showed variations (Kemp & Reid, 1965). Some farmers used copper sulfate to treat *Trichomonas gallinarum*, but it gave varying (Kemp & Reid, 1965). It gave good results against *H. meleagridis* when applied in vitro (Stepkowski and Klimont, 1980; Kenyon, 2015). Copper sulfate caused toxicity when used above 500 ppm and that was the lowest concentration used at that time, so there is a need for an optimum titration level at which it will not cause toxicity but can reduce the blackhead in birds (Christmas & Harms, 1979)). Recently, some farmers described that copper sulfate gives good results against *H. meleagridis* by using its high dose, but it needs to be confirmed in vivo. Hence there is no single product that will work every time against the disease but the combination of different products sometimes gives good results.

Managemental measures

Therapeutic substances have promising importance for the control of histomonosis but the importance of management practices to control histomonosis has a major role in the prevention of the disease. Various recent control measures for histomonosis described by the different field reports in the United States of America are given (Liebhart et al., 2017). For housing problems, a daily change of bedding or litter is recommended after each flock is removed. It may help to prevent the spreading of the disease (Clark & Kimminau, 2017). Immediate and accurate diagnosis using advanced techniques i.e., PCR, histopathology, or wet mount is recommended (Clark & Kimminau, 2017). Biosecurity is also an important thing that can reduce the risk of the transmission of blackhead disease. Direct contact of farm birds with wild birds should be restricted to control the transmission of disease from farm to nearby farm or house to the house of a farm (Clark & Kimminau, 2017). Intervention strategies depend upon the conditions before the occurrence of blackheads on the farm, climate, soil, weather, litter, etc. (Steven & Emily, 2017). Eimeria infection has been shown to cause coccidiosis, which may exaggerate histomoniasis in the broiler (McDougald & Hu, 2001). Treat the floor or litter with copper sulfate, salt, lime, or a combination of all of these. It has also been

reported that increasing the depth of litter can decrease the access of *H. gallinarum* to the floor, so it can prevent the spread of the disease (Maslić-Strižak et al., 2018). Avoid stress or excessive physiological activity that may increase the risk of blackhead. Excessive wet bedding is a major risk factor for the development and propagation of *H. meleagridis*. When turkey and broiler farms are close to each other or working together. There is a high risk of biosecurity of communication and the spread of the disease, to avoid these risks still use an approved vermifuge. Control the intestinal parasites like ascarids to avoid disease in both the turkey and broiler. The use of walls and fences in barns can prevent direct transmission during illness outbreaks and transmission to the entire home ((Hu et al., 2004). As we know *H. meleagridis* survives in more basic pH=8.0. It can therefore be hypothesized that a higher pH may increase the chances of survival of *H. meleagridis* whereas a lower pH may decrease the chances of survival. It has been shown that caeca pH significantly increased when the broiler is kept off feed for 12h to 24h which enhances the chances of development and survival of *H. meleagridis* (Hess et al., 2015). Some farmers used acetic acid in the water, but it increases the *H. meleagridis* in birds. Hence, there is a need for research on using the acid water or acidic feed to ensure that either it increases or decreases the chances of *H. meleagridis* in birds. It is described that *H. meleagridis* has limited survival in the environment, but *H. gallinarum* is harder and can survive for a much longer period in the environment. It has been known from research that *H. meleagridis* can survive at 4ºC temperature for 5 months inside *H. gallinarum* and produce more severe infections in turkey than those of fresh *H. melegridis* (Lund et al., 1975). Another scientist also described that *H. meleagridis* can survive for 2 years at 4ºC temperature in *H. gallinarum* but it did not survive in an environment outside the ova (Long, 1966). According to some field reports, flies and Darkling beetles can indirectly contribute to the spread of the disease. So, controlling those beetles and flies can control the spread of vectors and causative agents. It is important to break the cycle of *H. meleagridis* to prevent from huge losses in poultry industry for prevention purpose separate the ill and healthy birds, and cleaning with disinfectant is necessary as *H. meleagridis* is susceptible to disinfectants.

Conclusion

Histomonosis is an emerging disease in chickens and turkeys worldwide. There is currently no effective, safe, approved and commercially available chemotherapeutic product in the market. There are no effective and commercial herbal products against blackhead. No working vaccine is commercially available. There are other treatments that have different dosages and product combinations, but they do not always work against histomonosis. So, to avoid this disease we should take careful and strict precautions. Scientists must find an effective treatment that will give good results in vivo or in vitro under all conditions.

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