Chapter 13

Herbal Treatment of *Salmonella* Pullorum Infected Broilers with Cinnamon: A Comprehensive Review

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ABSTRACT

The poultry industry plays a significant role in the country's GDP, being a major agricultural stakeholder. The presence of certain viruses and bacteria can lead to fatal diseases in poultry. One of the major bacterial diseases is salmonellosis, which has a high morbidity and mortality rate causing significant economic losses all over the world. The losses are exacerbated by an emerging antibiotic/ antimicrobial resistance. Being a global threat, it is crucial to carefully choose antibiotics or shift to antibiotic alternatives. Cinnamon and its derivatives may be a viable alternative to antibiotics for treating salmonellosis due to their antimicrobial properties. Cinnamon possesses antioxidant, antidiabetic, antifungal, and antibacterial properties, and can replace the irrational use of different antibiotics to treat various *Salmonella* infections including Pullorum disease. This chapter provides a comprehensive overview of cinnamon's pharmacological properties in preclinical and clinical investigations against bacterial infection and highlights the crucial need for additional research to provide a thorough and definitive conclusion for its ideal application in the treatment of *Salmonella* Pullorum infection in poultry.

KEYWORDS
Salmonella Pullorum, Cinnamon, Phytochemical, Antimicrobial Resistant, Poultry.

Received: 21-June-2024
Revised: 28-July-2024
Accepted: 10-August-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Rehman T, Rehan S, Qureshi AS, Kausar R, Nawaz S, Shareef MU, Abdullah M, Murtaza G, Rashid S, Usman M and Muneer H, 2024. Herbal treatment of salmonella pullorum infected broilers with cinnamon: a comprehensive review. In: Abbas RZ, Khan AMA, Qamar W, Arshad J and Mehnaz S (eds), Complementary and Alternative Medicine: Botanicals/Homeopathy/Herbal Medicine. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 115-122. https://doi.org/10.47278/book.CAM/2024.144

INTRODUCTION

The poultry industry is responsible for providing a significant portion of the protein requirement and a source of livelihood in numerous countries, including Pakistan. In the past decade, this industry has been affected by various diseases. The major concern in this sector is Pullorum disease, mainly caused by *Salmonella* Pullorum (*S.* Pullorum) (Javed et al., 2018). This disease occurs at a very young stage about 2-3 weeks of age. The chicks that survive the disease outbreak and even do not show any clinical signs and symptoms become carriers for the spread of the disease to other flocks or even to consumers (Collett et al., 2020). The morbidity or mortality in the chicken flock due to Pullorum disease is very high and it is mainly dependent on the flock's age, management, nutrition, exposure rate, and disease stress in the flock (Berhanu and Fulasa, 2020). *S.* Pullorum is a motile, asporogenous, rod-shaped bacterium in the family Enterobacteriaceae and the tribe Salmonellae. This is characterized by causing Pullorum disease in poultry and can persist in the environment for months to several years when conditions are favorable. The extracellular lipopolysaccharide in *Salmonella* is an important tool of pathogenesis that interacts with the immune system of the respective host to induce an inflammatory response and septic shock including fever that eventually causes death (Coburn et al., 2007).

The multidrug-resistant bacterial infections are increasing day by day due to the irrational use of antibiotics. The rising global problem of antibiotic resistance requires suitable alternatives or substitutes in comparison to the currently available antibiotics. An emerging strategy to cope with this issue is the use of antibacterial substances acquired or developed from natural resources. Specifically, for the treatment of *S.* Pullorum, florfenicol is usually used in field practice. The minimum withdrawal period for florfenicol is around 25 days, and if it is used excessively in salmonella cases, there will be a higher chance of antibiotic residue being transferred to the human body after consumption of contaminated meat. Cinnamon

could be an alternative to treat salmonellosis due to its antimicrobial activities and it is also safe for human consumption. *Trans*-cinnamaldehyde which is obtained from the bark of cinnamon trees can be successfully used as an alternative antimicrobial compound against *S.* Pullorum. Besides its significant antimicrobial properties, *trans*-Cinnamaldehyde has many other therapeutic properties including its anti-diabetic, anti-inflammatory, and antioxidant effects (Singh et al., 2021). Cinnamaldehyde commonly known as "dar cheeni", an aromatic aldehyde, reported having antibacterial activity against a variety of foodborne pathogens. It is the main component of cinnamon bark, and possess good inhibitory effect on various bacteria and fungi (Doyle and Stephens, 2019). The cinnamaldehyde (a major portion of cinnamon extract) was previously evaluated as an antibacterial agent against various gram-negative bacteria. Therefore, understanding of the antibacterial mechanism of these derived compounds will aid in the development of new antibacterial substances (Utchariyakiat et al., 2016).

This chapter discusses various *Salmonella* virulence factors that are important in the pathogenesis of salmonellosis. These factors include the stages, mechanism of pathogenesis in conjunction with systemic infection, commonly used treatments, and a brief discussion of the characteristics of cinnamon and its application in the treatment of salmonellosis in poultry.

***Salmonella* Pullorum**

S. Pullorum causes an acute disease in young chickens with high mortality known as Pullorum disease. Almost all birds of different breeds are susceptible to this disease. The Pullorum disease is more susceptible to young chicks aged less than 14 days, however, in adult birds, the disease can be present in chronic form. The clinical signs of pullorum disease may include less feed intake, dehydration, depression, and white watery diarrhea. Whereas early infected chicks show mortality without exhibiting any clinical sign of the disease. Furthermore, the reduced growth rate and poor feathers development are common in the surviving birds. In adult birds, the signs and symptoms are not shown but they act as a carrier. Pullorum disease also has zoonotic importance, like poultry products and by-products contribute a great deal to human salmonellosis (Snoeyenbos, 2019). Salmonellosis causes about 94 million food-borne cases annually (World Health Organization, 2015). *Salmonella* mainly causes gastroenteritis at a young age and shows a systemic infection, septicemia, and eventually death in immunocompromised or elder patients. Mainly salmonellosis occurs by consuming different food items contaminated with various *Salmonella* serovars. These food items include eggs, chicken, or pork but nowadays, disease occurrence is increasing because of consumption of contaminated nuts, fruits, and vegetables (Ferrari et al., 2019). *Salmonella* in different healthy individuals can cause watery diarrhea, abdominal pain, nausea, vomiting, and fever which is termed as self-limiting gastroenteritis. Some affected individuals may suffer from profuse "cholera-like" diarrhea. However, in some individuals, diarrhea with blood and mucus is also reported. The infection is invasive and usually limited to the underlying tissue of the intestine (Manatsathit et al., 2002).

Transmission of *S.* Pullorum

S. Pullorum is mainly transmitted by two main sources of transmission in chicks, such as vertical transmission, and horizontal transmission as shown in Fig. 1. In horizontal transmission *S.* Pullorum shed through the feces of the chicken, contributes as a major source of transmission among chicks in a flock. The other sources may also include water, feed, and litter. The transmission through direct or indirect contact such as the respiratory route usually causes death at a very early age in chickens (Wales and Davies, 2020). The vertical transmission occurs when the contamination occurs in the eggshell membrane, albumen, and yolk. The pathogen localization in the ovule before the ovulation is also the main mode of vertical transmission. This transmission may result in embryonic death and chick mortality (Klyachko et al., 2007).

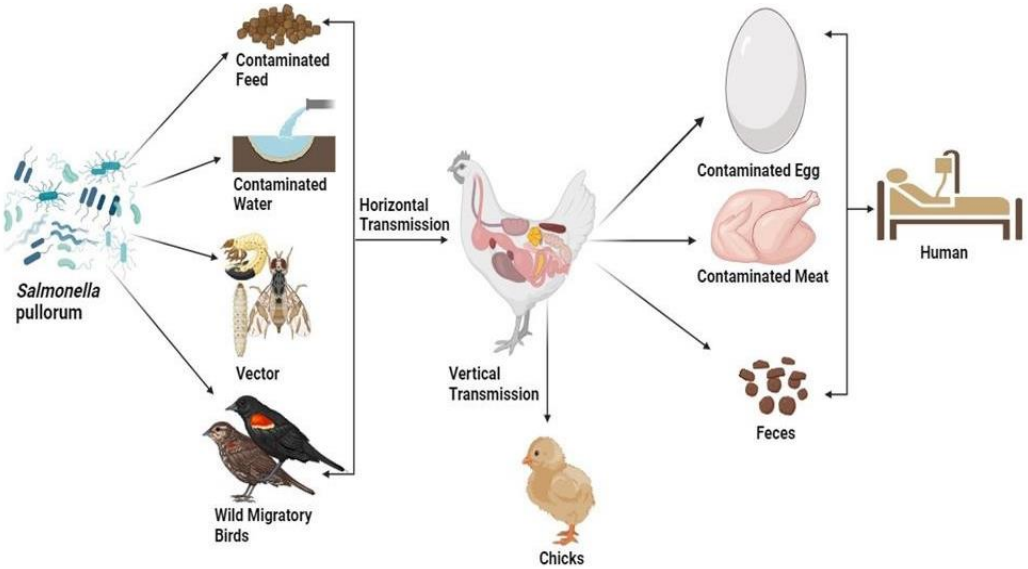

Fig. 1: Horizontal and Vertical Transmission of *S.* Pullorum

Salmonella Virulence Factors

The initial attachment of the bacterial cell to the host has a key role in the pathogenesis of that pathogens. In *Salmonella*, the different specialized structures are present on the bacterial cell wall. It has many virulence factors such as various types of secretion systems, many types of fimbrial and afimbrial adhesins, flagella, capsules and plasmid (Sora et al., 2021). The extracellular filamentous structure having the complex apparatus and the binding site at its tip is known as fimbriae. The fimbriae are mainly of three types, which are based on different assembly mechanisms. The fimbriae functions include biofilm formation, cell-cell attachment, intestinal persistence, and bacterial aggregation. Its numbers vary with the serovars, and its role depends on the type of serovars. *Salmonella* fimbriae plays an important role in understanding the new insight into *Salmonella* pathogenicity (Rehman et al., 2019). The *Salmonella* genetic structure reveals the cluster of genes localized in the chromosome region that mainly controls the virulence of pathogens known as pathogenicity islands. These genes are mainly acquired through horizontal transmission. The pathogenicity islands mainly consist of multifunctional virulence genes that are specific for their phenotype. The *Salmonella* Pathogenicity Island (SPI) has various types such as SPI-1, SPI-2, and so on. These SPIs have specific functions and roles in the pathogenicity of *Salmonella* for example SPI-1 encodes various genes for the invasion of the epithelial cells and plays a vital role in intestinal secretion and inflammatory response (Que et al., 2013).

Pathogenesis

The virulence factors including flagella, fimbrial adhesins, plasmids, and toxins facilitate the *Salmonella* to establish infection in the host. In the small intestine, the pathogen forms a biofilm, aggregates at the site of infection, and invades the intestinal cells. *Salmonella* infects and multiplies within the different types of cells including mononuclear phagocytic cells in the chicks (Setta et al., 2012). The digestive system is the principal site for the infection and the multiplication of *Salmonella*. *S.* Pullorum infection mainly targets the bursa of Fabricius in the chicks. The organism is ultimately taken up by the macrophages after the invasion from the intestinal mucosa and enters the main bloodstream causing bacteremia. In blood, *Salmonella* travels to the different body organs including the liver, lungs, kidney, and spleen. Through blood, the pathogen also travels and infects the reproductive organs in the chicks. Different organs show pathological changes. *Salmonella* forms the intracellular vacuole rather than the multiplication in the cytoplasm like other various pathogens (Jantsch et al., 2011). The macrophage engulfs the *Salmonella* in the lamina propria in sub-epithelial space. After the macrophages engulf the *Salmonella,* it causes the apoptosis of the macrophage (Yang et al., 2019). The clinical signs include white diarrhea which is a typical sign of the pullorum disease with high mortality. Affected chicks show generalized infection and swollen tissues including the spleen, liver, and kidney with different-sized hemorrhages in respective tissues (Islam, 2023).

Treatment

Commercial layers and broilers infected with pullorum disease can be treated by the application of antibiotics via oral or intramuscular route. However, antibiotic treatment of pullorum disease is contraindicated in the case of breeder flocks. The culling of pullorum-infected flocks is always recommended. For the treatment of systemic infections, it is suggested to use antimicrobial drugs like beta-lactams, aminoglycosides, and fluoroquinolones in recommended doses (Muller et al., 2018). The treatment of the infected birds is the only available option for preventing the transmission of the disease and decreasing the mortality rates. To control the infection in birds, antimicrobial drugs can be used orally or intramuscularly. Before the application of antimicrobials, the antibiotic sensitivity test is recommended to avoid the issue of antimicrobial resistance (AMR) (Gray et al., 2021). The presence of R-plasmid in *Salmonella* causes this bacterium to show resistance against multiple drugs including antimicrobials such as penicillin, oxytetracycline, aminoglycosides, and sulfa drugs, therefore, we have to make careful choices of antibiotic or have to shift to antibiotic alternatives to overcome the antimicrobial resistant (Singh et al., 2010). Cinnamon and its derivatives exhibit antimicrobial properties, suggesting their potential as alternative antibiotics for treating salmonellosis. Furthermore, these compounds are considered safe for human use.

Cinnamon and Its derivatives used as Natural Antimicrobial Agents

Cinnamon has been utilized as a spice as well as a perfume in rubbing oils during biblical times. Cinnamon was also used by Egyptians as a fragrance to preserve the bodies in the past years, however, due to its antibacterial, antiviral, and antifungal properties, it is being used in the fields of medical, veterinary, and agriculture as a bactericidal, and fungicide during recent years (Yang et al., 2019). The cinnamon plant contains different bioactive compounds and essential oils in its leaves, bark, and root. Cinnamyl acetate and coumarin are found in the fruit of cinnamon. Eugenol, cinnamaldehyde, and eucalyptol are predominantly found in the leaf oil, while trans-cinnamaldehyde, camphor, linalool, and benzoic acid, is the primary or fundamental compound present in the cinnamon bark or root bark oil (Basavegowda and Baek, 2022). In recent studies, edible antimicrobial films containing cinnamaldehyde has caused the inactivation of the foodborne pathogens by various mechanisms (Benbettaïeb et al., 2019; Zhu et al., 2014, 2020). The presence of non-pathogenic organisms causing food spoilage is also reduced in cinnamaldehyde incorporated antimicrobial films. So, various derivatives of cinnamaldehyde can be used as natural antimicrobial agents against a variety of microorganisms in a cost-efficient manner. In recent studies, *Trans*-cinnamaldehyde is used for further development of its various derivatives Apart from

mechanism of actions, many studies have been carried out to test the antibacterial properties of *trans*-cinnamaldehyde and its derivative compounds (Doyle and Stephens, 2019; Usai and Di Sotto, 2023). The antibacterial mechanism of cinnamon is shown in Fig. 2.

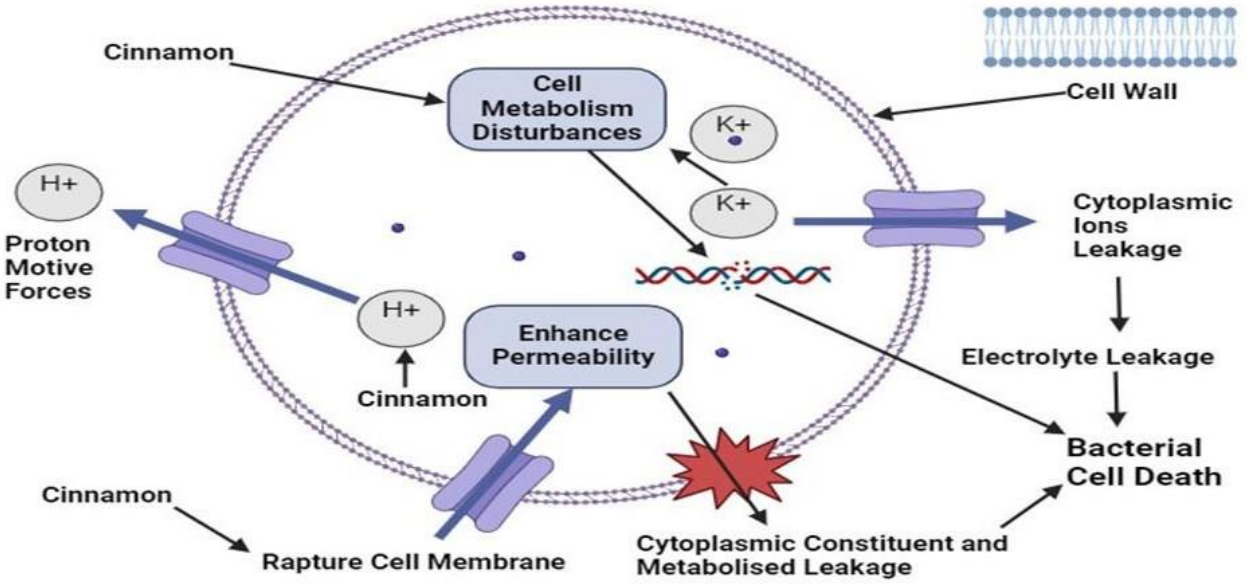

Fig. 2: Cinnamon's Antibacterial Mechanism of Action

Cinnamaldehyde

The main source of cinnamaldehyde is the species from the genus *Cinnamomum,* which is found in many states of India. Cinnamaldehyde is widely found in majority of the Indian food, cosmetic, and medicinal products. So, it can be stated that cinnamaldehyde is highly consumed by the human population in India (Jayaprakasha and Rao, 2011). Cinnamaldehyde is "Generally Recognized as Safe" (GRAS) by the United States Food and Drug Administration (FDA) and the Council of Europe has given "A" status to Cinnamaldehyde which means it may be utilized in foodstuffs (Doyle and Stephens, 2019). Besides its uses in foodstuffs, cinnamaldehyde also possesses various medicinal, and Ayurveda properties such as antibacterial, antifungal, antidiabetic, and antioxidant properties of cinnamon. Cinnamon has been employed as an anti-ulcer, anti-inflammatory, and anticancer agent. The risk of colon cancer can be decreased by cinnamon by enhancing colon health. Cinnamon acts as a coagulant to stop bleeding. Additionally, cinnamon promotes tissue regeneration and improves uterine blood circulation (Murtaza et al., 2024).

Yang et al. (2015) studied, *the antiplatelet and anti-thrombotic properties of* cinnamaldehyde. The cardiovascular effects including lowering of blood pressure and left ventricular systolic pressure have also been observed in some studies using anesthetized rats. After contractions stimulated by the application of norepinephrine, PGE2α, and potassium, cinnamaldehyde caused rat aorta to relax. These studies suggest that cinnamaldehyde shows cardiovascular effects as it carries out signals beyond the receptors (Yang et al., 2015).

Cinnamon (*Cinnamomum zeylanicum*) is said to be, one of the oldest medicinal plants. It is a valuable spice that is currently being used across the world. It is native to Sri Lanka and South India. Important chemical constituents of cinnamon are cinnamaldehyde, eugenol, and Tran's cinnamaldehyde. The specific fragrance and different biological activities of cinnamon are because of these chemicals. E-cinnamaldehyde is a part of essential oil extracted from cinnamon and possesses an anti-tyrosinase activity (Suriyagoda et al., 2021). A study conducted by Chao et al. (2008) evaluated the effects of cinnamon and reported the antibacterial activities of this herbal plant. Another study was conducted by Mathew and Abraham. (2006) evaluated the antioxidant properties of cinnamon and found them significant in their studies. Similarly, Tanwar (2019), revealed the anti-diabetic, anti-ulcer, and anti-inflammatory activities of cinnamon. Feed intake is also reported to be improved by the inclusion of cinnamon alone or in combination with essential oils in the poultry diet. Didehdar et al. (2022) evaluated the efficiency of cinnamon in terms of protecting against various kinds of bacteria including *S. aureus, E. coli, S. epidermis, P. aeruginosa, H. pylori, E. faecalis, Salmonella* spp., and *parahaemolyticus*. Due to its various medicinal and preventive properties, the importance of cinnamaldehyde is increasing day by day (Shariati et al., 2022). Cinnamaldehyde has been shown to treat complex metabolic conditions including type-2 diabetes.

In a study conducted on mice, cinnamaldehyde was used to observe the changes in parameters like excessive eating due to a high-fat diet, levels of digestive hormones, inflammation, and breakdown of adipose tissue. The microorganisms including *Lactobacillus, Bifidobacteria*, and *Roseburia* were collected and counted from cecal contents after giving cinnamaldehyde to the mice. It was found that cinnamaldehyde inhibited the accumulation of lipids and also changed the expression of genes toward lipolytic phenotype on preadipocyte cell lines when it was used at the concentration of 40 μM

(Li et al., 2013). When administered *in vivo*, cinnamaldehyde not only caused a decrease in high-fat diet-induced weight gain, but also decreased the leptin and leptin/ghrelin ratio in circulating blood. Moreover, changes in the serum levels of free fatty acids and glycerol were also observed due to lipolytic roles of cinnamaldehyde. At the genetic level, there was an increased expression of the lipolytic gene in the white adipose tissue and also an increased expression of an anorectic gene in the hypothalamus due to the use of cinnamaldehyde (Khare et al., 2016). A decrease in the inflammatory genes' expression was observed due to cinnamaldehyde in the visceral fat tissue and also the serum levels of interleukin-1β were fall. However, no change was observed in the population of selected gut microbes obtained from the cecal contents. It was concluded from the study that cinnamaldehyde can promote the lipolysis of adipose tissues, can decrease the inflammation and fasting-induced weight gain, and can also play a role in stabilizing the levels of leptin and other energy-related hormones when given to high-fat diet-fed mice (Tuzcu et al., 2017). Cinnamaldehyde and its associated compound possess various bioactive characteristics as discussed in Table 1.

Table 1: The Bioactive Characteristics of Cinnamaldehyde and Associated Compounds

Property/Effect	Compound	Mechanism of Action	Description	Reference
Antibacterial Activity	Cinnamaldehyde	Disrupts the integrity of bacterial cell membranes, Inhibiting bacterial growth.	Effective against both *B. subtilis and E. coli* bacteria.	(Doyle and Stephens, 2019)
Cardiovascular Effects	Cinnamaldehyde	Inhibits the aggregation of platelets and promotes Vasodilation through the release of nitric oxide.	Lowers blood pressure and exhibits antiplatelet and vasodilatory effects.	(Lu et al., 2022)
Antidiabetic Effects	Polyphenols	Enhances the body's sensitivity to insulin and reduces cholesterol synthesis.	Improves insulin sensitivity and lowers cholesterol levels.	(Zhang et al., 2008)
Hematological Effects	Thymol and carvacrol	Stimulates the production of red blood cells but may reduce the count of immune cells.	Stimulates the generation of red blood cells while potentially decreasing immune cell counts.	(Saadat Shad et al., 2016)
Hepatoprotective Effects	Carvacrol and thymol	Protects the liver by lowering serum levels of ALT and AST enzymes.	Safeguards the liver by reducing serum ALT and AST enzyme levels.	(El-Sheikh et al., 2022)
Antioxidant Effects	Cinnamaldehyde	Acts as an antioxidant, shielding cells from oxidative stress.	Protects cells from damage caused by oxidative stress.	(Azab et al., 2011)
Anti-inflammatory Effects	Cinnamaldehyde	Suppresses pro-inflammatory pathways.	Exhibits anti-inflammatory properties by inhibiting signaling pathways.	(Murtaza et al., 2024)
Neuroprotective Effects	Cinnamaldehyde	Enhances antioxidant defenses and mitigates oxidative stress.	Protects nerve cells by enhancing antioxidant defenses.	(Lv et al., 2017)
Lipid-lowering Effects	Polyphenols	Inhibits enzymes involved in the synthesis of cholesterol.	Blocks enzymes responsible for cholesterol synthesis, reducing lipid levels.	(Chao et al., 2008)
Anticancer Effects	Cinnamaldehyde	Inhibits the proliferation of cancer cells and induces Programmed cell death.	Suppresses cancer cell growth and triggers Apoptosis.	(Murtaza et al., 2024)

Effect of Cinnamaldehyde on Meat Quality and FCR

Several parameters like weight loss on cooking, intensity of red and sheer force of breast meat of birds fed with phytogenic based diets have been evaluated in many previous studies, discussed below. Effects of cinnamaldehyde on meat quality and FCR of poultry have been illustrated in Fig. 3. A study was conducted in which birds were given diets having carvacrol and thymol and the results showed an increase in intensity of red and sheer force of breast meat of birds (Prioriello, 2020). According to a study conducted by Mastromatteo et al. (2009) the increase in red intensity will negatively affect the sensory evaluation scores and may eventually decrease the utilization rates of such breast meat. However, these findings were opposite to that of previous study as they found that the use of thyme essential oil and thymol caused a decline in the sheer force in breast meat (Rimini et al., 2014). Moreover, studies showed that no effect was observed on the oxidant status of breast meat of birds fed with phytogenic or zinc bacitracin in diet. In a study, a prominent increase in the activity of Glutathione S-transferases and reactive oxygen species was observed after cooling of meat for 4 days. This increase in activity of enzymes was believed as a defending mechanism against the reactive oxygen species (ROS) (Reis et

al., 2018). The phytogenic feed additives prevented the formation of ROS because the ROS levels were found to be same in both control groups and PFA treated groups. The peroxidation of lipid was found to be elevated in the birds given phytogenic-based diets. The performance of Glutathione S-transferase also remained unchanged in the birds fed with a phytogenic-based diet as Glutathione S-transferase has role in inhibiting the lipid peroxidation. So, it was concluded from the study that the lipid peroxidation caused by freezing temperatures was not controlled by the thymol and carvacrol-based phytogenic diets (Karásková et al., 2015).

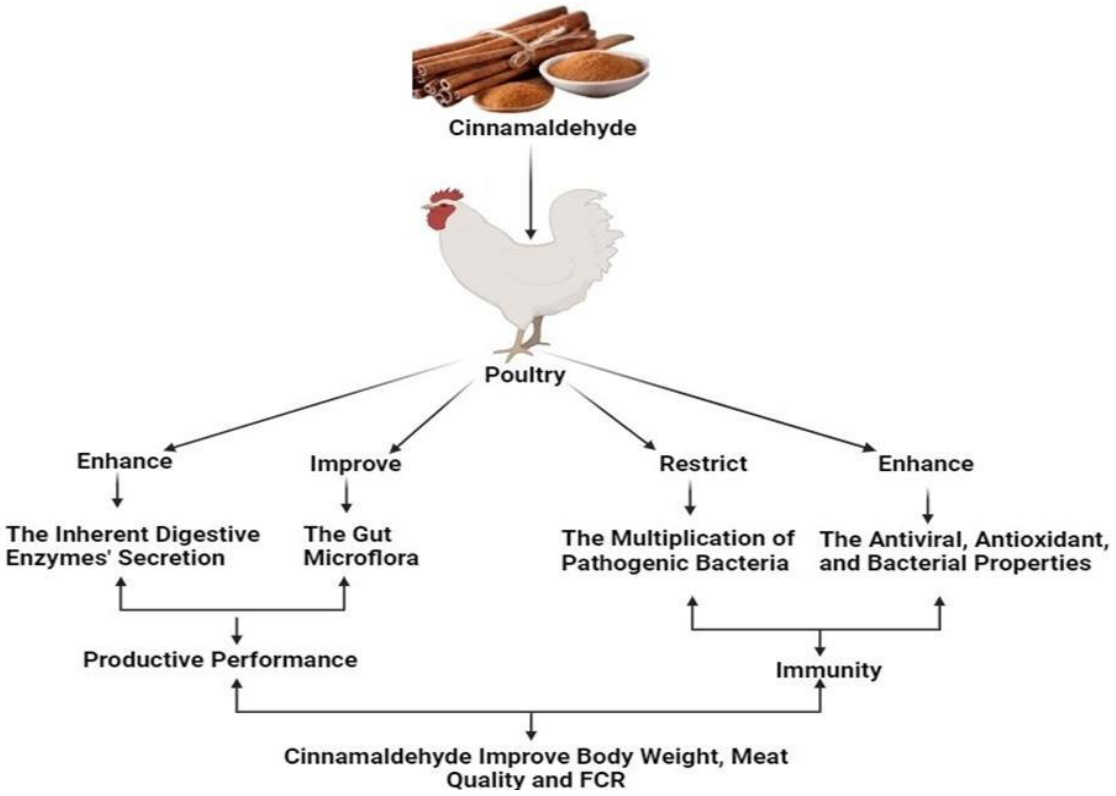

Fig. 3: Cinnamaldehyde Effect on Body Weight, meat quality and FCR.

Conclusion

Cinnamon, a well-known phytochemical plant, is widely used in medicine worldwide. It contains a number of components that exhibit significant antibacterial effects on various bacterial infections, including *S.* Pullorum. Cinnamon bark, oils, and its active compounds have been proven to be safe for consumption without any adverse effects. Cinnamon and its derivatives pose antimicrobial properties and can be used as an antibiotic replacement for patients infected with *S.* Pullorum. Various cinnamon derivatives have been evaluated for health benefits, but still more research is needed, for its generalized use against the bacterial infections.

REFERENCES

Azab, K. S., Mostafa, A.-H. A., Ali, E. M. M., and Abdel-Aziz, M. A. S. (2011). Cinnamon extract ameliorates ionizing radiation-induced cellular injury in rats. *Ecotoxicology and Environmental Safety, 74*(8), 2324-2329.

Basavegowda, N., and Baek, K.-H. (2022). Combination strategies of different antimicrobials: an efficient and alternative tool for pathogen inactivation. *Biomedicines, 10*(9), 2219.

Benbettaïeb, N., Debeaufort, F., and Karbowiak, T. (2019). Bioactive edible films for food applications: Mechanisms of antimicrobial and antioxidant activity. *Critical Reviews in Food Science and Nutrition*, 59(21), 3431–3455. https://doi.org/10.1080/10408398.2018.1494132

Berhanu, G., and Fulasa, A. (2020). Pullorum disease and fowl typhoid in poultry: a review. *Br. Journal Poultry Science, 9*, 48-56. Chao, L. K., Hua, K.-F., Hsu, H.-Y., Cheng, S.-S., Lin, I. F., Chen, C.-J., and Chang, S.-T. (2008). Cinnamaldehyde inhibits pro-inflammatory cytokines secretion from monocytes/macrophages through suppression of intracellular signaling. *Food and Chemical Toxicology, 46*(1), 220-231.

Coburn, B., Grassl, G. A., and Finlay, B. B. (2007). Salmonella, the host and disease: a brief review. *Immunology and Cell Biology, 85*(2), 112-118.

Collett, S. R., Smith, J. A., Boulianne, M., Owen, R. L., Gingerich, E., Singer, R. S., and Stewart-Brown, B. (2020). Principles of disease prevention, diagnosis, and control. *Diseases of Poultry*, 1-78.

Shariati, A., Didehdar, M., Chegini, Z., Tabaeian, S. P., and Razavi, S. (2022). Cinnamomum: The new therapeutic agents for inhibition of bacterial and fungal biofilm-associated infection. *Frontiers in Cellular and Infection Microbiology, 12*, 930624.

Doyle, A. A., and Stephens, J. C. (2019). A review of cinnamaldehyde and its derivatives as antibacterial agents. *Fitoterapia, 139*, 104405.

El-Sheikh, S. M. A., Bahaa, H. M., Galal, A. A. A., Metwally, M. M. M., Said, M. A., Alattar, R. H., and Fahmy, E. M. (2022). Gastroprotective, hepatoprotective, and nephroprotective effects of thymol against the adverse effects of acetylsalicylic acid in rats: Biochemical and histopathological studies. *Saudi Journal of Biological Sciences, 29*(6), 103289.

Ferrari, R. G., Rosario, D. K. A., Cunha-Neto, A., Mano, S. B., Figueiredo, E. E. S., and Conte-Junior, C. A. (2019). Worldwide epidemiology of Salmonella serovars in animal-based foods: a meta-analysis. *Applied and Environmental Microbiology, 85*(14), e00591-00519.

Gray, P., Jenner, R., Norris, J., Page, S., and Browning, G. (2021). Antimicrobial prescribing guidelines for poultry. *Australian Veterinary Journal, 99*(6), 181.

Islam, M. M. (2023). Pathological and Molecular Investigation of Hepatomegaly and Splenomegaly Syndrome in Poultry in Chattogram.

Jantsch, J., Chikkaballi, D., and Hensel, M. (2011). Cellular aspects of immunity to intracellular Salmonella enterica. *Immunological Reviews, 240*(1), 185-195.

Javed, M. T., Muhammad, G., Ahmad, N., Lodhi, L. A., Iqbal, Z., Anjum, A. D., and Saleemi, M. K. (2018). Livestock and Poultry Health Issues and Way Forward. In *Developing Sustainable Agriculture in Pakistan* (pp. 561-593): CRC Press.

Jayaprakasha, G. K., and Rao, L. J. M. (2011). Chemistry, biogenesis, and biological activities of Cinnamomum zeylanicum. *Critical Reviews in Food Science and Nutrition, 51*(6), 547-562.

Karásková, K., Suchý, P., and Straková, E. (2015). Current use of phytogenic feed additives in animal nutrition: a review.

Khare, P., Jagtap, S., Jain, Y., Baboota, R. K., Mangal, P., Boparai, R. K., and Kondepudi, K. K. (2016). Cinnamaldehyde supplementation prevents fasting-induced hyperphagia, lipid accumulation, and inflammation in high-fat diet-fed mice. *Biofactors, 42*(2), 201-211.

Klyachko, O., Stein, B. D., Grindle, N., Clay, K., and Fuqua, C. (2007). Localization and visualization of a Coxiella-type symbiont within the lone star tick, Amblyomma americanum. *Applied and Environmental Microbiology, 73*(20), 6584-6594.

Li, R., Liang, T., Xu, L., Li, Y., Zhang, S., & Duan, X. (2013). Protective effect of cinnamon polyphenols against STZ-diabetic mice fed high-sugar, high-fat diet and its underlying mechanism. Food and Chemical Toxicology, 51, 419–425. https://doi.org/10.1016/j.fct.2012.10.024

Lu, L., Xiong, Y., Zhou, J., Wang, G., Mi, B., and Liu, G. (2022). The therapeutic roles of cinnamaldehyde against cardiovascular diseases. *Oxidative Medicine and Cellular Longevity, 2022*.

Lv, C., Yuan, X., Zeng, H.-W., Liu, R.-H., and Zhang, W.-D. (2017). Protective effect of cinnamaldehyde against glutamate-induced oxidative stress and apoptosis in PC12 cells. *European Journal of Pharmacology, 815*, 487-494.

Manatsathit, S., Dupont, H. L., Farthing, M., Kositchaiwat, C., Leelakusolvong, S., Ramakrishna, B. S., and Surangsrirat, S. (2002). Guideline for the management of acute diarrhea in adults. *Journal of Gastroenterology and Hepatology, 17*, S54-S71.

Mastromatteo, M., Lucera, A., Sinigaglia, M., and Corbo, M. R. (2009). Combined effects of thymol, carvacrol and temperature on the quality of non conventional poultry patties. *Meat Science, 83*(2), 246-254.

Mathew, S., and Abraham, T. E. (2006). Studies on the antioxidant activities of cinnamon (Cinnamomum verum) bark extracts, through various in vitro models. *Food Chemistry, 94*(4), 520-528.

Muller, A. E., Huttner, B., and Huttner, A. (2018). Therapeutic drug monitoring of beta-lactams and other antibiotics in the intensive care unit: which agents, which patients and which infections? *Drugs, 78*(4), 439-451.

Murtaza, G., Nadeem, M., Asghar, S., Mobashar, M., Kauser, R., karamat, H., and Adil, M. (2024). Unveiling the Medicinal and Ayurvedic Marvels and Mysteries of Cinnamon. *Journal of Xi'an Shiyou University, Natural Science Edition, 20* (02), 422-440.

Prioriello, D. (2020). Modern issues in poultry meat quality: heat stress mitigation by prebiotic delivered in ovo and emergent myopathies in breast muscle.

Que, F., Wu, S., and Huang, R. (2013). Salmonella pathogenicity island 1 (SPI-1) at work. *Current Microbiology, 66*(6), 582-587. Rehman, T., Yin, L., Latif, M. B., Chen, J., Wang, K., Geng, Y., and Ouyang, P. (2019). Adhesive mechanism of different Salmonella fimbrial adhesins. *Microbial Pathogenesis, 137*, 103748.

Reis, J. H., Gebert, R. R., Barreta, M., Baldissera, M. D., Dos Santos, I. D., Wagner, R., and de Lima, J. L. F. (2018). Effects of phytogenic feed additive based on thymol, carvacrol and cinnamic aldehyde on body weight, blood parameters and environmental bacteria in broilers chickens. *Microbial Pathogenesis, 125*, 168-176.

Rimini, S., Petracci, M., and Smith, D. P. (2014). The use of thyme and orange essential oils blend to improve quality traits of marinated chicken meat. *Poultry Science, 93*(8), 2096-2102.

Saadat Shad, H., Mazhari, M., Esmaeilipour, O., and Khosravinia, H. (2016). Effects of thymol and carvacrol on productive performance, antioxidant enzyme activity and certain blood metabolites in heat stressed broilers. *Iranian Journal of*

Applied Animal Science, 6(1), 195-202.

Setta, A., Barrow, P. A., Kaiser, P., and Jones, M. A. (2012). Immune dynamics following infection of avian macrophages and epithelial cells with typhoidal and non-typhoidal Salmonella enterica serovars; bacterial invasion and persistence, nitric oxide and oxygen production, differential host gene expression, NF-κB signalling and cell cytotoxicity. *Veterinary Immunology and Immunopathology, 146*(3-4), 212-224.

Singh, B. R., Agarwal, M., Chandra, M., Verma, M., Sharma, G., Verma, J. C., and Singh, V. P. (2010). Plasmid profile and drug resistance pattern of zoonotic Salmonella isolates from Indian buffaloes. *The Journal of Infection in Developing Countries, 4*(08), 477-483.

Singh, N., Rao, A. S., Nandal, A., Kumar, S., Yadav, S. S., Ganaie, S. A., and Narasimhan, B. (2021). Phytochemical and pharmacological review of Cinnamomum verum J. Presl-a versatile spice used in food and nutrition. *Food Chemistry, 338*, 127773.

Snoeyenbos, G. H. (2019). Avian salmonellosis. In *Handbook of Zoonoses, Second Edition, Section A* (pp. 303-310): CRC Press.

Sora, V. M., Meroni, G., Martino, P. A., Soggiu, A., Bonizzi, L., and Zecconi, A. (2021). Extraintestinal pathogenic Escherichia coli: Virulence factors and antibiotic resistance. *Pathogens, 10*(11), 1355.

Suriyagoda, L., Mohotti, A. J., Vidanarachchi, J. K., Kodithuwakku, S. P., Chathurika, M., Bandaranayake, P. C. G., and Beneragama, C. K. (2021). "Ceylon cinnamon": Much more than just a spice. *Plants, People, Planet, 3*(4), 319-336.

Tang, X. Y., Gao, J. S., Yuan, F., Zhang, W. X., Shao, Y. J., Sakurai, F., and Li, Z. D. (2011). Effects of Sophy β-glucan on growth performance, carcass traits, meat composition, and immunological responses of Peking ducks. *Poultry Science, 90*(4), 737-745.

Tanwar, E. (2019). Assessment of Antibacterial, Anti-Inflammatory and Antioxidant Effects of Cinnamommum Zeylanicum (CINNAMON)–An In-Vitro Study.

Tuzcu, Z., Orhan, C., Sahin, N., Juturu, V., and Sahin, K. (2017). Cinnamon polyphenol extract inhibits hyperlipidemia and inflammation by modulation of transcription factors in high-fat diet-fed rats. *Oxidative Medicine and Cellular Longevity, 2017*.

Usai, F., & Di Sotto, A. (2023). trans-Cinnamaldehyde as a Novel Candidate to Overcome Bacterial Resistance: An Overview of In Vitro Studies. Antibiotics, 12(2), Article 2. https://doi.org/10.3390/antibiotics12020254

Utchariyakiat, I., Surassmo, S., Jaturanpinyo, M., Khuntayaporn, P., and Chomnawang, M. T. (2016). Efficacy of cinnamon bark oil and cinnamaldehyde on anti-multidrug resistant Pseudomonas aeruginosa and the synergistic effects in combination with other antimicrobial agents. *BMC Complementary and Alternative Medicine, 16*, 1-7.

Wales, A., and Davies, R. (2020). Review of hatchery transmission of bacteria with focus on Salmonella, chick pathogens and antimicrobial resistance. *World's Poultry Science Journal, 76*(3), 517-536.

World Health Organization. (2015). WHO estimates of the global burden of foodborne diseases: Foodborne disease burden epidemiology reference group 2007-2015. World Health Organization. https://iris.who.int/handle/10665/199350

Yuan, Z., Ouyang, P., Gu, K., Rehman, T., Zhang, T., Yin, Z., & Yin, L. (2019). The antibacterial mechanism of oridonin against methicillin-resistant Staphylococcus aureus (MRSA). *Pharmaceutical biology*, *57*(1), 710-716.

Yuan, Z., Dai, Y., Ouyang, P., Rehman, T., Hussain, S., Zhang, T., & Yin, L. (2020). Thymol inhibits biofilm formation, eliminates pre-existing biofilms, and enhances clearance of methicillin-resistant Staphylococcus aureus (MRSA) in a mouse peritoneal implant infection model. Microorganisms, 8(1), 99.

Yang, L., Wu, Q.-Q., Liu, Y., Hu, Z.-F., Bian, Z.-Y., and Tang, Q.-Z. (2015). Cinnamaldehyde attenuates pressure overload-induced cardiac hypertrophy. *International Journal of Clinical and Experimental Pathology, 8*(11), 14345.

Zhang, W., Xu, Y.-c., Guo, F.-j., Ye, M., and Li, M.-l. (2008). Anti-diabetic effects of cinnamaldehyde and berberine and their impacts on retinol-binding protein 4 expression in rats with type 2 diabetes mellitus. *Chinese Medical Journal, 121*(21), 2124-2128.

Zhu, L., Olsen, C., McHugh, T., Friedman, M., Jaroni, D., and Ravishankar, S. (2014). Apple, Carrot, and Hibiscus Edible Films Containing the Plant Antimicrobials Carvacrol and Cinnamaldehyde Inactivate Salmonella Newport on Organic Leafy Greens in Sealed Plastic Bags. *Journal of Food Science, 79*(1), M61–M66. https://doi.org/10.1111/1750-3841.12318

Zhu, L., Olsen, C., McHugh, T., Friedman, M., Levin, C. E., Jaroni, D., and Ravishankar, S. (2020). Edible films containing carvacrol and cinnamaldehyde inactivate Escherichia coli O157:H7 on organic leafy greens in sealed plastic bags. *Journal of Food Safety, 40*(2), e12758. https://doi.org/10.1111/jfs.12758