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Editorial

Phytogenics as an Alternative to Antibiotics: Chemical Mechanism behind Antimicrobial Activity of Essential Oils

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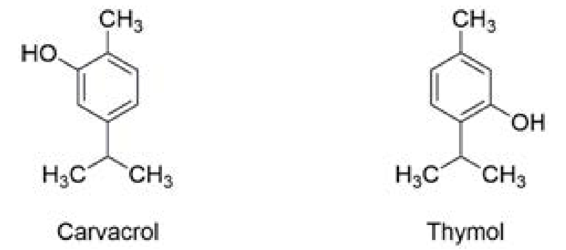
INTRODUCTION

Since the 1950s, antibiotics have been the "silver bullet" for the treatment of diseases in both the medical and livestock industries. The use of subtherapeutic antibiotics in broilers not only prevents disease outbreaks but also increases meat yield and feed conversion.[1] The mode of action for the added growth promoter effects of antibiotics stems from their ability to control microbial populations in the gut, decreasing toxic microbial byproducts and limiting competition for nutrients in the gastrointestinal tract (GIT).[2,3] These growth promoting effects have made antibiotics a common feed additive in the poultry industry.[4] However, decades of exposing microorganisms to low doses of antibiotics has created a selection pressure for antibiotic-resistant bacteria.[5] In a 2017 study in Ghana, over sixty percent of *Staphylococci* isolates from poultry farms and farm workers were resistant to multiple antibiotics, including tetracycline, one of the most common antibiotics in the poultry industry.[6] The European Union banned the use of food animal growth-promoting antibiotics in 1986. In the USA, the guidelines for Industry issued by the Center for Veterinary Medicines of the Food and Drug Administration (FDA, 2012) recommend use of antibiotics only for the prevention, control and treatment of infections in animals but not for the promotion of growth, increased performance, and improved feed efficiency Alternatives to antibiotics are, therefore, needed in order to continue the efficiency and sustainability of the poultry production. A promising alternative is phytogenic essential oil. In this editorial, we will review how the structure of phytochemicals within essential oils contributes to the antimicrobial activity and growth promotion in broilers.

ANTIMICROBIAL MECHANISM OF ESSENTIAL OILS

Derived from plants and herbs, essential oils contain antimicrobial phytochemicals that modulate microbial populations in the GIT to prevent disease and promote growth, even after vaccination or when challenged with high doses of microbes, including *Clostridium perfringens*.[7-9] Terpenoids act as non-specific bactericidal antimicrobials at high doses by altering the structure and function of the cytoplasmic membrane and disrupting membrane protein binding and ATP synthesis.[10] Terpenoids ability to interfere with the phospholipid bilayer structure and integrity is due to the positioning of the hydroxyl group and the hydrophobicity of the benzene ring and substituents.[11] Carvacrol and thymol are terpenoids in essential oils from herbs like thyme and oregano that have become increasingly more popular as feed additives in the poultry industry.[12] They are both substituted phenols but differ in the location of the hydroxyl group on the aromatic ring. As seen in Figure 1, carvacrol has a hydroxyl group bonded in the ortho position relative to the methyl group and thymol has the hydroxyl in the meta position.

Figure 1. *Chemical Structures of Terpenoids*



When comparing the antimicrobial activity of these terpenoids, carvacrol differs in its mode of action due to the difference in chemical structure of these compounds. In the case

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of thymol, interactions between the polar heads of bilayer membranes and the hydroxyl group, coupled with the hydrophobicity of the rest of the molecule, results in a disruption of membrane integrity, causing increased membrane permeability and fluidity.[13] This fluidity alters the proton motive force in the cell through the leaking of ions, such as H^+, causing cytoplasmic coagulation.

It also interferes with the holding of membrane proteins, which contributes to the leakage of ions and intracellular molecules such as ATP.[14] Carvacrol also increases membrane permeability. However, the positioning of the hydroxyl group near methyl rather than isopropyl, as in the case of thymol, enables the molecule to act as a proton exchanger and more easily form hydrogen bonds.[15,16] By bringing H^+ into the cytoplasm and facilitating the movement of K^+ out, the H^+ gradient needed for ATP synthesis is disrupted. When exposed to carvacrol, the ATP pool within the cell is depleted and there is an increase in intracellular ATP.[17] In the case of Gram negative bacteria, the hydrogen bonding capacity of carvacrol and its small size allows it to pass more readily through the outer membrane via porins.[11,17,18] This allows access to the cytoplasmic membrane and aids in the antimicrobial capacity of carvacrol. The significance of the free hydroxyl group and delocalized electron system is demonstrated by the lack of antimicrobial capacity of carvacryl acetate and menthol when compared to carvacrol. Carvacryl acetate shares the hydrophobic properties of carvacrol but lacks the hydroxyl group, replaced with a carboxylic acid. The inability to form hydrogen bonds reduces the molecules ability to disrupt the integrity of the cytoplasmic membrane. In menthol, the benzene ring is replaced with a 6-carbon single bonded ring, removing the delocalized electron system. This inhibits the molecules proton exchanging abilities.[19]

When analyzing the use of thymol and carvacrol as feed additives, their stability at varying pH is crucial to their effectiveness in the GIT. In the broiler GIT, the pH ranges from 2.5 to 8.[20] When compared to other essential oil components, carvacrol and thymol maintained antimicrobial activity against multiple organisms after exposure to pH values from 2 to 7.[21] The ability of essential oils to decrease microbial population in the GIT results in less competition for nutrient absorption, decreased microbe fermentation, and a more stable pH. In terms of growth promotion, these terpenoids have been shown to increase body weight and average daily gain in a manner comparable to antibiotic growth promoters.[22,23] The reduced fermentation and pH stability decreases the decarboxylation of limiting amino acids and provides optimal conditions for digestive enzyme activity, resulting in an increased digestibility of nitrogen and availability of nutrients, promoting overall growth.[24,25]

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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