Chapter 51

# Herbal Remedies to Replace Tilmicosin in Poultry

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## ABSTRACT

Poultry has been used as a protein source in many countries around the world as an alternative to beef and mutton. The spread of chronic respiratory diseases results in a great loss of poultry production. *Mycoplasma gallisepticum* is one of the major microbial agents causing chronic respiratory infections in poultry. Tilmicosin is widely used to treat chronic respiratory infections in poultry and after five to seven days of regular treatment the bird gets better. The use of antibiotics against the *Mycoplasma gallisepticum* gives very satisfying results but the long term use of these antibiotics produce resistance in the microbial agent against these antibiotics. This situation comes up with a new solution which is the use of herbal medicine to treat poultry flocks. The concept of using herbal products against diseases is not new, in China many herbal products have been used to treat many medical conditions for almost the last 4000 years. Many herbal products including Andrographolide, Chinese herbal medicine formula, *Lonicera japonica* extract, Meniran Extract, Methanol extracts Garlic, Glycyrrhiza and Neem, and Extract of Indonesian wild ginger are being used to treat chronic respiratory diseases. There is no risk of resistance while using herbal medicine also there are no hidden side effects of them.

**KEYWORDS**
Chronic respiratory disease, poultry, herbal products, *Mycoplasma gallisepticum*, tilmicosin, Andrographolide, Chinese herbal medicine formula, *Lonicera japonica* extract, Meniran Extract, Methanol extracts Garlic, Glycyrrhiza and Neem, and Extract of Indonesian wild ginger.

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## INTRODUCTION

The huge problem in the treatment and the control of *Mycoplasma gallisepticum* is the development of different phenotypic variations. Also the current situation of the antibiotic resistance of different bacteria makes it difficult to control the disease. Tilmicosin is widely used against the *M. gallisepticum* in poultry for a long time. The long term use of antibiotics in poultry results in the development of resistance in the poultry industry. The use of antibiotics as a growth promoter in poultry is another way to resist (Gharaibeh and Al-Rashdan, 2011). Antibiotic residues in milk, meat and eggs is another side effect of long term use of antibiotics and the aftermath of this is the transfer of antibiotic resistant bacteria to the humans. Other side effects include allergic reactions, immunological and pathological reactions. Vaccination and antibiotics are the only way to treat the chronic respiratory diseases but the resistance of the bacteria against the antibiotics impart the need for another way of treatment. This results in the use of herbal medicine to treat different diseases including *M. gallisepticum* infections. The use of herbal products as a treatment regime is incredibly increasing worldwide (Ishfaq et al., 2021).

### Tilmicosin against CRD in Poultry

For a long time, macrolides have been used against different bacterial infections. These antibiotics did their actions by inhibiting the synthesis of bacterial protein. The antibiotic binds to the ribosomal RNA of bacteria and stops the protein

synthesis (Vester and Douthwaite, 2001). Tilmicosin is a macrolide which is a broad- spectrum antibiotic. Tilmicosin has a bacteriostatic effect which is synthesized from tylosin only for veterinary use. Tilmicosin is very effectively used against *Mycoplasma* spp. and many Gram-positive organisms (Prescott and Baggot, 1993). In poultry, Tilmicosin is used to treat many chronic respiratory infections caused by *M. gallisepticum* (MG), *Mycoplasma synoviae*, *rhinotracheale*, and *Pasteurela multocida* (Figure 1) (Jordan and Horrocks, 1996; Kempf et al., 1997; Varga et al., 2001).

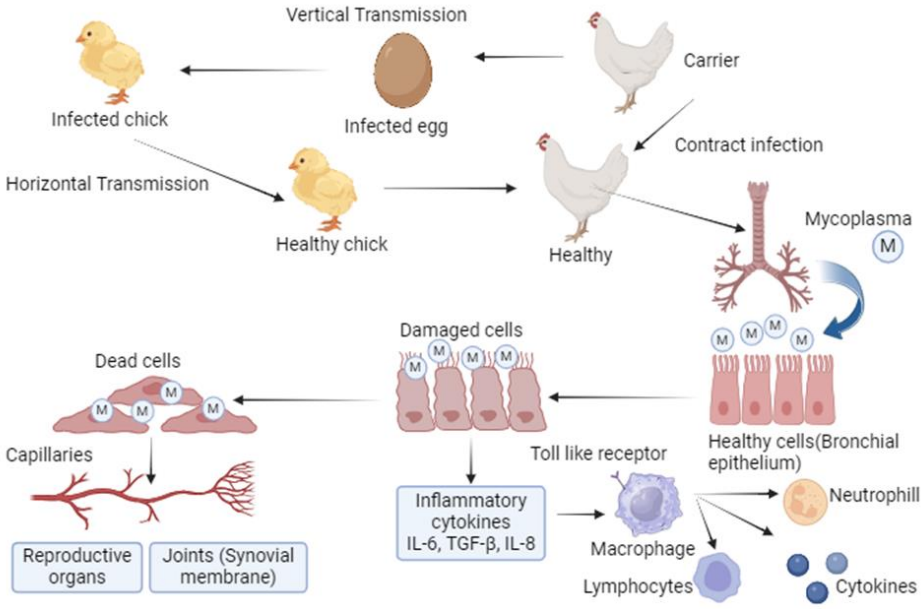


**Fig. 1:** Transmission of *Mycoplasma gallisepticum* and its pathogenesis (enters in the airways and destroys the cilia of epithelial cells, systemic invasion, causes immunosupression, srops protein and DNA synthesis) in poultry.

**Mode of action of Tilmicosin**

The classification of antibiotics is based on their mode of action as all types of antibiotics for example penicillin, cephalosporin, tetracycline, macrolides, aminoglycosides, and quinolones have different ways to response against the microbial agents. Tilmicosin belongs to the macrolide, a group of antibiotics which is isolated from a bacteria belonging to genus Streptomyces, present in soil (Riviere and Papich, 2013). Macrolides did their work by inhibiting the biosynthesis of protein in bacteria (Fig. 2). Tilmicosin is basically prepared from desmycosin after chemical alterations (Yazar et al., 2001).

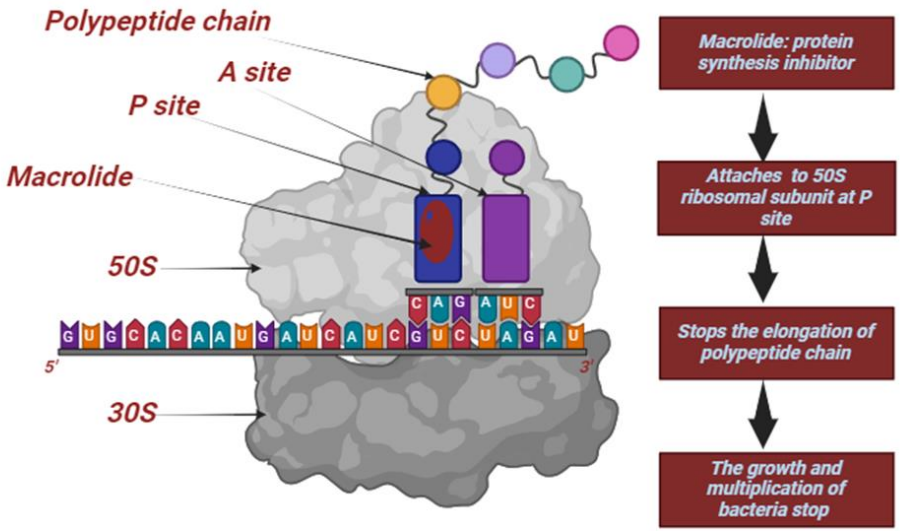


**Fig. 2:** Mechanism of action of Macrolide (Tilmicosin).

**Uses of Tilmicosin in Poultry**

The use of tilmicosin in water has very promising effects on chicken against MG including decrease in the formation and degree of lesions on the air sacs (Charleston et al., 1998). The use of tilmicosin at a dose rate of 20mg/kg of body weight for the clinical outbreaks of the MG is thought to be the best way of treatment. This protocol should be followed for five days continuously (Garmyn et al., 2019). The broiler chicken treated with tilmicosin and lincomycin has less or no mean gross air sac and microscopic tracheal lesions compared to those chickens which were untreated. This clears the fact that tilmicosin has very effective results against the mycoplasmosis in chickens (Amer et al., 2009). It is shown by a study that the spiramycin also shows good results against MG in broilers. It reduces the microscopic and gross lesions and also decreases the severity of arthritis. The clinical signs of the disease in treated flock was much lower as compared to those

infected flock which is untreated (Elazab et al., 2021). Many studies reveal that the tilmicosin promisingly reduces microscopic lesions and also decreases the re-isolation rate at 20% and in some other findings the re-isolation rate decreases upto 0% (Abd El-Ghany, 2009; Zakeri and Kashefi, 2011).

**Herbal Treatment Options Instead of Tilmicosin in Poultry**

The term polypharmacology means the action of an antimicrobial agent at more than one target simultaneously, the latest approach of modern drug discovery (Anighoro et al., 2014; Kuenzi et al., 2017). Through this way natural products are used for treatment (Figure 3) of different diseases which is way better than the same old drugs which are single targeted (Ho et al., 2018). Natural products with the phenomenon of poly-pharmacological profiles defend the host against many diseases with novel therapeutic benefits (Fang et al., 2018; Ishfaq et al., 2021; Wang et al., 2022). The treatment of MG with vaccines is no more effective (Yang et al., 2021). The humoral response of the vaccine against MG is neither as effective nor can clear the pathogen which in turn results in the failure of the vaccine. The genetic variation of MGis also the cause of vaccine failure (Matyushkina et al., 2016). Antibiotics or antimicrobial agents can stop the microbial agent but only for a small period of time. As soon as the drug delivery stops the recurrence of infection is confirmed (Gharaibeh and Al-Rashdan, 2011). These circumstances lead to the need of another effective way of treatment which is not only cheap but also safe to use. The herbal medication is the safest way for treatment of many infections including mycoplasmosis.

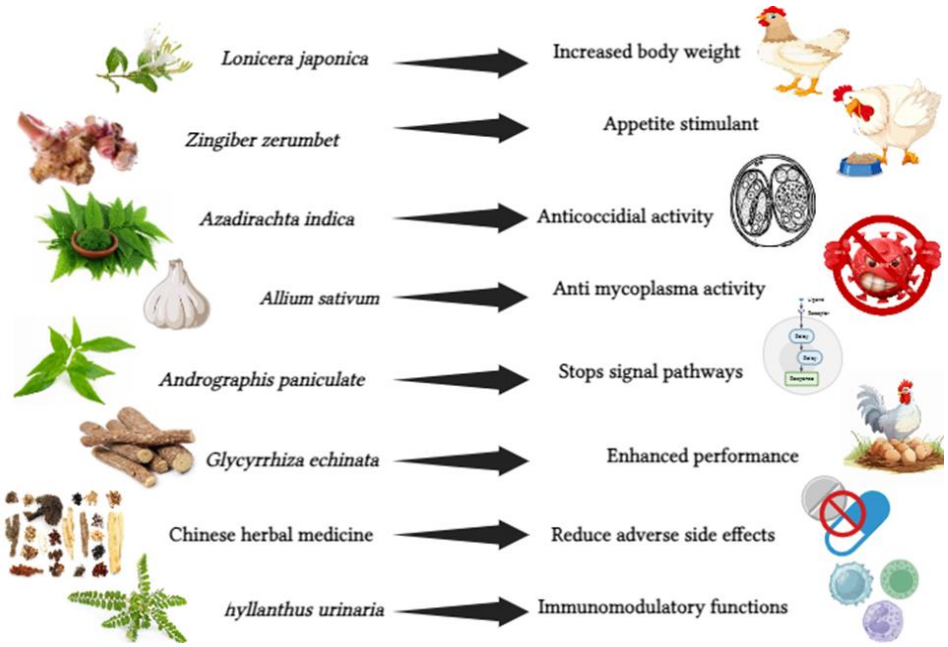


**Fig. 3:** Herbal treatment options in poultry.

**Andrographolide**

The main etiological agent for the chronic respiratory disease in chicken is MG The primary symptoms of the chronic respiratory disease is the inflammation of the respiratory tract and apoptosis. Andrographolide (Andro) is a small natural compound. It is famous for its natural properties including Anti-inflammatory action and anti-pathogenic effect (Luo et al., 2022). *Andrographis paniculate* (*A. paniculate*) has been used in China, India, Japan, Korea, and some other Asian countries for the last 2000 years as a medicinal food. It is known to treat many diseased conditions in humans for instance myocardial ischemia, pharyngitis, and respiratory diseases (Dai et al., 2019). Andro is a small natural molecule which was extracted from Traditional Chinese Medicine which was made up from *A. paniculate* (Kim et al., 2019). The natural molecule of Andro works by inhibiting the protein expression of MG which in turn decreases the adhesion of MG to the chicken lungs and AEC ll. It has been proved through many studies that MG causes inflammation of the air sac, tracheal tissue and lungs. It also causes damage to the chickens (Wu et al., 2019; Niu et al., 2020). It is confirmed that the administration of Andro is safe in chickens and AEC ll and have no adverse side effects. Andro is considered a very effective herbal product against MG as it stops the signal pathways of JAK/PI3K/AKT in the chicken.

**Chinese Herbal Medicine Formulae**

Recently Chinese herbal medicines have gained scientists' interest with their little toxicity and side effects. Beyond these effects there is no drug resistance and no drug residuals associated with the Chinese herbal medicine (Maryam et al., 2020). In China the use of Chinese herbal medicine to deal with different diseases is almost 4000 years old (Yi and Chang, 2004; Xutian et al., 2009). Old data of use of herbal medicine shows that for the treatment of chronic respiratory disease, a single Chinese herb has very prominent effects (Niu et al., 2020; Zou et al., 2020; Zou et al., 2021). Besides this the Chinese herbal formulae is made by using traditional Chinese medicine formula principles which helps to reduce the adverse side effects and helps in getting better therapeutic benefits (Su et al., 2016). This use of this formula to treat chicken has no

deleterious effects on the health of normal chicken but it can enhance the performance of the chicken which is infected by MG. It also repaired the damage caused by MG to the air sac and tracheal tissue of the chicken. The histopathological data shows that the Chinese herbal formulae also helps in repairing the inflammation of lung and trachea and inhibits the expression of inflammatory cytokines induced by MG (Wang et al., 2022).

***Lonicera japonica* Extract**

Herbs and spices have amazing properties which include antioxidant, antimicrobial, anti-helmintic, immune modulator and growth promoting abilities. These properties belong to the biologically active components of these herbs for instance terpenoids, phenolics, glycosides and alkaloids (Huyghebaert et al., 2011). *Lonicera japonica* Thunb is a very famous medical plant also known as the Japanese honeysuckle. It has many pharmacological and broad spectrum biological properties which includes anti-oxidative (Kim et al., 1994), anti-tumour (Yip et al., 2006), hepato-protective (Hu et al., 2008), antiviral (Houghton et al., 1993), anti-inflammatory (Lee et al., 1998), and antibacterial activities (Shan et al., 2007; Rahman and Kang, 2009; Shang et al., 2011). The primary natural extracts of *L. japonica* which act as natural medicine against many diseases are essential oils, organic acids, flavones, saponins, iridoids, and inorganic elements. The most important compound of *L. japonica* is the chlorogenic acid which is a bioactive organic acid. The chlorogenic acid is found in rich amounts in the flower bud of *L. japonica*. It has various pharmacological effects against many diseases. Many research studies show that the pharmacological effects of *L. japonica* extracts have amazing results in the chickens infected with MG. The results of use of *L. japonica* against MG is as good as achieved by tylosin tartrate. It reduces the chance of body weight loss in chickens infected with MG. Also in the FCR of birds shows that the use of plan based medicinal products have almost the same outcomes as the chemotherapeutic drugs (Giannenas et al., 2003; Saini et al., 2003). To get the best results, chlorogenic acid was given in drinking water to the poultry flock infected with MG at a dose rate of 190ug per day per bird. The liquid chlorogenic acid is prepared at a rate of 1g/ 1000 ml of water which is then used in drinking water for poultry flock. Various studies show that the use of chlorogenic acid results in increased body weight, less individuals with the infection of MG (Müştak et al., 2015).

**Meniran (*Phyllanthus urinaria*) Extract**

Currently the use of herbal medicine is widely spreading around the globe specially to treat the disease which affects the production of livestock. Among many of the herbal products used for treatment of animal diseases, Meniran plats are specifically used for the treatment and prevention of chronic respiratory disease. Meniran (*Phyllanthus niruri Linn*) has been known for the possession of bioactive compounds which have antimicrobial activities. These bioactive compounds are terpenoids, alkaloids, flavonoids, saponins, and tannins (Sreenivas, 1999). The statistical data of various researches shows that the use of Meniran extracts in chicken infected with MG, the body weight increases and the feed conversion ratio (FCR) decreases which shows the excellent performance of the flock (Hidanah et al., 2017). When the chicken is infected with chronic respiratory disease or MG bacteria, it results in a low weight gain and high feed conversion ratio. This happened due to the low appetite which in turn results in less feed consumption by the bird (Bell and Weaver, 2002). Meniran contains chemical compounds which help in enhancing the bird's appetite (Sutton, 2011). Some studies show that Meniran plants also have the benefits of immunomodulatory functions (Gunal et al., 2006). This means that they can help in repairing and restoring the immune system against diseases (Sreenivas, 1999). The natural compounds of Merinan extracts including alkaloids and tannins are well known for their inhibitory response against the microbial agent (Wahju, 2004). The Merinan plant also has the active compounds of phenol class such as flavonoids, alkaloids, saponins, and tannins. Among all the compounds, flavonoids are the one with the ability to denature proteins. With the ability, flavonoids destroy the cell wall proteins of the bacteria which changes its permeability (North and Bell, 1990).

**Methanol Extracts Garlic, Glycyrrhiza and Neem**

By using the micro dilution method, the minimum inhibitory concentrations (MICs) was determined for the methanol extracts. Herbal plants which include garlic, Glycyrrhiza and Neem were used for the methanol extracts against the three isolates of MG. The procedure was done at the University Diagnostic Lab, University of veterinary and animal sciences, Lahore. The protocols given by (Al-Momani et al., 2007) were used to do this procedure only with minor changes. The results of the study by (Muhammad et al., 2015) reveals that garlic has no adverse side effects on the two isolates of MG. These results were very close to the (Al-Momani et al., 2007) data according to which *Allium sativum* (garlic) shows anti mycoplasma activity against almost six different Mycoplasma species. This shows that garlic can be used in poultry for its amazing therapeutic activities against many gram positive and gram negative bacteria especially against MG (Bakri and Douglas, 2005). Studies show that the aqueous garlic extracts have astonishing therapeutic activities and protect the host from various gram positive and gram negative bacteria (Iwalokun et al., 2004).

**Extract of Indonesian wild Ginger**

In Indonesia, three species of wild ginger are very popular which are as follows: *Zingiber zerumbet* (L.) Smith with local name lempuyang gajah, *Zingiber amaricans* BL. with local name lempuyang pahit and the *Zingiber aromaticum* (Vahl.) with local name lampuyang wangi. The size of every part of the plant is different from one another in all three species. *Zingiber amaricans* is the smallest among all of them. The rhizome of *Zingiber zerumbet* L. Sm. is well known for its high efficiency as

an appetite stimulant, its rhizome is much bigger in size with yellow flesh. The rhizome of *Zingiber amaricans* BL. is also used to enhance appetite but it is smaller in size with bitter taste. In the case of *Zingiber aromaticum*, the rhizome is fragmented and used for its effective results as a slimming agent (Wahyuni et al., 2013). The phytochemical studies about *Zingiber zerumbet* are still ongoing and reveal that the plant is of much Importance. Different compounds were isolated from the plant including sesquiterpenes (Kader et al., 2010; Yob et al., 2011), terpenoid, flavonoids (Nag et al., 2013), tannins (Prakash et al., 2011), and some aromatic compounds. Volatile oil from the rhizome of *Zingiber zerumbet* have different chemical compounds for example zerumbone, humulene, camprene, a-caryophyllene and champhene (Dai et al., 2013).

**Conclusion**

The resistance of microbial agents against antibiotics is one of the major issues faced by the practitioners and farmers all over the world. This alarming situation draws the attention of pharmacists to find an alternative and better way to fight against the bacteria. This ends with the discovery of herbal products which have been used in many Asian countries for the last 4000 years. Herbal products have many beneficial effects with almost no adverse side effects. The use of herbal products in poultry gives wonderful results and the production increases. Poultry is a source of protein used in many countries but the antimicrobial resistance causes a serious economic loss to poultry industries. The chronic respiratory diseases result in weight loss and mortality of the flock. The herbal products and treatment methods used to fight against the MG and the results are very satisfied.

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