

Review Article

An Updated Review on the Role of Ginseng and Thyme Vulgaris in the Prevention and Control of Avian Viral Diseases with a Special Reference to Newcastle Disease Virus

Ahmed El- Sebai¹, Hesham A. Khalifa¹, Sabry Abd El-Motaal¹, Ola Hassanin^{2*}

¹Department of Pharmacology, Faculty of Veterinary Medicine, Zagazig University, Egypt.

²Department of Avian and Rabbit Medicine, Faculty of Veterinary Medicine, Zagazig University, Egypt.

*Correspondence

Ola Hassanin

Department of Avian and Rabbit Medicine, Faculty of Veterinary Medicine, Zagazig University, Egypt.

E-mail address: olafalcon2001@yahoo.com

Abstract

Because of the growing dangers of viral infections, the use of herbal plant oils is gaining popularity among medical practitioners and large-scale livestock producers. Several studies have shown that herbal extracts could be used as an antiviral agent in animal feed or as a prophylaxis and remedy. Herbs, in addition to being a less expensive and safer alternative, may reduce the incidence of drug resistance and may modulate the immune system in the prevention of viral-related diseases. The main topic of this review is to focus on the antiviral and immunomodulatory potentials of thyme vulgaris and Ginseng, as well as their bioactive chemical components. The beneficial roles of the two herbaceous plant and their extracts upon avian viruses proofed in many earlier reports. Hence, the two herbs could have immune stimulant, antioxidant, and anti-inflammatory benefits as well as adjuvant effects with poultry vaccines.

KEYWORDS

Ginseng, Ginsenoid, Thyme, Chicken, NDV

INTRODUCTION

The use of plants as traditional medicine against viral diseases in the production of animals have been described and practiced worldwide. Which began following World War II in Europe, and the research was later developed worldwide. Viral diseases continue to be a major threat to the poultry production sector. Prevention and control of avian viral diseases mainly depend on application of intensive vaccination programs to poultry flocks. This strategy led to evolve of new virus strains that can skip the currently applied vaccination umbrella. Additionally, the use of antiviral drugs may develop virus resistance. Therefore, application of novel and innovative strategies become necessary to limit the spread of different avian viral diseases such as Newcastle disease virus (NDV), Avian Influenza virus (AIV) and Infectious Bronchitis virus (IBV). Herbal medicine is a promising pathway that proofed to restrict health problem worldwide. Various herbal extracts or their essential oils (EOs) possess a strong antiviral, immunomodulatory, anti-inflammatory and antioxidant roles. The certain EOs can interfere with the structure of the viral envelope and with the penetration of the virus into the host cell or block viral proteins that are necessary for the virus to enter the host cells.

Due to the detrimental effects of antibiotics in animal feeds as a growth promoter and development of antibiotic resistant bacteria as well as antibiotic residues, which persuades research to follow other alternatives and substitutes. Herbal extracts possess organic substances such as phytobiotics which can improve

chicken body performance (Ghazalah and Ali, 2008; Herawati, 2010), and exhibit antibacterial and antiviral activities (Dorman and Deans, 2000). Additionally, herbal products can improve the gut health and immunity (Cross *et al.*, 2007; Noruzi *et al.*, 2022) with their antioxidant effects (Naidoo *et al.*, 2008).

Herbal essential oils are, by definition, complex mixtures of volatile organic chemicals that are produced spontaneously in various plant parts as a byproduct of their secondary metabolism. Given that phenolics, terpenoids, aldehydes, ketones, ethers, and epoxides dominate the chemical makeup of essential oils, it follows that these must have antimicrobial properties against a variety of diseases. The primary mechanism of herbal oils' antiviral activities has been identified as capsid disintegration and viral expansion, which stop a virus from adhering to host cells and infecting them. Additionally, certain viruses' hemagglutinin (a crucial membrane protein that is present in many viruses and facilitates entry into the host cell), is inhibited by essential oils. Ginseng and Thyme are the most mention-worthy herbal plants.

Ginseng

Ginseng, or *Panax ginseng* root, has long been used as one of the best known herbal remedies (Kiefer and Pantuso, 2003). Ginseng possesses ginsenoside, phytosterols, polyacetylenes, polyphenolic compounds, acidic polysaccharides, carbohydrates, sugars, organic acids, nitrogenous substances, amino acids, vitamins, and minerals (Lü *et al.*, 2009; Cui *et al.*, 2016). About 30

ginsenosides, or ginseng saponins, have been isolated and identified in raw and processed ginseng (Kang and Min, 2012). Ginseng saponins, also known as ginsenosides, are thought to be the primary active element of ginseng root (Kiefer and Pantuso, 2003). Most ginsenosides belong to dammarane family which have 17 carbons in a four-ring structure with various sugar moieties. Ginsenosides are classified into four groups based on their aglycone skeleton. The protopanaxadiol (PPD) (e.g., Rb1, Rb2, Rb3, Rc & Rd); the protopanaxatriol (PPT) (e.g., Re, Rf, Rg1 & Rg2) groups are the most active ginsenosides. On the other hand, the oleanane (e.g., Ro); and the ocotillos (e.g., R2, F11) groups are rare ginsenosides (Lü *et al.*, 2009; Leung and Wong, 2010; Kang and Min, 2012).

It is widely known for its antioxidant and anti-inflammatory properties which help in regulating blood sugar levels, boosting the immune system, enhancing brain function, limiting cancer and fighting fatigue (Attele *et al.*, 2002; Yuan *et al.*, 2012; Gui *et al.*, 2016; Liu and Fan, 2018; Hong *et al.*, 2021; Najafi *et al.*, 2021). In case of microbial infections, ginseng have been found to boost the immune response of T helper (Th) cells through improving the cytokine production of Th1 (IFN- γ , TNF- α , and IL-2) and Th2 (IL-4, IL-10, and IL-13) as reported by Heo *et al.* (2016). Furthermore, ginsenosides are promising adjuvant candidates in a variety of animal vaccines for their proper immune stimulatory and antiviral properties (Yang *et al.*, 1983; Chang-Xiao and Pei-Gen, 1992; Hu *et al.*, 2003; Rivera *et al.*, 2003; Shi *et al.*, 2007; Sun *et al.*, 2007).

Ginsenosides from root (GS-R) are expensive which limit their use for livestock and poultry industry. Panax ginseng's stems and leaves, in addition to the roots, contain saponins with similar chemical composition and pharmacological activities. In comparison to the GS-R, saponins from ginseng stems and leaves (GSLs) are more affordable due to the recycling of the stems and leaves, which were previously disposed as waste upon retrieving the roots (Xie *et al.*, 2005).

Ginseng immune stimulant and antiviral properties against poultry viral infection

Many experimental trials were applied which used GSLs as feed additive to evaluate its immune stimulant and antiviral capabilities. For example, in a trial to solve the problem of low antibody immune responses induced by the live NDV vaccine, several studies were investigated the effect of ginseng stem-leaf saponins (GSLs) to live NDV vaccine for immunization in chickens. In a comparison study, oral administration of GSLs in drinking water either before or after NDV immunization resulted in higher NDV-HI Ab titers, IgA+ cells, intestinal intraepithelial lymphocytes and lymphocyte proliferation activity in the instance of administration of GSLs before vaccination compared to after vaccination (Zhai *et al.*, 2011). Furthermore, the study found that giving GSLs in drinking water at a dosage of 5 mg/kg body weight for 7 days dramatically improved humoral and intestinal mucosal immune response in chickens vaccinated with live ND vaccine. It worth to mention, the same research group evaluated later the GSLs with live infectious bursal disease (IBD) vaccine (Zhai *et al.*, 2014). Hence, it has been found that oral administration of GSLs, at a dosage of 5 mg/kg body weight for 7 days prior to live IBDV vaccination enhanced the humoral and intestinal immune responses to IBDV with higher protection against virulent IBDV challenge. Not only on healthy birds but also the GSLs could be a potent immunostimulant in the immunosuppressed birds (Yu *et al.*, 2015). Oral administration of GSLs to cyclophosphamide-immunosuppressed chickens 7 days prior to chicken vaccina-

tion with inactivated bivalent NDV and AIV vaccine led to recover of humoral Ab responses to the bivalent vaccine, splenocyte induced-proliferation, and the numbers of IgA+ cells. Addition of selenium to the GSLs (GSLs-S) and used them as adjuvant to live NDV vaccine, increased NDV-specific HI, NDV-specific IgA and the numbers of IgM+, IgG+ and IgA+ plasma cells in hardier glands (Ma *et al.* 2020). The immunomodulatory activities of GSLs-Se can be raised from the stimulation of toll-like receptor signaling pathway and the mitogen-activated protein kinases signaling pathway.

Ginsenoside-Rg1 are the most active and abundant component in ginseng and existed in high quantities in stem and leaves. Oral supplementation of ginsenoside-Rg1 at a dosage of 1 mg/kg body weight in drinking water for 7 days significantly increased IBDV antibody, IFN- γ , and IL-6 responses, and lymphocyte proliferation in chickens immunocompromised with cyclophosphamide (Bi *et al.*, 2018). It also decreased H₂O₂ oxidative stress of splenic lymphocytes. The downregulation may be via regulating the expression of genes related to Toll-like receptors, peroxisome proliferator-activated receptor signaling pathway, and cytokine-cytokine receptor interaction (Bi *et al.*, 2019). A dietary supplementation of commercial preparation of ginsenoside-Rg1 at a dosage of 300mg/kg body weight improved the intestinal health and the secretion of sIgA from intestinal mucosa, immune organ index, serum IgG, IgM, and IgA, serum complement C3 and C4, and anti-inflammatory cytokines (IL-1 β , IL-2, and IL-10) (Song *et al.*, 2021).

The other active components of ginseng saponins could have immune stimulant, antioxidant, and anti-inflammatory roles similar to Rg1. One such example, the encapsulated ginsenoside Rb1 with chitosan nanoparticles could induce upregulation and long lasting IBDV-specific IgG as well as antiviral and anti-inflammatory cytokines and chicken dendritic cells (DCs) as adjuvant effect for live IBD vaccine (Song *et al.*, 2022). Similarly, ginsenoside-Rg3 is also another immune stimulate, antioxidant and anti-inflammatory candidate which deserve further future study (Bi *et al.*, 2022)

The Root extract of the Indian ginseng, *Withania somnifera*, has very limited number of research. As, it has been found that it inhibited IBDV infection and induce nitric oxide production in vitro and in vivo (Ganguly *et al.*, 2018). Oral supplementation of ginseng polysaccharides (GPS) upregulated the AIV-HI-Ab responses and expression of cytokines (IL-2, IL-10, I FN- γ , and TNF) to H5 AIV vaccine in a dose-dependent manner (Abdullahi *et al.*, 2016). Furthermore, the dose of 400 mg/kg body weight exerted the most beneficial immune stimulant effects, and the authors recommended the commercial use of GPS as adjuvant with AIV-H5 vaccine.

Thyme

Thyme vulgaris (T.V.) is one of the most popular wild edible plants (WEPs) that can grow spontaneously. The plant itself has the potential to fulfil a variety of nutritional requirements that are important for the overall health (Shumsky *et al.*, 2014). Thyme is the herbaceous plant (dried aerial parts) among several members of the genus *Thymus* of aromatic evergreen perennial herbaceous plants in the mint family Lamiaceae. It is an herb with a distinct smell with strong relation to oregano. The flowers, leaves, and oils are commonly used to flavor foods and are used as medicine. This herb has gained popularity due to its antioxidant activity, which limits lipid peroxidation, as well as its antibacterial, anticoccidial, and antifungal properties (Dorman and Deans, 2000; Jamroz *et al.*, 2003; Noruzi *et al.*, 2022). Thymol and carvacrol, two phenolic compounds derived from the thyme

plant, have antioxidant and antibacterial properties (Althunibat *et al.*, 2016). These compounds exert positive effects in poultry health and production (Hashemipour *et al.*, 2013; Hosseini and Meimandipour, 2018).

Fresh thyme has one of the highest antioxidant levels and is high in minerals and vitamins, both of which are necessary for good health. It is high in phytonutrients, minerals, and vitamins, all of which are essential for good health. These nutrients are well-known for their disease-preventing and health-promoting characteristics that contribute to the benefits of this herb. The leaves have iron, selenium, potassium, calcium, magnesium, and manganese.

Thymol, the main essential oil constituent in thyme, is well known for its antioxidant, anti-inflammatory and antimicrobial activity. Its usage in food, as well as dried thyme leaves, is limited almost entirely to the meat industry and as condiment to replace or decrease the use of unhealthy synthetic additives. It has been shown to possess antiseptic, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, expectorant, antispasmodic, carminative, diaphoretic, sedative, anti-rheumatic, and even anti-cancer, anti-hyperlipidemic and anti-hyperglycemic action. Its phenolic constituent is primarily involved in thyme's antioxidant activity.

Thyme vulgaris antiviral properties

The essential oils extracted from T.V. have been found to interfere with the virus envelope and to mask viral components required for attachment, penetration, or entry into host cells. The in ovo treatment of NDV with T.V. extracts reduced NDV replication by more than 56 folds (Rezatofghi *et al.*, 2014). Prior to NDV vaccination, broiler chickens were given 33.33 g/liter of commercial essential oil containing thyme oil, which resulted in a lower mortality rate, clinical signs, and postmortem lesion score than ND vaccines alone in response to vNDV challenge. Furthermore, when compared to the NDV vaccinated only group, thymol reduced hemagglutination inhibition titers and viral shedding one week after challenge. Surprisingly, thymol demonstrated an antiviral effect on vNDV in vivo (in chickens) as a preventive measure, as well as some therapeutic effect by decreasing viral shedding titers, mortality rate, severity of clinical signs and postmortem lesions, as well as a decrease in serum malondialdehyde level (Rezatofghi *et al.*, 2014; El-Shall *et al.*, 2020). The previous suggested that the antiviral role of T.V. is strongly correlated with the EO antioxidant properties.

Thyme vulgaris immune stimulant properties

Herbs high in flavonoids, such as *Thymus vulgaris* improve the antioxidant activity of vitamin C and improve vitamin C immune function. When broiler chickens' drinking water was replaced with a mixture of cinnamon, thyme, and turmeric infusions, their immune responses to the NDV vaccine were improved when compared to the control group and those who received only turmeric infusion (Sadeghi *et al.*, 2012). The preceding points to the synergistic effect of combining different herbs or their extracts. As a result, combining thymol and carvacrol increased immune responses in a dose-dependent manner, improving hypersensitivity reaction, total and IgG anti-sheep red blood cell titers, and reducing the heterophil to lymphocyte ratio (Hashemipour *et al.*, 2013). The increase in haematological parameters correlated with increases in superoxide dismutase and glutathione peroxidase activities and decreases in malondialdehyde levels in thigh muscle, serum, and liver. Thyme in a dosage of 3, 6 or 9 g/kg basal layer diet, can improve the immune system by increasing immu-

noglobulin concentrations (IgG, IgA and IgM) (Abd El-Hack and Alagawany, 2015). In this study, the increases in the immunological parameters were also correlated with increases in serum superoxide dismutase activity, reduced glutathione concentration and reduction in the malondialdehyde concentration. Even at dosage of 1g/kg basal diet, a significant increase in spleen lymphocyte count was observed in chicken fed on basal diet supplement with thyme alone or plus formic acid (5g /kg) (Ragaa *et al.*, 2016).

In consistent, thyme essential oils (TEO) have been used experimentally in many research trials as immune stimulants and growth promoter. Thyme essential oils can promote protein metabolism, enhance lipolysis and strengthen the immune function in broiler chickens in a dosage of 0.1 and 0.25 mg/kg (Zhu *et al.*, 2014). Thyme oil may exert its immunomodulatory effect via its antioxidant activity through decreasing MDA concentration in duodenum mucosa and kidney, improved immunoglobulin A (IgA) concentration in duodenum mucosa, stimulated phagocytic activity in blood, improved intestinal barrier integrity (Placha *et al.*, 2014). Additionally, entrapment of TEO with chitosan nanoparticles guarantee TEO sustained release and improved broiler performance via the promoting the physiological status and modulating intestinal microbiota (Hosseini and Meimandipour, 2018).

On the other hand, in a very limited number of reports, it has been found that Thyme extract has no effect on antibody response against Newcastle vaccine virus (Talazadeh *et al.*, 2015; El-Shall *et al.*, 2020).

CONCLUSION

Based on the evidence presented so far, we can conclude that both ginseng and thyme vulgaris, as well as their extracts, could serve as promising immune stimulants, vaccine adjuvants, and antiviral-therapeutic alternatives to improve poultry health and the socioeconomic situation of poultry breeders.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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