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The Beneficial Effects of Components of Garlic (*Allium sativum L.*) in the Poultry Industry

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Abstract

Plant-based antimicrobial agents are readily available, cost-effective, and exhibit low toxicity, making them promising alternatives in combatting microbial infections. Among these plants, garlic (*Allium sativum*) stands out for its traditional medicinal use in effectively combating various microorganisms. In the poultry industry, preventing avian virus and bacterial infections is paramount for chicken husbandry. However, using conventional drugs poses potential risks to human health. Garlic, a widely used Asian plant in traditional medicine for various pathologies, has shown potential as an herbal prophylactic remedy against viral and bacterial infections. Recently, researchers explored garlic and its derivatives as a scientific strategy in veterinary practices for diverse purposes, such as improving poultry production characteristics and acting as antibiotic growth promoters. This comprehensive review delves into garlic and its derivatives as preventive and corrective treatments for viral diseases in laying hens and broilers. The paper highlights their potential effectiveness and safety as a natural means to enhance poultry health and welfare while mitigating the risks associated with conventional drug usage in the food industry.

Keywords

Garlic, Antiviral, Veterinary, Chickens, *Allium sativum*

1. Antibiotic Growth Promoters Used in Animal Husbandry

Antibiotic growth promoters (AGPs) used in animal husbandry production have been prevalent in the food industry [1]. These promoters enhance animal performance and prevent and treat bacterial diseases [2] [3]. Nevertheless, the prolonged usage of such substances has resulted in undesirable consequences, including bacterial resistance, drug residues, and potential risks to human health [4] [5]. The use of AGPs in animal production has given rise to several concerns among scientists, policymakers, and consumers due to the associated risks [6]. Below is a concise summary of the hazards linked to the use of antibiotics to enhance animal performance:

1) **Antibiotic resistance**: One of the most significant risks is developing and spreading antibiotic-resistant bacteria [7]. Continuous exposure to low doses of antibiotics promotes the survival and proliferation of resistant bacteria in the gut [8] [9]. These resistant bacteria can transfer their resistance genes to other bacteria [10], including those that cause animal and human diseases [11]. The resulting antibiotic resistance threatens effective infection control and treatment options, jeopardizing animal, and human health.

2) **Transfer of antibiotic residues**: Using antibiotics in animal production can lead to antibiotic residues in animal-derived food products [12]. Consuming these residues can adversely affect human health, including allergic reactions and potential long-term health consequences [13]. Strict regulations and monitoring are necessary to ensure that antibiotic residues in animal products remain within safe limits.

3) **Disruption of gut microbiota**: Antibiotics can alter the composition and diversity of the gut microbiota [14]. The gut microbiota is crucial in maintaining digestive health, immune function, and overall well-being [15]. Disrupting the balance of gut bacteria can lead to digestive disorders, reduced nutrient absorption, and compromised immune responses, making animals more susceptible to infections and diseases [15] [16].

4) **Environmental impact**: Antibiotics in animal production can enter the environment through manure and wastewater runoff. This contributes to soil contamination, water bodies, and surrounding ecosystems [17]. Antibiotics in the environment can promote the development of antibiotic-resistant bacteria in wildlife and aquatic organisms [18], further amplifying the problem of antibiotic resistance.

5) **Consumer perception and demand**: Growing public concern about the

risks associated with antibiotic use in animal production has influenced consumer preferences and purchasing decisions [19]. Many consumers seek products produced without antibiotics, driving the demand for antibiotic-free and organic animal products [20]. Failing to address these concerns can have economic implications for the agricultural industry.

To address these risks, regulatory agencies and the agricultural sector are implementing measures to reduce the use of AGPs. These include promoting responsible antibiotic use, implementing antibiotic stewardship programs, promoting alternatives such as probiotics and vaccines, and encouraging good animal husbandry practices to prevent diseases [21]. It is crucial to prioritize sustainable and responsible animal production practices that minimize the risks associated with antibiotic use, preserving the effectiveness of antibiotics for both animal and human health.

2. Bacterial Diseases in Poultry

In the poultry industry, several bacterial infections pose significant risks to the health and productivity of poultry flocks. These infections can lead to economic losses and adversely impact poultry welfare [22]. To address and prevent such challenges, AGPs are a common practice to enhance poultry performance and prevent disease outbreaks. However, the overuse and prolonged administration of promoter antibiotics in poultry production have raised concerns about potential negative consequences. One of the major risks is the development of antibiotic-resistant bacterial strains [23], which can render infections difficult to treat and threaten both poultry and human health [24]. Additionally, antibiotic residues in poultry products can raise food safety concerns and contribute to antibiotic resistance, affecting human medicine [13]. The following are some of the principal bacterial infections in the poultry industry:

1) Salmonellosis: *Salmonella* spp. is a significant concern in poultry production, as consuming contaminated poultry products can cause human foodborne illnesses [25]. *Salmonella* infections in poultry can lead to decreased egg production, increased mortality, and compromised flock health [26].

2) Colibacillosis: *Escherichia coli* is a common bacterial infection in poultry. It can result in various clinical manifestations, including respiratory infections, septicemia, and diarrhea [27] [28]. Colibacillosis can lead to reduced growth rates, decreased feed conversion efficiency, and increased mortality in affected birds [29].

3) Clostridial infections: *Clostridium perfringens* is a bacterium commonly associated with necrotic enteritis, a severe intestinal disease in poultry. It can lead to severe economic losses due to increased mortality rates and reduced growth performance [30]. Clostridial infections are often associated with poor management practices and imbalances in the gut microbiota [31].

4) Pasteurellosis: *Pasteurella multocida* is the primary pathogen responsible for pasteurellosis in poultry. It causes respiratory tract infections, leading to symptoms such as coughing, sneezing, nasal discharge, and swollen sinuses [32].

Pasteurellosis can decrease feed intake, impair growth, and increase mortality rates [32] [33].

5) Mycoplasmosis: *Mycoplasma gallisepticum* is a bacterium that causes chronic respiratory disease in poultry [34]. Infected hens can experience respiratory symptoms, reduced egg production, and decreased egg quality. Mycoplasma infection is also transmitted to the offspring [35].

6) *Staphylococcus* infections: *Staphylococcus aureus* and other *Staphylococcus* species can cause infections in laying hens, leading to various reproductive disorders and *Staphylococcus* contamination of eggs through bacterial entry into the egg during formation or via external contamination of the eggshell [36].

Determining the most lethal infection relies on various factors, including the strain of the pathogen, the flock's general health, and the specific conditions in the poultry production environment [37]. All these infections can cause severe damage to poultry health and, in certain situations, can be fatal. Notably, *P. multocida*, *C. perfringens*, *Salmonella* spp, and Colibacillosis are highly lethal due to their elevated pathogenicity levels [38]. This heightened pathogenicity significantly amplifies the observed mortality often witnessed in poultry production facilities.

3. AGPs in Poultry

AGPs have been widely used in the poultry industry for several decades to improve growth rates, feed efficiency, and overall performance of birds [39]. The primary goal of using AGPs is to promote faster weight gain and better feed utilization, which leads to increased profitability for poultry producers. AGPs are typically administered in subtherapeutic doses, meaning they are given at levels below those needed to treat bacterial infections [40]. Commonly used AGPs in poultry include chlortetracycline, penicillin, bacitracin, and virginiamycin [41]. However, concerns have arisen over time regarding the potential negative consequences of using AGPs in poultry production. One of the major concerns is the development of antibiotic-resistant bacteria [4]. The subtherapeutic use of antibiotics in poultry can create selective pressure, leading to the emergence of pathogenic bacteria resistant to the antibiotics used as AGPs. These resistant bacteria can spread to humans through the food chain, posing a significant public health risk [42].

As a result of these concerns, some countries and regions have imposed restrictions or outright bans on the use of AGPs in poultry production [43]. Additionally, consumers have increasingly demanded antibiotic-free poultry products, further driving the poultry industry to explore alternatives to AGPs.

4. Use of Alternatives to AGPS in Poultry

To address these challenges, poultry producers use alternative strategies such as probiotics, prebiotics, phytogenics, and other natural additives to improve gut health and support growth without relying on AGPs [40]. These alternatives aim to enhance overall health and welfare while reducing the risk of antibiotic resistance and ensuring the production of safer and healthier poultry products for consumers. There is a growing need to explore alternative solutions in veterinary medicine. Many natural molecules, including essential oils, chitooligosaccharides, and probiotics, exhibit growth promoter activities without compromising animal performance [44] and reducing human health risks. Utilizing such substances in animal feed can help reduce the risks associated with antibiotic use while maintaining animal health. Thus, the search for new alternatives, particularly plant-based solutions, has become a global health priority [45]. Here are some of the leading alternative strategies employed in poultry production:

1) Probiotics: Generally, they are beneficial microorganisms that can improve the gut microbiota composition and promote a healthy digestive system in poultry [46]. They help maintain a balanced microbial environment, enhance nutrient absorption, improve immune function, and inhibit the growth of pathogenic bacteria. Probiotics can be administered through feed or water to improve gut health and reduce infection susceptibility [47].

2) Prebiotics: These are non-digestible substances that selectively stimulate the growth and activity of beneficial bacteria in the gut. They act as a source of nutrition for probiotic bacteria, promoting their proliferation and enhancing their beneficial effects [48]. Common prebiotics in poultry production include fructooligosaccharides (FOS), inulin, and mannose-based oligosaccharides [49].

3) Organic acids: Organic compounds, such as acetic acid, formic acid, citric acid, and lactic acid, have antimicrobial properties and can help control pathogens in the gastrointestinal tract. They create an acidic environment that inhibits harmful bacteria growth while promoting beneficial bacteria growth [50]. Organic acids are commonly used as feed additives or incorporated into drinking water.

4) Herbal extracts: Various plant extracts and essential oils have been found to possess antimicrobial and immune-enhancing properties. These natural compounds can be used as alternatives to antibiotics in poultry production [51]. For example, garlic, oregano, thyme, and cinnamon extracts have shown promising results in improving gut health, enhancing immune function, and reducing bacterial and viral infections [52].

5) Vaccination: Vaccination is essential in preventing and controlling infectious diseases in poultry. Vaccines are developed to stimulate the immune system and provide protection against specific pathogens. By vaccinating poultry against common diseases, producers can reduce the reliance on antibiotics for disease treatment [53].

6) Improved management practices: Implementing good husbandry practices, such as maintaining proper hygiene, ensuring adequate ventilation, optimizing diet formulations, and minimizing stress, is crucial in preventing disease outbreaks [38] [54]. These practices help strengthen immune systems and reduce the need for therapeutic interventions.

These alternative options provide viable approaches to reduce the use of antibiotics in poultry production while maintaining the health and welfare of the birds. A combination of these strategies, tailored to specific farm conditions and disease challenges, can contribute to sustainable and responsible poultry production.

5. Benefices of Garlic (*Allium sativum L.*)

Originally hailing from western Asia and the Mediterranean coast, garlic has a rich history of traditional medicinal use. Belonging to the *Liliaceae* family, it is now classified as *Amaryllidaceae* [55] [56]. Over the years, garlic has been employed to treat various pathological disorders, encompassing infections, leprosy, asthma, diarrhea, constipation, intestinal worms, headaches, dysentery, and fever [57]. 12/11/2023 Improvements comment N. 4 Its versatile properties also inhibit the proliferation of viruses, fungi, and bacteria [56] [58]. Garlic (*Allium sativum*) has gained recognition for its potential health benefits in various organisms, including animals. In the veterinary industry, garlic has diverse applications, serving various purposes [59]. Here are some common uses of garlic in medicine:

1) **Boosting the immune system**: Garlic is renowned for its immune-enhancing properties, attributed to its sulfur compounds, notably allicin [60] [61]. Studies have demonstrated the ability of allicin to stimulate the immune system. In veterinary medicine, garlic supplements or extracts are commonly employed to bolster the immune function of animals, especially during times of stress, illness, or when the immune system requires reinforcement [62].

2) **Natural antibiotic and antimicrobial effects**: Garlic exhibits antimicrobial activity against many bacteria, fungi, and parasites. Allicin and other sulfur compounds in garlic are believed to be responsible for their antimicrobial properties. Garlic can be used as a natural alternative to conventional antibiotics in some instances, particularly for mild infections or as a preventive measure [63].

3) **Cardiovascular health**: Garlic has been studied for its potential cardiovascular benefits. It can help regulate blood pressure, reduce cholesterol levels, and improve blood circulation. In veterinary medicine, garlic supplements are sometimes used to support animal heart health, especially in cases of mild hypertension, or as a preventive measure for specific cardiovascular conditions [64].

4) **Insect repellent**: Garlic has insect-repelling properties and can be a natural alternative to chemical-based insecticides [65]. It is particularly effective against fleas, ticks, and mosquitoes [66].

5) **Digestive health**: Garlic can support digestive health. It promotes healthy gut flora and may help prevent specific gastrointestinal issues. Garlic extracts or supplements are sometimes used to alleviate mild digestive disturbances or as a general digestive tonic [67].

6. Garlic Chemical Components and Bioactive Molecules

The composition of garlic bulbs encompasses a variety of macromolecules. These include approximately 65% water, 28% carbohydrates (sucrose, starch, fructose, and glucose), 2% protein, and 1.2% amino acids like leucine, arginine, aspartic acid, and glutamic acid. Additionally, garlic contains approximately 1.5% fiber, phenols, fatty acids (such as linolenic acid, linoleic acid, palmitic acid, and oleic acid), and trace elements. Notably, about 2.3% of garlic's constituents consist of essential sulfur molecules, which include alliin, cysteine, s-allyl cysteine, s-allyl-mercapto cysteine, allicin, isoalliin, methiin, diallyl sulfides, diallyl disulfides, diallyl trisulfides, and other sulfur compounds. Furthermore, garlic bulbs contain many other beneficial components, such as vitamins, saponins, enzymes, flavonoids, triterpenes, steroids, and pantothenic acid (**Figure 1**) [58] [68] [69]. The diverse array of macromolecules and compounds in garlic contributes to its potential health benefits and makes it a valuable ingredient in various culinary and medicinal applications.

Garlic clove boasts notable concentrations of organosulfur compounds, dipeptides, and amino acids [70]. Moreover, garlic contains polyphenols, a group of molecules known for their protective effects against oxidative stress on cellular components, membranes, and nucleic acids [71]. A diverse array of polyphenols has been identified in different garlic varieties, including gallic acid, chlorogenic acid, caffeic acid, epicatechin, luteolin, quercetin, hyperoside, ferulic acid, allyl isothiocyanate, and others [56]. These polyphenols contribute to the potential health benefits of garlic and its multifaceted applications in culinary and medicinal practices.

However, alliin takes the spotlight as the primary sulfur component in garlic. This essential compound arises when garlic undergoes mechanical manipulation, leading to the release of alliinase from vacuoles. The alliinase enzyme is crucial in transforming alliin into allicin and other thiosulfinates [58] [68]. Consequently,

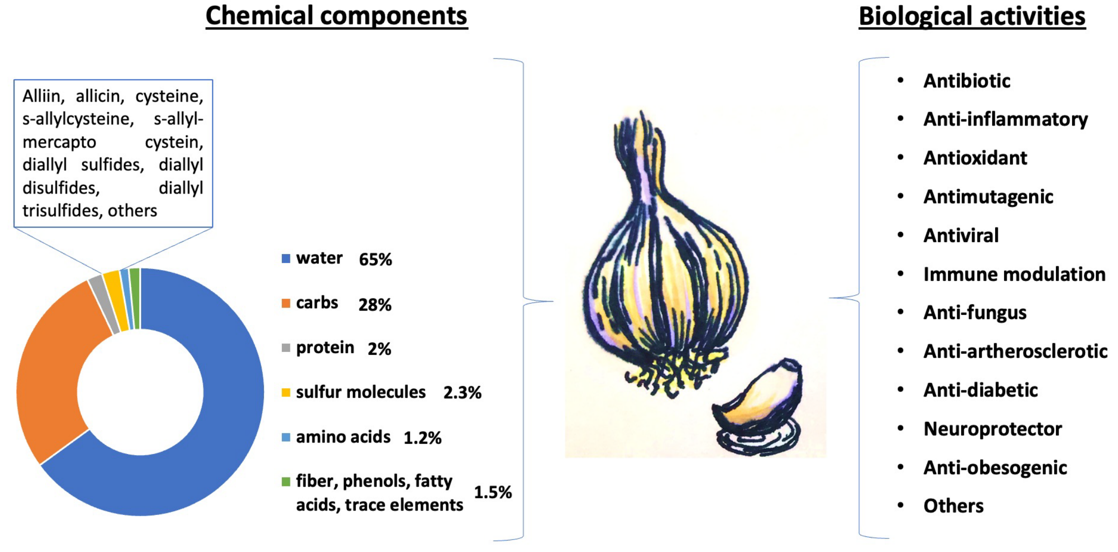

Figure 1. Chemical components and biological activities of garlic. Raw garlic exhibits a broad spectrum of biological activity. The diverse chemical constituents of sulfur compounds play a pivotal role in guiding its beneficial effects.

under the influence of enzymes, allicin (diallyl thiosulphate) can undergo further transformations, giving rise to an array of other sulfur compounds known as allium. Some of these compounds include diallyl sulfide, diallyl disulfide, diallyl trisulfide, ɣ-glutamyl-S-allyl-cysteine, methyl allyl disulfide, methyl allyl sulfide, ajoene, vinyl dithiins, and S-allyl-L-cysteine sulfoxides [3] [68] [72]. Water-based and alcohol-based extracts of garlic yield organosulfur compounds such as s-allyl cysteine, s-allylmercapto-L-cysteine, and s-methyl cysteine. These non-volatile molecules are more stable compared to volatile organosulfur compounds. Notably, many of the health benefits attributed to garlic are linked to these particular compounds [68].

7. Biological and Therapeutic Effects of Garlic

Research has demonstrated the diverse biological roles of garlic, encompassing anti-inflammatory, anti-mutagenic, anti-microbial, anti-fungal, anti-atherosclerotic, anti-diabetic, hepatoprotective, hypolipidemic, antioxidant, neuroprotective, anti-allergy, anti-obesity, nephroprotective, and immune-modulatory properties (**Figure 1**) [3] [55] [56] [68] [70] [73] [74]. In traditional medicine, garlic is widely recognized for its antibiotic properties. Various pathogenic organisms, including bacteria, protozoa, fungi, and viruses, have been found to be susceptible to the effects of fresh garlic [75]. The key phytochemicals responsible for its antibacterial activity are the oil-soluble organosulfur compounds, such as ajoenes, allyl sulfides, and allicin. These compounds exhibit distinct antibacterial properties, serving as bactericides, antitoxins, and antibiofilm agents [9]. According to previous reports, *Clostridium difficile*, *Lactobacillus acidophilus*, *Streptococcus* species, *Staphylococcus aureus*, *Listeria monocytogenes*, *Enterobacter*, *Enterococcus*, species of *Campylobacter*, *Vibrio*, *Shigella*, *Salmonella*, and *E. coli* [56] [68], are sensible to garlic preparation with antimicrobial activity.

Biomolecules from garlic also exhibit antioxidant activities, primarily against reactive oxygen species, decreasing lipid peroxidase and lipoprotein oxidation [55] [76]; besides, its antibiotic properties of fresh garlic (non-aged and aged garlic) extracted with different solvents. Total phenol and flavonoid extracted in distilled water of aged garlic results in higher activity than non-aged garlic. In addition, the scavenging activities of purified water extract of aged garlic are superior in its antibacterial effect; therefore, aged garlic results in more potent antioxidant and antibiotic effects than fresh garlic [55]. Sulfur molecules from garlic (allicin, diallyl trisulfide, diallyl disulfide) react with thiol groups of critical enzymes of microorganisms (enzyme-like alcohol dehydrogenase, thioredoxin reductase, and disulfide bonds) [68] [75], affecting bacterial surveillance. Proteomics assay in the cytoplasm of *E. coli* treated with allicin showed 73 s-thioallylated proteins. Due to allicin reaction with low molecular weight cellular thiols such as glutathione, oxidative stress is generated, Supporting the antibacterial mechanism of allicin [68] [77].

Moreover, diallyl trisulfide downregulates NF-kB and TNF-a activity in animal models of acute lung injury induced by lipopolysaccharides (LPS) administration [78]. Water-based extract from different types of garlic with a variety of concentrations of allicin by using the halo-test antimicrobial activity of garlic was evaluated against *Bacillus cereus*, *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa*; demonstrating no relevance on the concentration of allicin present on these extractions; also demonstrated its possible use in food and pharmaceutical industries [56]. The antimicrobial spectrum of garlic extracts also includes antifungal (*Candida albicans* and *Penicillium funiculosum*) by modifying the expression of essential genes in the fungal metabolism [68] [72].

Garlic offers another advantage overall as an antiviral agent; fresh garlic extracts possess inhibitory properties against influenza virus replication while regulating immune and inflammatory responses [73] [75] [79]. Moreover, pre-clinical and clinical studies highlight its active compounds, particularly organo-sulfates, as a potential treatment for multiple viral infections [69]. A systematic review was conducted to evaluate the utilization of garlic and its organo-sulfur derivatives in managing viral infections. The study made several key observations. Firstly, from the preclinical data analyzed, it was evident that garlic exhibits potent antiviral activity against various pathogenic viruses affecting humans. The mechanism of this action involves multiple aspects, such as obstructing viral entry into cells, inhibiting crucial viral molecules like RNA polymerase and reverse transcriptase, and impeding DNA synthesis.

Additionally, garlic was found to upregulate the ERK/MAPK signaling pathway while simultaneously down-regulating it. Regarding clinical trials, garlic demonstrated a prophylactic effect in preventing the transmission of viral infections among humans. The mechanism underlying this effect lies in enhancing the immune response against these pathogens, thereby establishing it as a viable strategy for mitigating viral infections [69].

Garlic and its derivatives have been shown to influence the replication cycle of various viruses, particularly those responsible for causing respiratory infections. This includes viruses like influenza, parainfluenza, coronavirus, porcine reproductive and respiratory syndrome, severe acute respiratory syndrome coronavirus, rhinovirus, Newcastle virus, and adenovirus [69]. The administration of garlic significantly affects these respiratory pathogens, potentially offering valuable therapeutic benefits in managing and preventing respiratory infections caused by these viruses.

To explore its antiviral properties, extensive research has been conducted on one of the organosulfur compounds, diallyl trisulfide. Investigations were carried out *in vitro* using human lung epithelial cells and in an *in vivo* murine model infected with H9N2 avian influenza virus (AIV). Various parameters, including viral titers, levels of inflammatory molecules, the antiviral immune response, and clinical and pathological signs in the animal model, were carefully examined. The findings from these studies have been highly promising. When administered as a prophylactic or corrective treatment, diallyl trisulfide significantly reduced viral load in both *in vitro* and *in vivo* models [73].

Additionally, the compound exhibited the ability to upregulate the expression of antiviral genes, bolstering the immune response against the viral infection. Moreover, diallyl trisulfide displayed the capacity to downregulate the expression of inflammatory cytokines, reducing pulmonary edema and tissue inflammation. These encouraging results underscore the potential of diallyl trisulfide as a therapeutic option for effectively combating viral infections and alleviating associated respiratory symptoms [73].

Garlic has demonstrated remarkable anticancer effects, particularly in reducing the risk of gastric and intestinal cancer, attributed to certain components that possess the ability to eliminate cancer cells [58] [80]. Moreover, extensive research has revealed that garlic contains many phytochemicals with potent anticancer properties. Among these, water-soluble organosulfur molecules, such as s-allyl cysteine, s-allyl-mercapto cysteine, allyl methyl sulfide, and their metabolites, particularly allyl mercaptan, have been identified as the primary bioactive components responsible for the cancer-preventive effects [58] [81]. The presence of these beneficial compounds in garlic highlights its potential as a natural and effective means of cancer prevention. A study was conducted to investigate the anticancer properties of a black garlic extract on HT29 colon cancer cells, focusing on its impact on cell proliferation and apoptosis. The results demonstrated that garlic effectively suppressed the growth of HT29 cells by inducing apoptosis and arresting the cell cycle. The molecular insights from this *in vitro* model revealed that the mechanism of action is associated with the PI3K/Akt signal transduction pathway, a crucial pathway in colon cancer development. Notably, garlic exerted its regulatory effects on this pathway by up-regulating PTEN and down-regulating Akt and p-Akt, as well as their downstream targets [82].

These findings align with previous studies, suggesting that the induction of apoptosis and the inhibition of cellular growth through G2/M phase cell cycle arrest may be the underlying mechanisms responsible for the cancer-preventive activities of sulfur molecules [56] [82] [83]. Additionally, garlic was found to activate metabolizing enzymes, inhibit reactive oxygen species, prevent DNA damage, and promote radical scavenging, further contributing to its potential as a preventive agent against cancer [68]. Overall, the research underscores the promising anticancer properties of black garlic extract and provides valuable insights into its mode of action at the molecular level.

A comprehensive assessment was conducted to examine the impact of garlic extracts on the growth of a cancer cell line called Caco-2. The *in vitro* treatment with garlic extract revealed a remarkable inhibition of cell proliferation, and this effect was found to be both time- and dose-dependent. Notably, a significant decrease in cell proliferation was observed four days after the treatment [56].

A detailed chromatographic study of the components in different garlic varieties indicated that the observed effect was attributed to a synergistic interaction of metabolites within the extract, including ascorbic acid. It was intriguing to note that the inhibition of cell proliferation was not solely attributable to the allicin content present in garlic, highlighting the potential involvement of various bioactive compounds working in concert to yield this noteworthy anticancer effect [56]. These findings underscore the multifaceted nature of therapeutic potential against cancer and shed light on the importance of its diverse bioactive components in mediating this beneficial response.

Furthermore, an investigation into the effects of a specific sulfur compound, s-allyl cysteine, on the growth of non-small cell lung carcinoma cells was carried out using *in vitro* and *in vivo* models. The study revealed compelling findings, demonstrating that s-allyl cysteine significantly impeded the proliferation of these cancer cells. In the *in vitro* model, the treatment with s-allyl cysteine effectively suppressed the activation of mTOR, NF-kB, and cyclin D1. The promising outcomes were also observed in the animal model, where the administration of s-allyl cysteine hindered the accelerated growth of metastatic cells in a mouse tumor model. This effect was associated with the suppression of mTOR and NF-kB signaling pathways. Based on these results, it is suggested that this sulfur compound derived from garlic could serve as a potent agent against the progression of non-small cell lung carcinoma [84]. These findings contribute to a growing body of evidence supporting the potential therapeutic value of garlic-derived compounds in combating cancer and highlight s-allyl cysteine as a promising candidate for further investigation in lung carcinoma treatment.

8. Applications of Garlic in Poultry

8.1. Effects of Garlic on Viruses of Poultry

In the poultry industry, infectious diseases caused by viruses and bacteria pose significant challenges [38]. These diseases can affect various stages of development and production, leading to substantial economic impacts on the industry [85]. Some of the most crucial viral diseases in commercial poultry include AIV [86], Newcastle disease [87], IBV [88], and Gumboro disease [89], among others. The industry employs various types of vaccines and control strategies [90]. However, despite these efforts, outbreaks of these diseases have occurred due to the failure of existing strategies [91]. Therefore, there is a pressing need to develop treatments targeting viral replication before field outbreaks occur. Notably, zoonotic agents significantly threaten human health [92]. The presence of these illnesses in human beings [93], livestock [94], and wildlife [95] has direct consequences for public health. An example of such a concerning pathogen is AVI H5N1 class 2.3.3.4b [96], which not only carries economic risks but also jeopardizes the well-being of the human population [97]. Another significant zoonotic condition is salmonellosis [25] [98], which leads to considerable economic losses and global health hazards in production [99]. Despite the implementation of diverse strategies such as antibiotics, probiotics, prebiotics [100], and vaccines [101] to manage and eradicate these issues, completely eradicating them from production flocks remains a formidable challenge [102]. Consequently, the current global trend is centered around integrating natural additives into poultry feed to reduce the use of antibiotics and explore innovative alternative solutions [103] [104]. These natural additives hold promising potential for enhancing poultry health and productivity while safeguarding public health.

An examination into the impact of garlic on broiler chickens and their immune response to AIV and Newcastle virus vaccination uncovered notable effects on rearing performance. These effects encompassed improvements in body weight and a reduction in mortality rates. Additionally, there was a discernible decrease in viral titers for both studied viruses. Moreover, animals that received garlic supplementation enhanced their hematological parameters [105]. Another study, which assessed the antiviral attributes of garlic extract against the influenza virus A/H1N1 in Madin-Darby Canine Kidney (MDCK) cell cultures, revealed a marked reduction in viral infectivity. This reduction was ascribed to garlic's inhibitory impact on virus penetration and proliferation within the cell culture, highlighting its potential as a potent natural antiseptic agent [75].

Furthermore, the effectiveness of garlic was evaluated with infectious bronchitis virus (IBV) strains Intervet 4/91 and M41. The study demonstrated that garlic extract exerted inhibitory effects on the virus replication phase of both strains in chicken embryos, albeit with varying degrees of effectiveness. The impact was particularly pronounced on sub-acute strains. Additionally, when used as a treatment after virus infection, garlic substantially affected both sub-acute and acute viruses [106].

The studies observe how garlic supplementation enhances immune responses and diminishes viral replication in poultry. They underscore garlic's potential as a natural additive in poultry feed, yet they do not specify recommended doses for commercial usage.

8.2. Effects of Garlic on Poultry Production Performances

An examination was conducted involving fermented garlic powder to assess its impact on production performance, egg quality, and the fatty acid composition of egg yolks in laying hens. The study revealed noteworthy outcomes, including an elevation in yolk height and color, increased white blood cells and lymphocyte concentration, and higher levels of monounsaturated fatty acids. Simultaneously, there was a reduction observed in plasma cholesterol and saturated fatty acids. The conclusion drawn from this investigation was that adding fermented garlic powder did not result in any detrimental effects on production performance [107]. Additionally, a 2% supplementation of garlic powder in the diet demonstrated improvements in various egg parameters, encompassing yolk weight, diameter, color, and chick length. Remarkably, it also decreased hen mortality, suggesting that incorporating 1% to 3% garlic powder into layer diets could enhance egg quality without adversely affecting performance [108]. Another positive outcome of garlic diet supplementation, achieved by introducing 1% garlic powder, was an increase in egg mass [109].

The effects of supplementing diets for Cobb-400 broiler chicks with 1% garlic, individually or in conjunction with ginger, were evaluated over 42 days. The results highlighted that combining garlic and ginger fostered higher feed intake, whereas garlic alone had a non-significant impact on this parameter. Furthermore, the combination led to increased body weight gain, concluding that garlic supplementation enhances broiler performance, serving as a potential alternative to antibiotic growth promoters [110]. This mixture of ingredients was found to influence broiler innate immune responses and enhance the clearance of multidrug-resistant *E. coli* O78 strains. An in-depth study was designed to assess the in-vitro antibacterial and ex-vivo immunomodulatory efficacy of *Allium sativum* (garlic) and *Zingiber officinale* (ginger) extracts in Sasso broiler chicks. The outcomes indicated that garlic extract displayed a broader antimicrobial spectrum against *E. coli* O78 and *S. aureus* isolates. Additionally, the mixture supplementation led to increased phagocytosis, improved bacterial activity, reduced nitric oxide levels, and stimulated IFN-γ and IL-1β cytokine expression levels. These findings suggested that supplementing with garlic and ginger is a safe approach for consumers, guarding against the formation of antibiotic toxic metabolite residues and providing protection against infections [111].

In vivo, the evaluation focused on the antimicrobial effects of garlic powder against *Clostridium perfringens* to prevent necrotic enteritis and enhance broiler chicken performance. Key performance parameters, including feed intake, weight gain, and feed conversion ratio, were analyzed. The findings indicated that garlic supplementation led to a reduction in feed intake while simultaneously improving the feed conversion ratio. Moreover, adding garlic was associated with decreased *C. perfringens* colony formation, suggesting its potential to prevent subclinical necrotic enteritis and enhance overall chicken performance [112] (**Figure 2**).

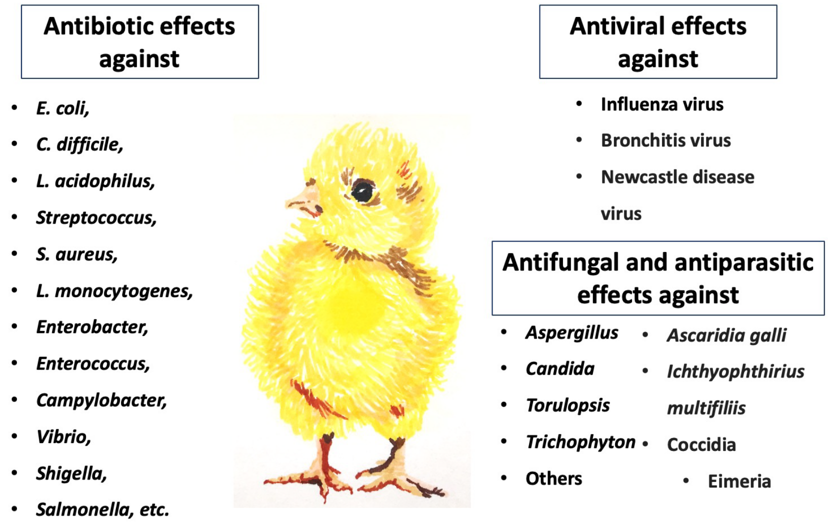

Figure 2. The impact of garlic on chickens. Scientific studies have illuminated various advantageous outcomes stemming from garlic supplementation in broiler chickens. These encompass its ability to confer antiviral, antiparasitic and antibiotic benefits. The accompanying figure outlines specific bacteria and viruses whose life cycles experience alterations due to the influence of garlic.

In conclusion, while acknowledging the positive impacts of both garlic and fermented garlic powder on poultry health and performance, further dedicated comparative studies concentrating on poultry could provide clearer insights into whether fermented garlic powder operates similarly to raw garlic. Conducting such research would facilitate a more comprehensive understanding of their relative effectiveness or unique characteristics in poultry applications.

8.3. Use of Garlic in Hepatic Intoxication

Garlic finds another application in veterinary medicine, serving as a potential preventive or corrective measure against hepatic intoxication caused by heavy metals, particularly Pb poisoning. This form of poisoning is prevalent in the environment where chickens destined for human consumption are raised. The efficacy of garlic in this context is rooted in its antioxidative prowess, attributed to key constituents like quercetin and allicin. Cai and colleagues assessed garlic's biological efficacy in Pb-poisoned chickens, specifically focusing on the impact of quercetin and allicin treatment. The study's findings unveiled the detrimental effects of Pb poisoning, encompassing impaired liver growth and development, circulatory system damage, and alterations in mitochondrial structure that triggered the activation of the mitochondrial apoptotic pathway within liver cells. However, the treatment exhibited a positive influence by enhancing antioxidant function in the liver and mitigating liver tissue damage through the PI3K signaling pathway [113].

The effects of garlic have been substantiated across various animal species, extending to ruminants. In the case of grazing lambs, the periodic administration of garlic extract has been shown to reduce serum cholesterol levels. This effect can curtail fat deposition in mutton, thus enhancing overall meat quality [3]. An ongoing exploration of garlic's potential in food animal husbandry involves its application in the bioremediation of methane emissions produced by ruminants. Notably, bioactive compounds derived from garlic, particularly organosulfur compounds, have effectively mitigated methane emissions during rumen fermentation. The composition of the microbial population closely guides this impact. Consequently, including garlic in ruminant feed is recommended as a strategic measure [114].

Garlic has been explored for its potential in veterinary medicine, particularly as a preventive or corrective measure against hepatic intoxication triggered by heavy metals, specifically lead (Pb) poisoning. While there's evidence suggesting garlic's efficacy in combating liver poisoning induced by heavy metals, studies have also indicated its positive impact on liver damage caused by various other factors beyond heavy metal toxicity [115].

Research has shown that garlic possesses hepatoprotective properties, effectively safeguarding the liver against damage induced by toxins, chemicals, drugs, and oxidative stress [116]. Garlic contains bioactive compounds such as allicin and antioxidants, contributing to its hepatoprotective effects [117]. These compounds aid in reducing oxidative stress, inflammation, and lipid peroxidation in the liver, thereby supporting liver health and regeneration [118]. Moreover, garlic's ability to modulate detoxification enzymes and enhance the antioxidant defense system in the liver is pivotal in protecting against liver damage caused by various factors, not limited to heavy metals [119]. It has shown promise in mitigating liver injury due to alcohol consumption, drug-induced toxicity, environmental toxins, and certain pathogens [120].

While garlic exhibits hepatoprotective potential against liver damage induced by various causes, further research is warranted to elucidate its mechanisms of action and efficacy in different liver-related conditions in veterinary medicine. Nonetheless, its multifaceted properties make it a compelling candidate for animal liver health management beyond heavy metal-induced toxicity.

8.4. Garlic and Bioactive Compounds against Fungi in the Poultry

Garlic and its components have been found to have antifungal activity against various fungi in poultry. Studies have shown that garlic extracts, such as ethyl acetate and methanolic extracts, exhibit fungicidal activity against plant pathogenic fungi like *Colletotrichum capsici*, *Fusarium oxysporum*, and *Sclerotium rolfsi* [121]. Garlic extracts have shown a broad-spectrum fungicidal effect against various fungi, including *Candida*, *Torulopsis*, and *Trichophyton [122]*. Additionally, garlic powder has been shown to reduce fungal load in poultry feed, especially at higher doses [123]. Garlic has also been found to be effective against plant pathogenic fungi, such as *Botrytis cinerea*, *Penicillium* expansum, and *Neofabraea alba* [124]. The bioactive compounds in garlic that exhibit antifungal properties in poultry include:

1) Allicin has been found to possess antimicrobial properties, including antifungal activity [125]. Allicin has been effective against fungi such as *Aspergillus flavus* and *Aspergillus parasitics*, which can cause aflatoxin contamination in poultry feed [126].

2) Diallyl sulfide is another bioactive garlic compound exhibiting antifungal activity. It has been shown to inhibit the growth of pathogenic fungi, including *Candida*, *Torulopsis*, and *Trichophyton* [117].

3) Ajoene is a sulfur-containing compound derived from garlic. It has been found to have antifungal properties and efficacy against various fungal infections [127].

These findings suggest that garlic and its components can be used as alternative strategies to control fungal infections in poultry, potentially reducing the need for antibiotics [128]. Further research is needed to explore the mechanisms underlying the antifungal activity of garlic and its components in poultry and to optimize their use as feed additives [129].

8.5. Garlic (*Allium sativum L.*) and Its Components against Parasites in the Poultry

Garlic (*Allium sativum L.*) has been recognized for its numerous health benefits for centuries. Predominantly known for its culinary uses, garlic has also been a remedy in traditional medicine [130]. Garlic and its components have been studied for their potential anti-parasitic effects in poultry. Several studies have shown that garlic extracts and powders can reduce oocyst counts and improve the health and performance of broiler chickens infected with coccidiosis [131] [132] [133]. Garlic and its derivatives inhibit the sporulation of coccidial oocysts in vitro [134]. Garlic can be used as a natural anti-coccidial component to reduce commercial anticoccidials' side effects and resistance in practice [131]. The effect of garlic powder combined with amprolium on coccidian in broilers and compared with commercial drugs. The treatment significantly reduced oocyst shedding and improved hematological indices in broiler chickens. Garlic powder can be used as an alternative to chemical drugs for the treatment of chicken coccidiosis [133]. A study tested the efficacy of garlic powder combined with amprolium in treating coccidiosis in broiler chickens. The combination of 48 mg of garlic powder and 48 mg of amprolium showed similar anti-coccidial effects as 28 mg of amprolium and sulphaquinoxaline. The treated groups showed a significant reduction in fecal oocyst count and increased weight gain compared to the untreated group [132]. Garlic has been found to have immunostimulatory, antimicrobial, and antioxidant properties, which may contribute to its anti-parasitic effects [135]. Birds supplemented with ginger and garlic showed improved feed intake, body weight, feed conversion ratio, oocysts shedding, lesion score, and histopathology compared to the positive control [135]. The protective effects of *Allium sativum* and *Aloe vera* aqueous extracts were investigated in broiler chickens infected with mixed *Eimeria* species. Supplementation with these extracts significantly reduced fecal oocyst shedding and intestinal lesions and improved feed conversion rate, suggesting their potential as alternative treatments for avian coccidiosis [136]. In an in vitro study, garlic powder showed higher efficacy (up to 80%) than turmeric powder (up to 66.6%) in reducing the viability of *Eimeria* oocysts. In an in vivo study, chicks supplemented with garlic powder had less severe clinical signs and lesion scores than those supplemented with turmeric powder, indicating that garlic powder was more effective in treating and controlling coccidiosis [137]. Broilers receiving *Aloe vera* gel and garlic powder had higher final body weight, feed intake, and lower FCR compared to the control groups, and adding *Aloe vera* gel and garlic powder decreased the serum activity of SALP, SGPT, and SGOT between the birds receiving *Aloe vera* and garlic powder with other groups [138]. The active components of garlic, such as allicin, have been shown to affect livestock, including growth promotion and antimicrobial activity positively.

Additionally, combining garlic with synthetic drugs, such as amprolium, has been found to reduce oocyst shedding further and improve hematological parameters in broiler chickens. Garlic is used as a treatment for helminth infections in organic layer farms in Europe, but its effectiveness has not been proven. A study was conducted to test the efficacy of a garlic product containing allicin against *Ascaridia galli* infection in chickens. The study found that allicin did not significantly reduce worm counts compared to the untreated group, while flubendazole eliminated the worms [139]. However, the allicin component of garlic has antihelmintic properties against *Ascaridia galli* in chickens [140]. Garlic has shown efficacy against various parasites in poultry (**Figure 2** and **Figure 3**).

In summary, garlic and its components have shown promising results in combating various parasites in poultry. Garlic and its components could be used as natural alternatives to synthetic drugs to control parasites in poultry. It is important to note that while garlic has shown potential against these parasites, further research is still needed to determine the optimal dosage and mode of administration for maximum effectiveness. Additionally, garlic should be used as part of an integrated approach to parasite control in poultry, along with proper hygiene, sanitation, and veterinary guidance.

9. Garlic in Human Clinical Trials, Prospects for Its Possible Application in Hens and Chickens

An international collaborative research effort has revealed a striking genetic commonality between chickens and humans, with over half of their genes being shared. The International Chicken Genome Sequencing Consortium conducted a comprehensive analysis of the genetic sequence of the Red Jungle Fowl (*Gallus gallus*), which serves as the ancestor of modern domesticated chickens. It was

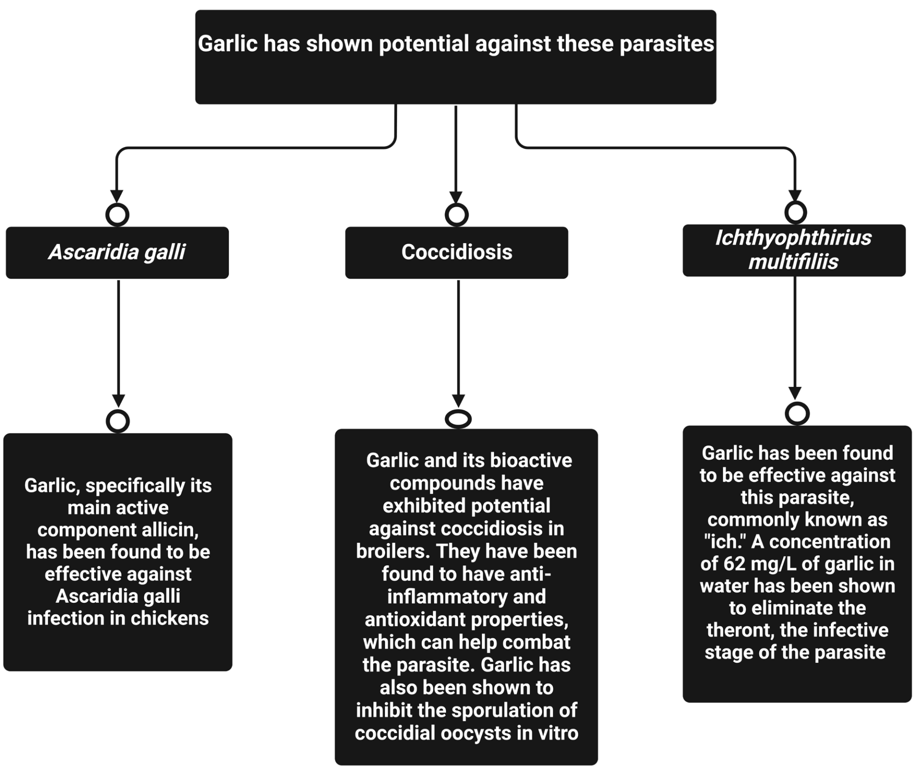

Figure 3. Garlic is effective against some parasites in poultry [139].

discovered that approximately 60 percent of chicken genes align with corresponding human genes. Nevertheless, researchers identified subtle sequence disparities among paired chicken and human genes, with an average similarity of 75 percent [141].

Leveraging this genomic resemblance between chickens and humans, we can explore the current applications of garlic in clinical trials and scientific contexts, which may lay the groundwork for potential future applications in veterinary settings. Several interventional clinical trials have been completed, as outlined in **Table 1** (https://clinicaltrials.go), highlighting the intersection of garlic research with this intriguing genetic connection.

Table 1. Clinical trials using garlic as a therapeutic strategy.

Title	Intervention	Country	Identifier
Comparative evaluation of antibacterial effect of *Allium sativum*, calcium hydroxide and their combination as intracanal medicaments in infected mature teeth	Permanent mature necrotic incisors associated with apical periodontitis in male children was selected. group I: $Ca(OH)_2$, group II: garlic extract, and group III: a mixture of $Ca(OH)_2$ and garlic extract.	Egypt	NCT05050071
Effect of aged garlic extract (AGE) on improving coronary atherosclerosis in people with type 2 diabetes mellitus	Dietary supplement: aged garlic extract.	United States	NCT03931434
Effect of aged garlic extract on atherosclerosis	For metabolic syndrome. Drug: aged garlic extract.	United States	NCT01534910
Effect of aqueous extract of garlic and nystatin mouthwash in denture stomatitis	Drug: garlic extract.	Iran	NCT01198223
Aged garlic extract (Kyolic) study at Lund University, Sweden	For coronary artery disease. The participants ingested 600 mg of aged garlic extract in two capsules two times a day *i.e.* 1200 mg/day during a period of one year	Sweden	NCT03860350
Garlic intake and biomarkers of cancer risk	Garlic treatment. Subjects will consume a garlic-free diet for 10 days. On day 11, subjects will consume 270 kcal white bread with 15 g margarine and 5 g crushed garlic.	United States	NCT01293591
Effect of a black garlic extract with greater concentration of bioactive compounds and lower content in undesired compounds on cholesterol LDL levels	Participants will intake a tablet with 250 mg of an aged black garlic extract with higher concentration of bioactive compounds S-allyl cysteine and alliin, and minor unwanted compounds such as simple sugars and furfural derivatives	Spain	NCT04010565
Effect of garlic tablet on carotid intima media thickness and flow-mediated dilation in patients undergoing angioplasty	Garlic tablet in adjunct to medical treatment.	Iran	NCT01948453
Allium sativum extract as an irrigation solution in pulpectomy of primary molars: 12 month *in-vivo* study	100 g of garlic cloves have been cleaned, peeled, and dried. Ethanol of 70% concentration was added for 60 seconds. Cloves were homogenized and filtered. The fully concentrated extracted was diluted to the concentration of 25% with distilled water to use as an irrigation solution	Egypt	NCT03795636

Continued

Effect of garlic extracts on changes in cerebral blood flow	Dietary supplement: 450 mg of garlic extracts, one intake in total.	Korea	NCT05349253
Double-Blind, randomized, cross-over trial of aged garlic extract for hypertension	Aged garlic extract, each capsule contains 600 mg of aged garlic extract powder.	Canada	NCT03211767
Identification of the antiplatelet compounds of garlic ex vivo	Dietary supplement: garlic powder added to ambient water consumed 2.7 g of garlic powder added to ambient water (equivalent to 8 g fresh or raw garlic) in a sandwich, once a day for four weeks. Dietary Supplement: garlic powder added to boiling water consumed 2.7 g of garlic powder added to boiling water (equivalent to 8 g of cooked garlic) in a sandwich, once a day for four weeks	United States	NCT00200785
Effect of aged garlic on vascular function and muscle oxygenation responses in the elderly	Dietary supplement: aged garlic extract. 2.400 mg (four capsules) of a nutritional supplement of aged garlic extract	Brazil	NCT04008693
Effectiveness of garlic oil in the treatment of arsenical palmer keratosis	Experimental: Patients of palmer arsenical keratosis. One soft capsule of garlic oil (10 mg) daily for 12 weeks. Active Comparator: Arsenic exposed controls. One soft capsule of garlic oil (10 mg) daily for 12 weeks.	Bangladesh	NCT01748669
Effects of monascus garlic fermented extract on serum triglyceride level	Dietary Supplement: Monascus garlic fermented extract.	Japan	NCT00938249
The effect of aged garlic extract supplementation on the immune system	Subjects will be asked to consume three capsules of 600 mg aged garlic extract (AGE) with food twice a day, for a total of 3.6 g per day.	United States	NCT01959646
Evaluation of the effect of the consumption of a combination of *Allium* extracts on the intestinal microbiota in healthy elderly resident volunteers	Garlic extract concentrate (equivalent to 2 garlic cloves) and onion extract concentrate (equivalent to 1 onion).	Spain	NCT05016999
Study of the effect of the consumption of a combination of *Allium* extracts on the incidence of symptoms of respiratory infections in healthy elderly residents	Garlic extract concentrate (equivalent to 2 garlic cloves) and onion extract concentrate (equivalent to 1 onion).	Spain	NCT04647071

10. Conclusions

The presence of viral and bacterial infections in animals raised for human consumption, notably chickens and eggs from laying hens, poses a dual risk—both to human health and the economic stability of the food sector. The utilization of preventive drugs introduces potential hazards to consumers. In contrast, based on scientific findings, garlic, a globally recognized edible plant, and herbal remedy, emerges as a safe option. Its application, including in chicken and hen diets, is supported by evidence of safety. The notable antiviral properties of garlic provide a distinctive advantage in disease prevention for broiler chickens, mitigating potential adverse effects on human well-being, contrasting with the widespread use of antibiotics and drugs. Garlic's bioactive compounds demonstrate antiviral potential, making supplementation with *Allium sativum* a valuable strategy in livestock breeding. This practice reduces infection risks, minimizes drug reliance, and bolsters consumer health.

Further exploration into garlic's applications in livestock for human consumption is necessary, considering its potential contributions to maintaining the health of chickens and laying hens. In conclusion, the traditional use of antibiotic growth promoters has conventionally enhanced poultry performance and profitability. However, mounting concerns about antibiotic resistance and evolving consumer preferences have driven the industry to seek sustainable alternatives that responsibly promote poultry growth and health. Ongoing research and innovation play pivotal roles in discovering effective and ethical ways to optimize poultry production while upholding food safety and animal welfare. Historically, antibiotics have been employed to control bacterial infections in poultry. Yet, heightened apprehensions regarding antibiotic resistance and potential risks have prompted stricter regulations and a pivot towards more prudent utilization. Notably, several antibiotics have been utilized to manage bacterial infections in poultry. It's essential to emphasize that antibiotics should be guided by veterinary expertise and adhere to regulations and withdrawal periods to prevent antibiotic residues in poultry products. In recent times, a concerted effort has been directed towards preventive measures, bolstering biosecurity and vaccination protocols, and promoting alternative antibiotic approaches such as probiotics, prebiotics, and immune-enhancing supplements. These initiatives aim to reduce reliance on antibiotics and foster sustainable poultry production.

Author Contributions

A.M-R. contributed to the planning, bibliographic revision, writing of the manuscript, and figure design; I.C-H., G.V-J., G.T-I., B.H., R.I.L-R., L.A.A-S, X.H-V., S.E-A., E. A-O., and A.S.M.Z-M. contributed to the writing of the manuscript and literature review. A.S.M.Z-M. and I.C.H. were responsible for the manuscript planning and revising. Funding acquisition, E.A-O., B.H. and G.T-I. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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