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REVIEW

Exploring Herbal Medicines for Human Infections Associated with Avian Influenza A Viruses: A Recent Outbreak

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Abstract

Avian influenza viruses, particularly H9N2 and H5N1 viruses, pose serious health hazards to people since they can cause severe respiratory illnesses and high death rates. The investigation of alternative therapeutics has been prompted by the limits of traditional antiviral treatments, including resistance and side effects. Herbal remedies, which have been utilized historically and empirically in many different cultures, are viable choices for treating these viral infections in addition to or instead of conventional therapies. This paper aims to investigate the effectiveness and ensure the safety of several herbal therapies in the management of human infections caused by H9N2 and H5N1. The principal modes of action of the plant, including their antiviral, immune-stimulating, and anti-inflammatory properties, have demonstrated encouraging potential in combating avian influenza. Additionally, these plants show promise as a synergistic alternative to traditional antiviral medications. In order to demonstrate their efficacy against the virus, clinical trials and case reports were analyzed. This review also addresses the incorporation of herbal remedies into traditional treatment plans, emphasizing the significance of quality control and standardized dosing. In conclusion, this study emphasizes the potential of herbal remedies as potent defenses against avian influenza viruses and encourages their use in broad therapeutic protocols to enhance public health resilience and improve patient outcomes.

Keywords Herbal therapy · Antiviral agents · Immunomodulation · Phytochemicals · Alternative medicine · Ethnopharmacology

Introduction

Avian influenza H9N2 and H5N1 are viral diseases caused by various strains of the influenza A virus, which have shown susceptibility to mutation and affect humans, with a fatality rate of 50% (Abubakar et al. 2023). Studies of more than 18 human cases emerged after the first H5N1 virus outbreak in poultry in southern China, and the infection rate extended to other regions (Sun et al. 2023). Current synthetic medications have also developed resistance, making them ineffective in preventing viral transmission and disease (Nistaneet al. 2024). The United States of America notified the World Health Organization (WHO) on April 1, 2024, clinically verified a case of influenza A (H5N1) in humans. On April 9, 2024, Viet Nam notified the WHO of viral influenza A (H9N2) viral contamination in humans (Dao et al.2024). This condition needs enhanced treatment methods that have not yet demonstrated resistance to the influenza virus in people and poultry.

These viruses have spikes of glycoprotein on their cell surface and are spherical in shape. The subtype of this virus is determined by the two surface proteins, neuraminidase and hemagglutinin, which have 11 and 18 identified subtypes, respectively. The most crucial proteins for virus adhesion and release from host cells are matrix (M2)

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proteins. Hemagglutinin and neuraminidase are glycoproteins that operate through sialic acid receptors on the target host cell. While neuraminidase increases the release of progeny viruses by cleaving sialic acids from extracellular molecules and cellular receptors, hemagglutinin initiates viral entrance by binding to receptors that contain sialic acid. The membrane protein M2 also forms an ion channel that is crucial for infection by viruses. Viral uncoating is stimulated by the ion channel activation, which acidifies the virion (Singh et al. 2023). The lipid bilayer that envelops the influenza virus is formed using the enzymes present in the host cell. The lipid bilayer forms an envelope to protect the virus from external factors during the dormant phase (Husain 2024).

Antiviral therapy is hindered by the arrival of drug-resistant viral strains. This results in natural resistance mutation acquisition. Drug-resistant influenza strains are more probable when the currently approved anti-influenza drugs, neuraminidase inhibitors, and M2-blockers are prescribed improperly to reduce poultry outbreaks or infections. Finding novel substitutes with strong activity and great safety is, therefore, constantly necessary. Historically, plant extracts and plant-based chemicals have been employed as reliable and beneficial both *in vitro* and *in vivo* antiviral resources to prevent the onset and recurrence of viral infection-related complications. Two main categories of medications are typically recommended to treat poultry influenza viruses. These are neuraminidase inhibitors (oseltamivir and zanamivir) and M2 receptor blockers (rimantadine and amantadine) (Dutta et al. 2023). The influenza virus has often demonstrated resistance to various medications. Overall, treating the influenza virus in poultry with these resistant medications is inappropriate.

Due to the virus' rapid mutation rate, alternative vaccinations may prove unsustainable in the long term. Because some viruses have developed antiviral resistance to the possible impacts of synthetic additions, herbal antiviral treatments have recently obtained special attention. Many compounds found in herbal plants have pharmacological and medicinal properties. Natural products are frequently a good substitute for manufactured medications because they typically have fewer negative effects (Sharma et al. 2023). Many reports have indicated that certain plants have anti-avian influenza properties (Dutta et al. 2023).

Because of their wide range of antiviral characteristics, herbal compounds derived from different plants are essential in the fight against viral diseases such as avian influenza A viruses H9N2 and H5N1. These compounds, which include alkaloids, flavonoids, polysaccharides, and phenolic compounds, exhibit direct antiviral effects by blocking the ability of the virus to replicate or penetrate host cells (Gangwar et al. 2024). Additionally, they frequently have immunomodulatory properties which strengthen the host's defenses against viral infections (Wang et al. 2024). Alkaloids in plants have broad-spectrum antiviral activity, whereas flavonoids in plants can stimulate immune cells and boost the generation of antiviral cytokines. Furthermore, polyphenols have strong antiviral activities by preventing viral attachment and fusion with host cells (Alarabei et al. 2023). Figure 1 demonstrates the transmission and symptoms of the avian influenza virus (AIV). By utilizing these plant-based compounds' combined potency, researchers aim

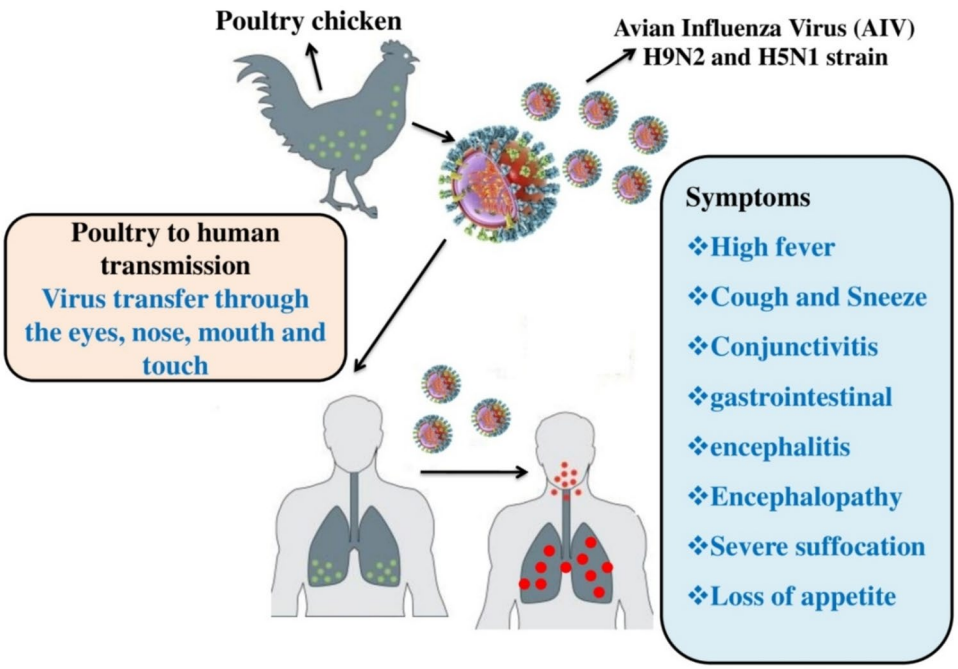


Fig. 1 Transmission and symptoms of avian influenza virus. This image depicts the transmission patterns and frequent clinical signs of avian influenza (H5N1) infection. Transmission is primarily accomplished through direct contact with infected birds, their droppings, or polluted habitats. In humans, the virus can be transmitted via respiratory droplets or by touching infected birds. In humans, symptoms can range from moderate respiratory difficulties like coughing and fever to severe illnesses including pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure

to develop herbal remedies or supplements that may reduce the severity of avian influenza infections or even prevent the virus from spreading, offering alternatives to traditional antiviral treatments. However, further investigation is necessary to fully comprehend the mode of action and maximize the therapeutic potential of these herbal constituents against human avian influenza viruses.

Search Strategy

A systematic search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and the Cochrane Library. The search covered articles published between 2010 and 2024. Keywords "Herbal medicine," "Phytotherapy," "Avian influenza," "H9N2," "H5N1," "Antiviral activity," "Immunomodulation," and "Anti-inflammatory" are used. Inclusion criteria focused on peer-reviewed articles, clinical trials, and systematic reviews discussing herbal therapies for avian influenza. Non-relevant studies, non-English articles without translation, and non-peer-reviewed sources were excluded.

Discussion

Structure and Pathogenicity

The RNA virus responsible for avian influenza has eight segments that are contained within its internal ribonucleoprotein (RNP). Twelve different proteins are encoded by these regions. In particular, segments 1 and 2 encode the viral polymerase complex PB1 and PB2, and polymerase acidic protein (PA), respectively; segments 3 and 4 encode hemagglutinin, neuraminidase, and nucleoprotein; segments 5 and 6 encode NP and NA. Segments 5 and 6 encode matrix protein M1 and matrix protein M2, which are essential for the viral envelope structure and function, and the matrix M1 and the membrane M2 proteins; and segments 7 and 8 encode for the non-structural proteins NS1 and NS2. Hemagglutinin, neuraminidase, and M2 are among the proteins that are embedded in the lipid bilayer of the virus (Chauhan and Gordon 2022). Through sialic acid receptors, hemagglutinin and neuraminidase are vital for facilitating viral fusion and entry into host cells. There are now 16 recognized subtypes of the influenza virus due to the antigenic variations between hemagglutinin and neuraminidase (Wu and Wilson 2020). The essential protein M1, generated by the host cell, supports the lipid bilayer and plays a critical role in the shape of the virus by forming a matrix around it (Brémaud et al. 2022). A heteromorphic RNA polymerase with the three subunits PB1, PB2, and PA is present in this matrix (Fan et al. 2019).

Figure 2 displays the avian influenza virus structure, illustrating its numerous components and their roles in aiding infection and reproduction in host cells. Drug development can focus on different phases of the viral life cycle. Interfering with the interaction between hemagglutinin and host cell sialic acid receptors is a typical method of inhibiting viral entrance (Long et al. 2019). Additionally, it prevents viral RNA replication by RNA polymerase blockage. Drugs may also prevent neuraminidase from causing its progeny viruses to be released from host cells (Yin et al. 2021). Passive methods may also be utilized to improve the immunity (innate) of host cells by increasing the generation of cytokines that cause death in infected cells (Dey et al. 2023). Based on their molecular composition and other attributes, such as the ability to kill poultry, the influenza virus subtypes are categorized as either highly pathogenic or low pathogenic (Kirkeby et al. 2024). Figure 3 clearly depicts important components and their involvement in the infectivity and pathogenesis pathways.

H9N2 Strain

In humans, avian influenza virus infections can lead to various diseases, varying from minor upper respiratory tract infections to more significant, occasionally fatal infections. In addition to respiratory symptoms, cases of gastrointestinal issues, conjunctivitis, encephalopathy, and encephalitis have been documented (Dutta et al. 2023). The H9N2 variant of AIV is broadly prevalent globally and has significant economic implications for the poultry industry. Despite being classified as low virulent, studies have shown that H9N2 is closely linked to highly pathogenic AIV strains such as H5N1, H7N9, and other epidemic variants (Sun et al. 2020). Given the threat posed by H9N2 AIV to both poultry industry safety and public health, there has been a growing focus on understanding its infection and transmission mechanisms (Liu et al. 2023). Avian influenza virus infection typically occurs after the viral protein hemagglutinin A binds to sialic acid receptors on respiratory epithelial cells, which causes membrane fusion and viral entry into the host cell (AbuBakar et al. 2023). Mammalian receptors have α−2,6-linked lactoseriestetrasaccharidec (LSTc) in *cis* conformation, whereas avian receptors are mainly made up of α−2,3-linked lactoseriestetrasaccharide a (LSTa) in *trans* conformation. H9N2 AIV exhibits a potent affinity for LSTa, but studies have shown that it can also bind to LSTc, enabling direct infection of mammals and humans under specific conditions. The L226-type H9N2 virus was found to multiply 100 times faster in human airway epithelial cells than the Q226-type virus, indicating the crucial function of L226 in mammalian infection (Xu et al. 2020). Figure 4 illustrates the structure of the avian H9N2 strain, highlighting specific genetic

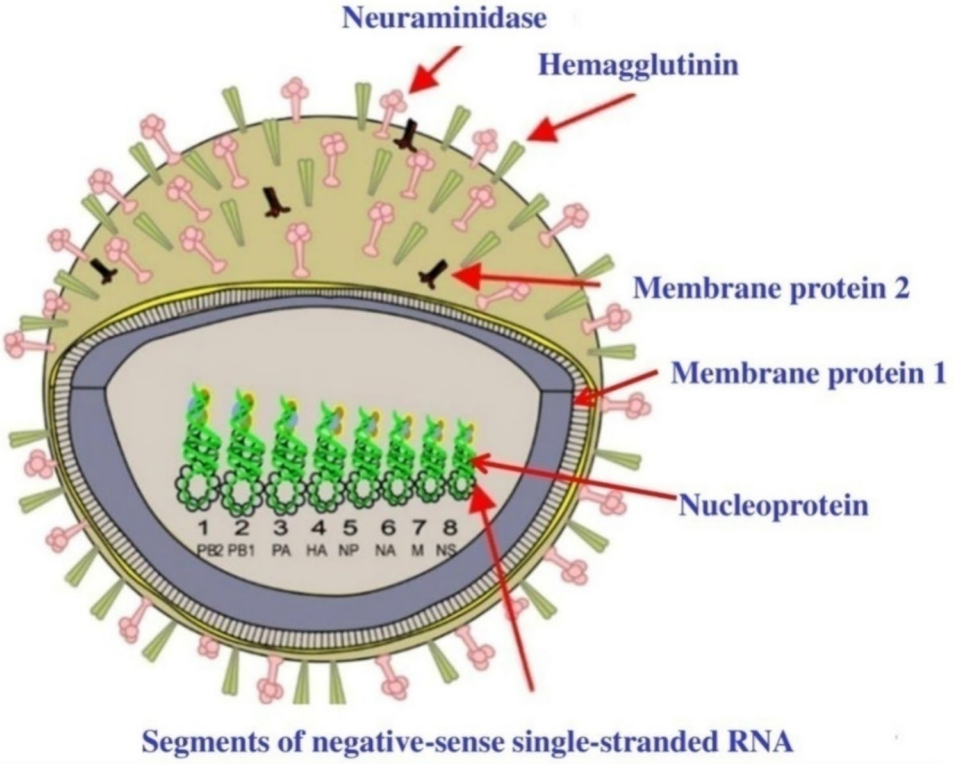


Fig. 2 Structure of the avian influenza virus. This schematic illustration depicts the avian influenza virus' spherical form with a lipid bilayer envelope. The outer membrane depicts surface glycoproteins such as hemagglutinin (HA) and neuraminidase (NA). The inner core is made up of matrix protein (M1) and nucleocapsid protein (NP). The nucleocapsid encloses the segmented RNA genome. The viral polymerase complex (PB1, PB2, PA) is associated with the vRNA segments, which are required for transcription and replication. The M2 protein, which is contained in the envelope, produces a proton channel that aids in the uncoating process of viral entrance

variations or mutations that contribute to its virulence or antigenic properties.

H5N1 Strain

The H5N1 virus belongs to the Orthomyxoviridae family, and it is categorized as a variant of the influenza A virus. A negative single-stranded RNA molecule that makes up the genome of the virulent avian influenza H5N1 virus has a length of roughly 13.5 kilobases. Eight distinct segments comprise its genome, and each is responsible for encoding a particular protein that is necessary for the virus to reproduce. Matrix protein M1 (252 amino acids), hemagglutinin (568 amino acids), matrix protein M2 (97 amino acids), neuraminidase (499 amino acids), nucleoprotein (498 amino acids), polymerase basic 2 (PB2: 759 amino acids), polymerase basic 1 (PB1: 757 amino acids), and non-structural proteins NS1 (225 amino acids) and NS2 (121 amino acids) are among these proteins (Noor et al. 2022).

The H5N1 virus utilizes its neuraminidase and hemagglutinin proteins to infect and spread effectively. Hemagglutinin binds the virus to host cell receptors, enabling viral entry through membrane fusion, while neuraminidase cleaves sialic acid–containing receptors to release newly formed virus particles, aiding in their dissemination (McAuley et al. 2019). Along with polymerase components PB1, PB2, and PA, the nucleoprotein envelops the viral genome to form the ribonucleoprotein complex (vRNP), which is essential for RNA transcription, replication, and packaging (Fan et al. 2019). The matrix protein M1 serves a crucial function in viral budding and vRNP transportation; in contrast, the M2 protein functions as a proton channel to preserve pH equilibrium during the viral life cycle (Dey and Mondal 2024). PB1, PB2, and PA together constitute the RNA polymerase that is accountable for the replication and transcription of viral RNA (Te Velthuis et al. 2021). The NS1 protein suppresses interferon production, aiding the virus in evading the immune response, while the NS2 protein aids in the nuclear distribution of vRNPs by connecting them to the cellular export machinery (Jiang et al. 2023).

H5N1 pathogenesis encompasses various mechanisms, including the replication of the virus and immune dysregulation. The upregulation of chemokines and cytokines, especially TNF-related apoptosis-inducing ligand, and the downregulation of CD8 + cell cytotoxicity are significant characteristics (Gobbo et al. 2022). Viral replication, either directly or through the development of cytokines and chemokines that support the interaction of numerous organs, causes these processes to produce significant inflammation and mortality (Dey et al. 2023). The virus often leads to influenza-related lymphopenia and reduced perforin action in cytotoxic T cells, impairing infected cells' clearance (Guo et al. 2021). The typical incubation period ranges from 2 to 5 days. Symptoms include headaches, respiratory problems, muscle pain, and, less commonly, bleeding gums, or conjunctivitis. H5N1 can affect

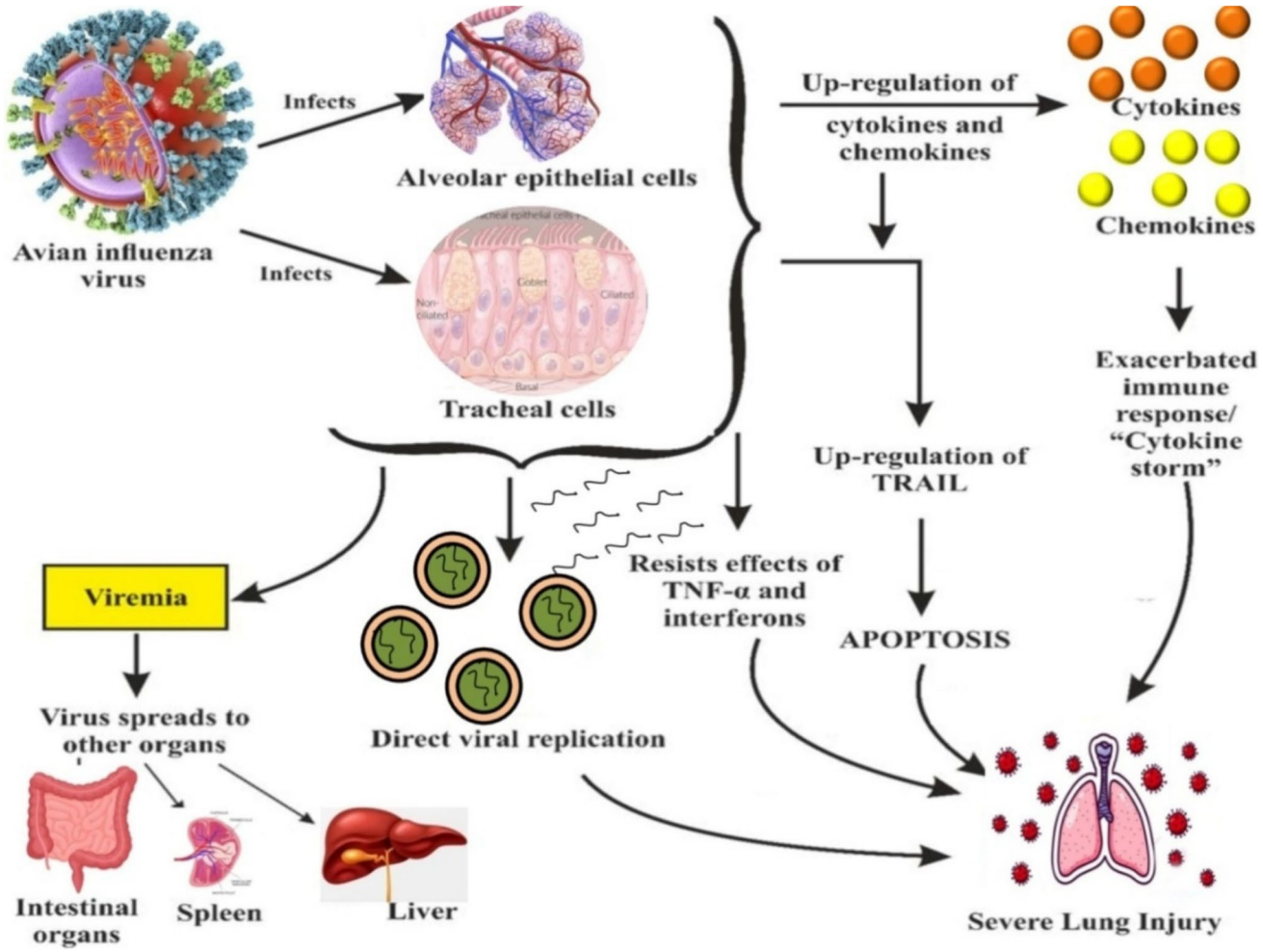


Fig. 3 Pathogenecity of avian influenza virus. The pathogenic pathways of the avian influenza (H5N1) virus in both humans and animals are shown in this image. The virus attacks respiratory tract epithelial cells during infection, setting off a series of immunological reactions that may result in inflammation, tissue damage, and systemic infection. The image illustrates how the virus causes cytokine storms, replicates inside host cells, and leads to serious side effects such organ failure and pneumonia. It also illustrates the intricacy of the pathogen's activity and its influence on public health by demonstrating how specific genetic alterations in the virus lead to enhanced virulence and the possibility of human-to-human transmission

the lungs, central nervous system, and digestive system, with severe lung damage commonly occurring (Imperia et al. 2023). Central nervous system involvement is more prevalent in H5N1 than seasonal flu, often occurring through the olfactory and trigeminal nerves (Siegers et al. 2023). Acute respiratory distress syndrome (ARDS), pancytopenia, and multi-organ failure, including respiratory and renal failure, respiratory bleeding, and pneumothorax, are potential consequences of severe occurrences (Imperia et al. 2023), along with high mortality rates associated with elevated viral loads and inflammatory cytokines and chemokines (Pawestri et al. 2020). Figure 5 depicts the structure of the avian H5N1 strain, emphasizing key genetic features or protein configurations associated with its high pathogenicity or potential for interspecies transmission.

Life Cycle

The influenza virus follows several steps for replication, including entry, replication, and release phases. When HA is first exposed to sialic acid receptors, it binds to those receptors in the α−2,3 linkage in chicken infection and the α−2,6 linkage in human infection (Du et al. 2023). The low pH of the surrounding environment subsequently induces morphological changes in HA as the virus enters the late endosomal portion of the cell, leading to the integration of the endosomal and viral membranes (Aganovic 2023). The viral genome can reach the cytoplasm because of this fusion, which prevents the virus from being degraded by lysosomes. This stage is crucial for the viral uncoating, which is required for the viral DNA to be transported (Borau and Stertz 2021). The activation of M2 channels during this

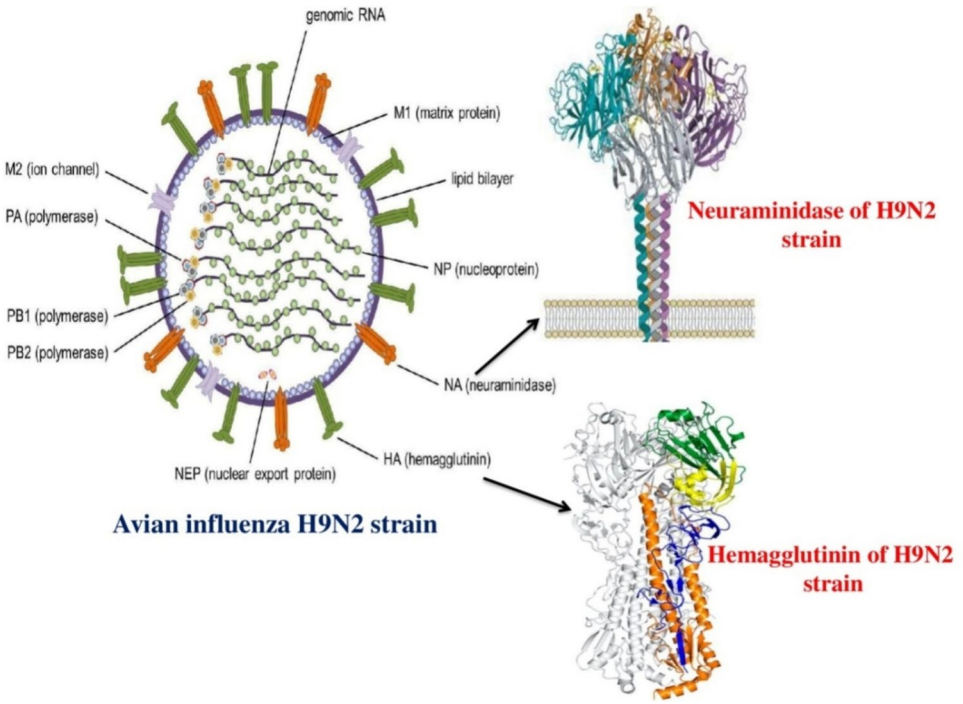


Fig. 4 Structure of avian H9N2 strain. The molecular structure of the avian H9N2 influenza virus strain is depicted in this picture. Hemagglutinin (HA) and neuraminidase (NA), two surface glycoproteins found in the virus' envelope, aid in the virus' ability to enter host cells and release its offspring, respectively. The RNA genome, matrix proteins (M1), and nucleoprotein (NP), which are essential for viral replication and assembly, are displayed as internal viral components. The antigenic locations on the HA and NA proteins, which are crucial for immune evasion and the possibility of zoonotic transmission, are also highlighted in the figure. The structure of H9N2 is a significant factor in its capacity to infect a wide spectrum of bird species and occasionally spill over to humans

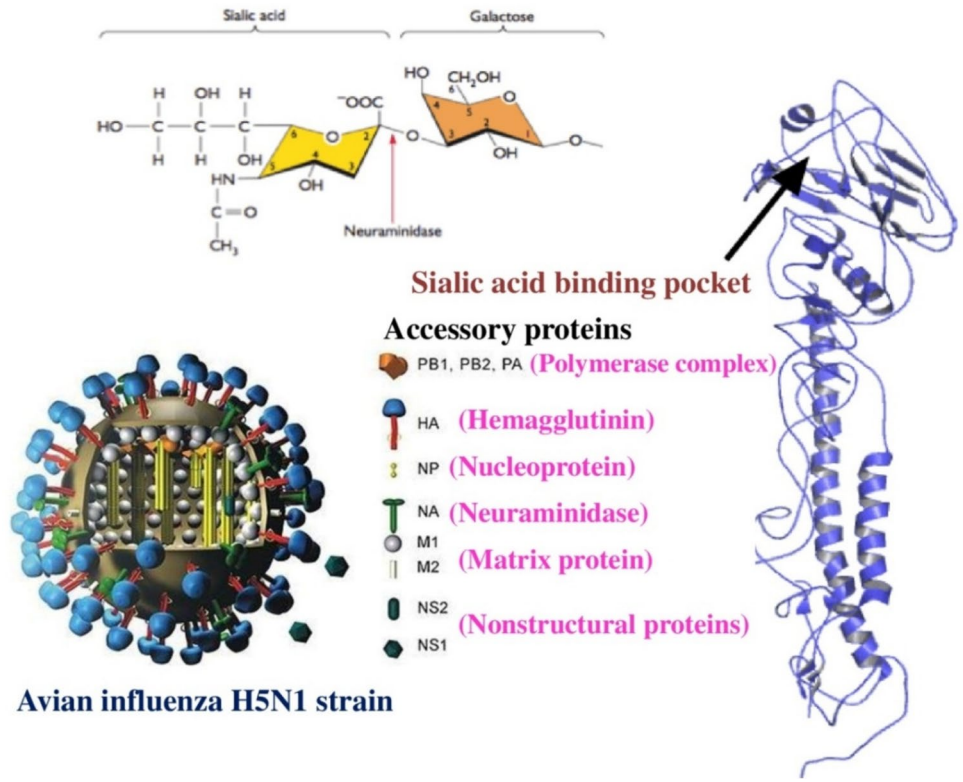


Fig. 5 Structure of avian H5N1 strain. The intricate structure of the avian H5N1 influenza virus is shown in this picture. Hemagglutinin (HA) and neuraminidase (NA), two important glycoproteins, are embedded in the lipid bilayer envelope that defines the virus. While the NA protein aids in the release of freshly produced virions from infected cells, the HA protein interacts to sialic acid-containing receptors on host cells, promoting viral entrance. It is demonstrated that the internal elements such as the matrix protein (M1), nucleoprotein (NP), and ribonucleoprotein complex (RNP) are essential for viral assembly and replication. The figure also highlights the highly pathogenic nature of H5N1, as it can undergo genetic changes, enabling it to infect both avian and human hosts, with potential for severe disease outcomes

phase results in an influx of potassium ions and acidification of the virion. Viral ribonucleoproteins (vRNPs) are released as a result of these modifications, which also cause conformational changes between M1 and NP (Mtambo et al. 2021). The vRNPs are carried into the host nucleolus once the viral uncoating process is finished, where they are replicated by the heterotrimeric viral RNA polymerase, which is made up of the PB1, PB2, and PA subunits. The host cell's messenger

RNA (mRNA) and complementary RNA (cRNA) levels rise as a result of this replication process (Moreira et al. 2021). Furthermore, the influenza virus employs a variety of secretory proteins to cause epithelial cells to release proinflammatory mediators, including TNFα (Latino and Gonzalez 2021). The viral genome is transferred from the nucleus to the cytoplasm via the nuclear export protein (NEP). After producing the genetic elements and viral proteins required for the entire virion, this viral genome passes through the packaging phase (Nguyen et al. 2023). In the last stage, the release of offspring viruses is facilitated by the viral NA's interaction with sialic acid receptors (McAuley et al. 2019). Figure 6 outlines the comprehensive life cycle of the avian influenza virus, including stages such as viral entry, replication, assembly, and budding, with a focus on host cell interactions and viral protein interactions crucial for successful infection.

Medicinal Plants with Antiviral Properties

The antiviral qualities of numerous botanicals and herbal extracts have been investigated. Herbal medicines usually possess the ability to enhance immunity, making them more capable of fighting viral infections (Sharma et al. 2023). Numerous studies have suggested that producing pro-inflammatory cytokines like interleukin (IL) 6 and 12 is enhanced by various plant extracts, which results in their immunomodulatory effects. Activated monocytes, macrophages, and dendritic cells secrete IL-12 (Saleh et al. 2021). IL-12 then stimulates T helper 1 (Th-1) cell responses, releases the cytokine interferon-gamma (IFN-γ), and increases the activity of the transmembrane glycoprotein CD + 8 in cytotoxic T cells, all of which have significance in the regulation of viral infections (Alspach et al. 2019). Additionally, research has demonstrated a connection between the generation of IL-6 by macrophages and the body's reaction to viral replication and its function in eliminating viral infections (Velazquez-Salinas et al. 2019). Therefore, phagocytosis, which is crucial for preventing viral infection, reproduction, and transmission, can be greatly enhanced by herbal products and botanicals having immunomodulatory properties. Cytokines with antiviral, antiproliferative, and immunomodulatory properties are type I interferons (IFN-α and IFN-β) (Alhazmi et al. 2021). Regarding anti-influenza plants and their antiviral mechanisms, most of the plants examined were discovered to impede the activity of viral hemagglutinin or neuraminidase. Furthermore, the antiviral properties of other herbal products and botanicals rely on the inhibition of viral nucleoprotein RNA levels and polymerase function (Peng et al. 2022).

In several phases of the viral life cycle, the effectiveness of herbal plants against avian influenza has been documented; certain herbs have inhibitory effects in more than one stage. For instance, aloe vera inhibited viral entrance and decreased viral replication (Español et al. 2022). Besides, ribonucleoproteins' production and viral release were both hindered by *Nitraria schoberi* L., Nitrariaceae (Zheleznichenko et al. 2018). Like *Echinacea purpurea* (L.)

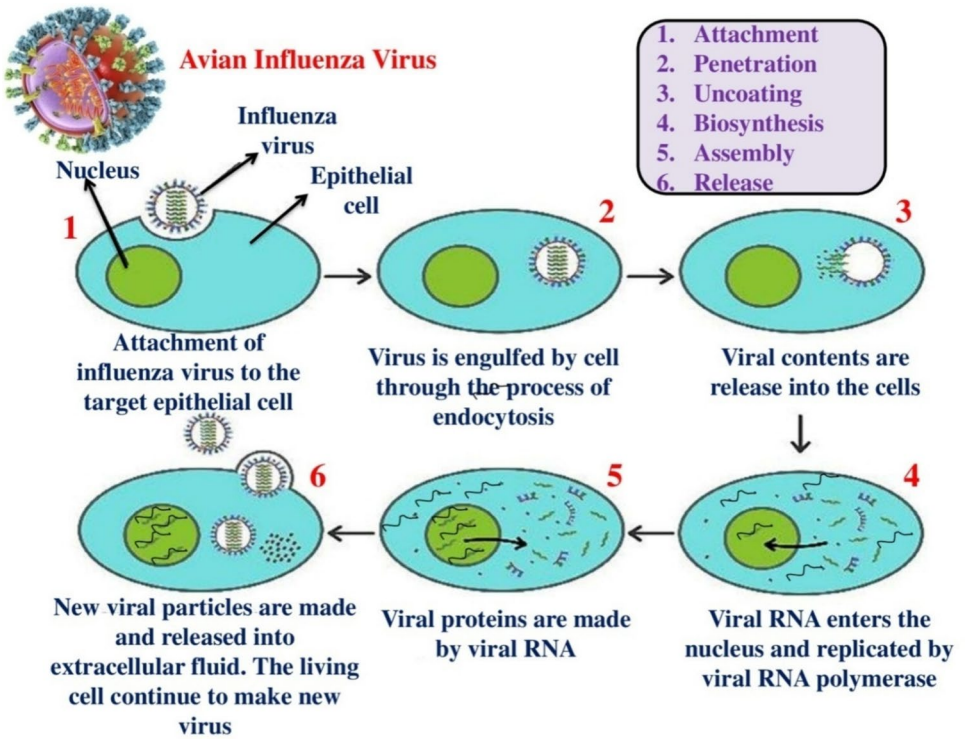


Fig. 6 Life cycle of avian influenza virus. The avian influenza virus' life cycle is depicted in detail in this picture. Viral attachment to host cell receptors through the hemagglutinin (HA) protein initiates the process, which is then followed by endocytosis. The virus releases its RNA genome into the cytoplasm after uncoating itself inside the host cell. Viral proteins are subsequently produced by transcription and translation of the RNA and assembled at the membrane of the host cell. By cleaving sialic acid receptors, neuraminidase (NA) packages and releases newly produced viral particles, enabling the virus to infect nearby cells. The crucial phase of viral replication is highlighted by this life cycle

Moench, Asteraceae, most plants appeared to function by inhibiting hemagglutinin-mediated viral entrance. *Allium sativum* L., Amaryllidaceae, inhibited pathogen growth by blocking viral replication, while members of the Zingiberaceae, *Zingiber officinale Roscoe* and *Curcuma longa* L. neutralized the virus by lowering cytokine release (Rasool et al. 2017). Although some other plants are effective against avian influenza, their processes are still unknown.

For a long time, researchers have been searching for natural inhibitors for avian influenza virus. Numerous studies have been conducted to explore plant-based chemical compounds that could potentially inhibit the avian flu virus. According to a report by Hegazy et al. (2023), various phytochemicals have been tested in both *in vivo* and *in vitro* settings for their effectiveness against the avian influenza virus. These studies have revealed that certain phytochemicals derived from plants, such as flavonoids, saponins, glycosides, and alkaloids, possess anti-avian influenza properties (Paul et al. 2023). Natural compounds derived from plants are essential to the development of novel drugs. They are suitable for use as extracts or purified compounds. Chaachouay and Zidane (2024) have revealed that a significant proportion of the global population, over 80%, uses traditional methods and medicinal herbs to treat various illnesses, including chronic and infectious respiratory ailments. Natural substances that have been isolated, such hemanthamine (He et al. 2013), gingerone A (Wang et al. 2020), and lycorine (He et al. 2013) have all been shown to have anti-influenza properties.

Echinacea purpurea

Purple coneflower contains many chemicals contributing to its antiviral properties, particularly against the avian influenza virus. The primary active compounds including *E. purpurea* are polysaccharides, alkylamides, flavonoids, glycoproteins, and phenolic compounds, including caftaric acid, chicoric acid, echinacoside, and chlorogenic acid, which are derivates of caffeic acid. These constituents exhibit immunomodulatory and direct antiviral activities. By promoting macrophages and natural killer cells, which are essential for early defense against viral infections, alkamides improve the immunological response. Polysaccharides and glycoproteins boost the production of cytokines, thereby enhancing the body's antiviral defense mechanisms. Caffeic acid derivatives possess antioxidant properties, which help in reducing oxidative stress and inflammation caused by viral infections. Therefore, these phytochemicals disrupt the cycle of viral replication, prevent the virus from infecting and fusing with host cells, and enhance the immune system by making *E. purpurea* a highly effective antiviral agent against the avian influenza virus (Burlou-Nagy et al. 2022; Novika et al. 2024).

Wang et al. (2024) assessed the impact of extracts of *E. purpurea* on avian influenza virus immunity in broilers. This study demonstrated that incorporating 2% of the crude drug or 0.5% EtOH extracts in feed, combined with AIV vaccination, significantly increased broiler body weight, enhanced antibody titers, reduced feed conversion ratio (FCR), and elevated secretory IgA (sIgA) levels. Additionally, *E. purpurea* and Moench extracts enhanced the activity of tight junction proteins (ZO-1, Occludin, Claudin-1) and key components of the TLR4-MAPK signaling pathway, including MyD88, TLR4, AP-1 genes, TRAF6, JNK, ERK, and MyD88 proteins. These findings indicate that *E. purpurea* and Moench extracts boost broiler production performance and enhance vaccine efficacy by modulating the TLR4-MAPK signaling pathway.

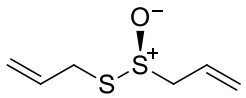
Sambucus nigra

Black elderberry (*Sambucus nigra* L., Viburnaceae) is recognized for its antiviral properties, particularly against avian influenza virus, because of its abundance of bioactive chemical constituents. The key compounds responsible for its antiviral effects consist of isoflavones, flavones, anthocyanins, flavanols, flavonoids (like rutin, anthocyanins, and quercetin), phenolic acids, vitamins, and lectins. Flavonoids have the ability to inhibit the neuraminidase enzyme, which is essential for viral replication and release from infected cells, thus halting the virus' spread. Anthocyanins, the pigment that gives elderberries their dark color, possess potent antioxidant and anti-inflammatory properties, aiding in reducing the damage caused by the virus and enhancing the immune response. Phenolic acids play a role in the antiviral effect by boosting the immune system and decreasing oxidative stress. Lectins can directly attach to viral glycoproteins, preventing the virus from attaching to and entering host cells. Consequently, some of the secondary metabolites in *S. nigra* disrupt diverse stages of the life cycle in the virus and fortify the body's immune defenses, making it a potent antiviral agent against the avian influenza virus (Mocanu and Amariei 2022; Seymenska et al. 2023).

Allium sativum

Garlic (*A. sativum*) demonstrated significant antiviral properties against the avian influenza virus due to its wide range of bioactive chemicals. Key compounds like allicin, ajoene, sterols, polyphenols, organosulfur compounds (such as diallyl sulfide and diallyl disulfide), and flavonoids like quercetin play a crucial role in this regard. Allicin (**1**), formed when garlic is crushed, is especially powerful, showing broad-spectrum antiviral effects by disrupting viral RNA synthesis and replication (Rouf et al. 2020). Ajoene (**2**) and other organosulfur compounds boost the immune response

by activating macrophages, lymphocytes, and natural killer cells, essential for targeting and eliminating viral particles. Additionally, these compounds have strong antioxidant and anti-inflammatory effects, helping to lower oxidative stress and inflammation associated with viral infections.



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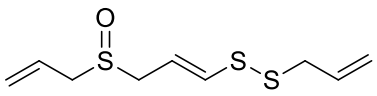

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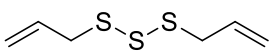
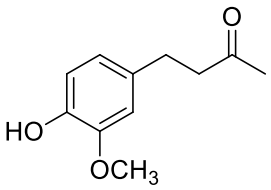
Diallyl trisulfide (**3**) was tested by Ming et al. (2021) for its ability to combat the H9N2 avian influenza virus, which suppressed inflammatory cytokines (IL-6, TNF-α), enhanced the expression of antiviral genes (IRF-3, RIG-I, interferon-β), and decreased virus loads in human lung A549 epithelial cells. These positive outcomes, which included decreased pulmonary edema and inflammation, were observed in diallyl trisulfide-treated H9N2-infected mice. The flavonoids found in garlic also enhance its antiviral efficacy by inhibiting viral enzymes and strengthening the immune system's ability to combat infections. These phytochemicals interrupt viral replication, improve immune function, and alleviate inflammation, establishing garlic as a potent antiviral agent against the avian influenza virus (Țigu et al. 2021; Ming et al. 2021).



3

Zingiber officinale

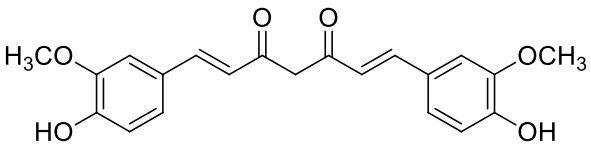
Ginger (*Z. officinale*) contains biologically active compounds such as paradols, gingerols, zingerone (**4**), shogaols, and volatile oils like zingiberene. Gingerols and shogaols are particularly noteworthy for their potent anti-inflammatory and antioxidant properties, which can help alleviate cellular damage and inflammation caused by viral infections (Yang et al. 2024). These compounds also boost immunity by boosting the function of T cells, natural killer cells, and macrophages, thereby enhancing the body's capacity to combat viral infections. Moreover, the volatile oils found in ginger have direct antiviral effects, inhibiting the replication and transcription of the virus. Zingerone and paradols also play a role in antiviral defense by disrupting viral envelope proteins crucial for the virus' ability to infect host cells (Abdel-Maksoud et al. 2023). Overall, the phytochemicals present in *Z. officinale* target various stages of the viral life cycle, enhance immune responses, and reduce inflammation, making ginger an effective antiviral agent against the avian influenza virus.



4

Curcuma longa

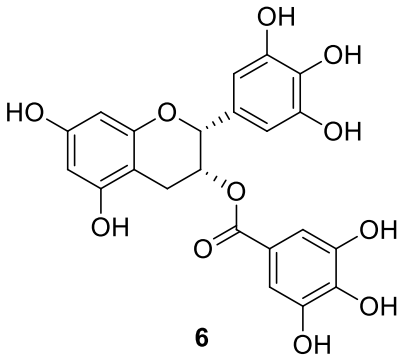
Turmeric (*C. longa*) demonstrated strong antiviral effects against the avian influenza virus. The key active ingredient is curcumin (**5**), accompanied by other curcuminoids and volatile oils such as turmerone. Curcumin is well-known for its potent anti-inflammatory and antioxidant characteristics, which aid in reducing cellular damage and inflammation caused by viral infections (John et al. 2024). It hinders viral replication by disrupting viral RNA synthesis and the function of viral proteases. Moreover, curcumin boosts the immune response by modulating the activity of diverse immune cells such as T cells, natural killer cells, and macrophages, thereby strengthening the body's defenses against viruses. Volatile oils like turmerone also possess antiviral properties, further impeding the virus' replication and transmission (Lai et al. 2020).



5

Camellia sinensis

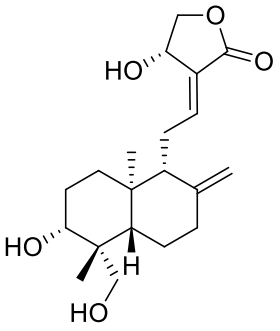
The evergreen shrub or small tree that produces tea leaves, native to South and Eastern Asia and grown as a major cash crop, is *Camellia sinensis* (L.). Kuntze, Theaceae, demonstrated potent antiviral properties against the avian influenza virus owing to its high concentration of catechins, such as epigallocatechin gallate or EGCG (**6**), theaflavins, flavonoids, and polyphenols. Among these, EGCG, the most prevalent catechin, stands out for its ability to hinder viral entry and replication by disrupting the viral envelope and impeding the virus's capacity to infect host cells (Aggarwal et al. 2022). Theaflavins, produced during the fermentation of tea leaves, inhibit the neuraminidase enzyme, which is vital for the replication and release of the virus. Moreover, the antioxidant characteristics of catechins and flavonoids alleviate oxidative stress and inflammation induced by viral infections, thereby bolstering overall immune function. These phytochemicals enhance the performance of immune cells such as macrophages and NK cells, thereby stimulating the body's antiviral defenses (Karthikeyan et al. 2020).



6

Andrographis paniculata

Andrographis paniculata (Burm.f.) Wall. ex Nees, Acanthaceae, also known as the "king of bitters," possesses various chemicals that contribute to its medicinal properties. Notably, the labdane diterpenes andrographolide, 14-deoxy-11,12-didehydroandrographolide, and 14-deoxyandrographolide, and the glucoside neo andrographolide are the key compounds found in this plant (Mehta et al. 2021). These compounds have demonstrated significant antiviral activity, particularly against the avian influenza virus. The primary mechanism of action involves inhibiting viral replication and enhancing the immune response of the host. Andrographolide (**7**), the main active constituent, has been observed to interfere with viral protein synthesis and regulate the immune system by increasing the production of antiviral cytokines (Jiang et al. 2021). This dual action not only reduces the viral load but also strengthens the body's natural defense mechanisms, making *A. paniculata* a promising candidate for combating avian influenza virus infections.



7

Miscellaneous Herbal Principles

Table S1 summarizes the antiviral functions of medicinal plants against the avian influenza virus. Figure 7 illustrates the antiviral mechanisms of medicinal herbs against the avian influenza virus, highlighting specific bioactive compounds present in herbs that inhibit viral replication, modulate host immune responses, or disrupt viral entry into host cells, thereby attenuating viral infectivity.

Zhi et al. (2024a, b) revealed that the extract of belamcanda, *Iris domestica* (L.) Goldblatt & Mabb., Iridaceae, an herb used in traditional Chinese medicine, exhibits notable antiviral properties against H9N2 AIV in specific pathogen-free (SPF) chicks. This study highlighted that the extract significantly modulates the expression of key inflammatory cytokines, such as IL-1, tumor necrosis factor-alpha (TNF-α), IL-6, and IL-2, all of which are vital to the host's immune response against H9N2 AIV infection. Chen et al. (2024) investigated the antiviral properties of the n-butanol extract *of Davallia marries H.J. Veitch*, Davalliaceae, against the avian influenza virus. This polar fraction demonstrated a broad antiviral spectrum with an EC_{50} of 24.32 ± 6.19 μg/ml and a selectivity index of 6. The study revealed that *n*-butanol extract inhibited avian influenza virus in the initial infection stage by preventing viral adhesion and penetration into host cells. Furthermore, the *n*-butanol extract inhibited IAV-induced cell–cell fusion, lowered neuraminidase activity, reduced plaque size, and decreased the expression levels of phospho-AKT. Ghoke et al. (2018) assessed the antiviral efficacy of *Acacia arabica* (Lam.) Willd., Fabaceae, and *Ocimum sanctum* L., Lamiaceae, leaf extracts against the H9N2 virus, utilizing an embryonated chicken egg model. Their findings indicated significant antiviral activity, particularly for *Ocimum* terpenoids and *Acacia* polyphenols, highlighting their potential as potent agents against the H9N2 virus. Senevirathne et al. (2023) investigated the antiviral properties of an aqueous

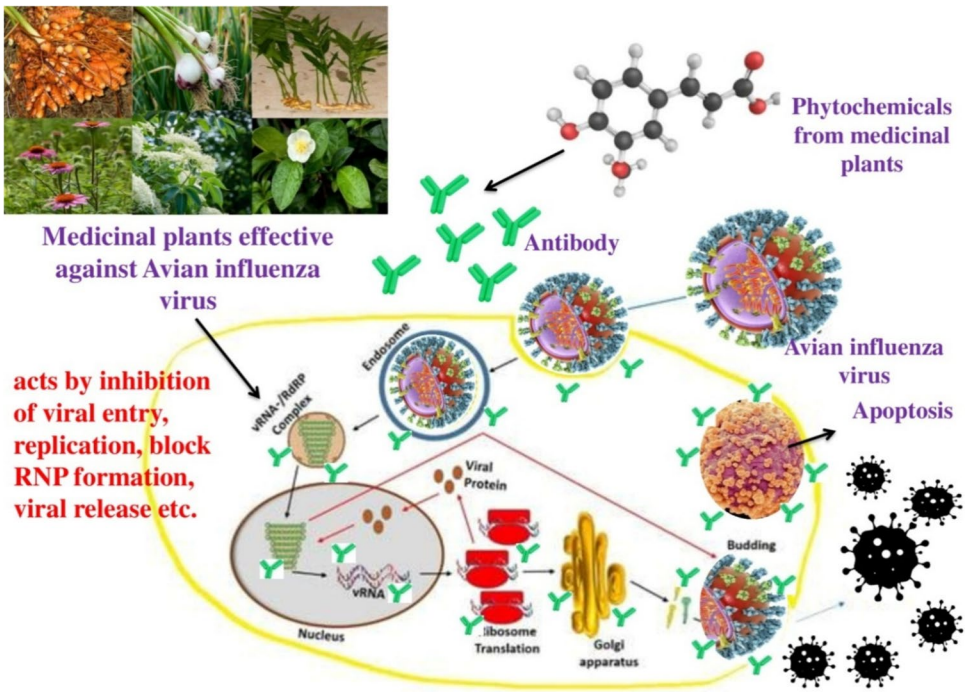
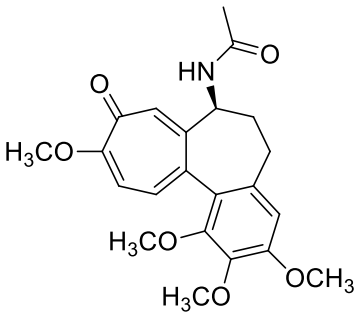


Fig. 7 Antiviral mechanisms of medicinal herbs against avian influenza virus. The image depicts how medicinal plants and their phytochemicals (flavonoids, alkaloids, terpenoids, and polyphenols) combat avian influenza. They prevent viral entrance by inhibiting hemagglutinin (HA) binding, impair viral replication by targeting RNA synthesis and protein production, and boost immune responses by increasing antibody and cytokine production. The picture also depicts how these compounds disrupt viral cellular organelles, blocking viral assembly and release, emphasizing the promise of plant-based medicines in avian influenza treatment

leaf extract of *Hellea speciosa* (J. Koenig) S.R. Dutta, Costaceae, against the H9N2 influenza strain, discovering that it elicited protective responses and enhanced immune activity against the virus. Shahzad et al. (2019) examined the antiviral effects of eleven Cholistani plants from Pakistan against the H9N2 strain. The study identified *Osyris compressa* A.DC., Santalaceae, *Neurada procumbens* L.*, Neuradaceae,* and *Solanum surattense* Burm.f, Solanaceae, as the most effective, as these plants were able to retain hemagglutination.

By interacting directly with the viral particles, in particular, *Melissa officinalis* L., Lamiaceae, volatile oil can potentially suppress the avian influenza virus (H9N2) at multiple stages of the reproduction cycle (Pourghanbari et al. 2016). Abou Baker et al. (2021) examined the antiviral characteristics of volatile oils extracted from *Salvia officinalis* L. and *Lavandula latifolia* Medik, both from the Lamiaceae, against H5N1 avian influenza virus. Whereas α-thujone and camphor were the main ingredients in salvia volatile oil, linalool and linalyl acetate were the main ingredients in lavender oil.

Hegazy et al. (2024) investigated the antiviral activity of nitrogenous alkaloids against Influenza A/H1N1 and H5N1 viruses, finding that colchicine (**8**), the racemate atropine (**9**), and pilocarpine (**10**) showed notable anti-H5N1 activities with IC_{50} values of 0.210, 0.111, and 2.3 µg/ml, respectively. The findings indicated that pilocarpine hydrochloride and atropine sulfate literally influence the virus through a cell-free virucidal effect, whereas colchicine primarily decreases viral infection by disrupting IAV replication and preventing viral adsorption. These findings underscore the potential of biologically active alkaloids, particularly colchicine, in combating influenza.



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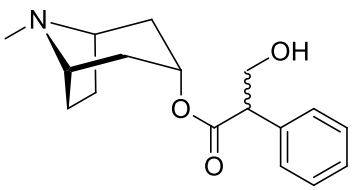

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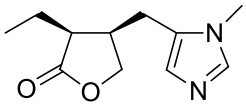
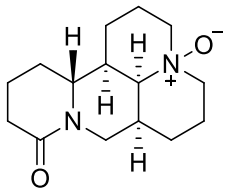


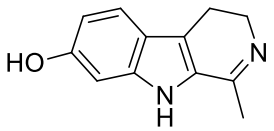
10

Zhi et al. (2024a, b) evaluated the antiviral efficacy of the quinolizidine alkaloid oxymatrine (**11**), isolated from the Fabaceae species *Sophora flavescens* Aiton and *S. tonkinensis* Gagnep, against H9N2 avian influenza virus. The study's results demonstrated that oxymatrine suppressed antiviral proteins PKR and Mx1 in a dose-dependent manner. It altered the expression of type I interferons (IFN-α, IFN-β) and essential cytokines (TNF-α, IL-6), which in turn affected TLR3 signaling and its downstream elements, such as IRF-3 and NF-κB. The antiviral activity of oxymatrine extended beyond TLR3-mediated pathways, highlighting its potential as a versatile antiviral agent.



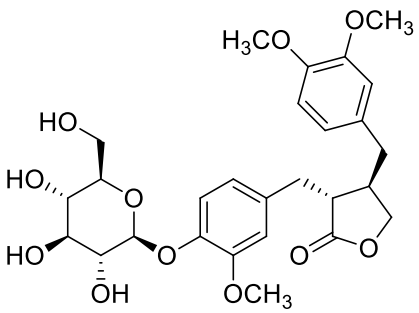
11

Hegazy et al. (2023) evaluated the anti-influenza activity of β-carboline indole alkaloids and indole against the avian influenza H5N1 strain, finding that harmalol (**12**), harmane, strychnine, and harmaline demonstrated potent anti-H5N1 effects with IC_{50} values of 0.02, 0.023, 11.85, and 3.42 µg/ml, respectively, outperforming the control drugs amantadine and zanamivir, which had IC_{50} values of 0.079 and 17.59 µg/ml, respectively.



12

Zhou et al. (2021) explored the antiviral potential of arctiin (**13**), a lignan glycoside extracted from *Arctium lappa* L., Asteraceae, against the H9N2 influenza strain. Their findings indicate that arctiin's anti-inflammatory properties in H9N2 virus infection are likely mediated by its antioxidant properties, activating the Nrf2/HO-1 pathway and inhibiting the RIG-I/JNK MAPK signaling pathway. Consequently, arctiin appears to be a promising candidate for preventing and treating H9N2 virus infections.



13

H5N1 and H9N2 Viral Infections in Humans

On 22 May 2024, Australia reported its initially confirmed first human case of avian influenza virus A (H5N1) (clade 2.3.2.1a) to the WHO, involving a 2.5-year-old girl who likely contracted the virus in Kolkata, India. Despite an unidentified infection source, the child recovered, and no family members exhibited symptoms. The current situation demonstrates the zoonotic potential of avian influenza from 2003 to May 2024; the WHO received 891 reports of H5N1 infections worldwide. Similarly, on 9 April 2024, Vietnam reported its first human case of avian influenza A (H9N2), a 37-year-old man from Tien Giang Province in severe condition, likely exposed near a poultry market. No additional cases were reported among his contacts. Avian influenza A virus infections in humans, primarily through contact with infected animals or environments, can range from mild to fatal. Since 2015, 99 global cases of A (H9N2) have been reported (Dutta et al. 2023). To combat avian viral infections in humans, certain medicinal plants (Jaganathan and Kumaradhas 2024; Selvankumar et al. 2024) have been utilized for treatment. These plants have bioactive substances with antiviral properties that may inhibit the spread of viruses and strengthen the body's defenses against these infections. Through various mechanisms, such as interfering with viral attachment and entry into host cells, blocking viral replication processes, and modulating immune function, these bioactive compounds help mitigate the severity of infection and reduce the risk of complications (Pal and Lal 2023). Shi et al. (2024) investigated the anti-influenza effect of the sangbaipi decoction, derived from antipyretic *Scutellaria baicalensis Georgi*, Lamiaceae, and *Coptis chinensis* Franch., Ranunculaceae, and antitussive herbs, *Morus alba*

L., Moraceae, and *Prunus armeniaca* L., Rosaceae. Their study employed both laboratory and animal models to assess sangbaipi decoction's efficacy. In MDCK cells infected with various influenza strains, this decoction exhibited significant antiviral activity with IC_{50} values varying from 0.80 to 1.25 mg/ml. Furthermore, sangbaipi decoction treatment in A549 cells reduced cytokine expression (TNF-α, IL-6, IL-1β) and improved survival rates, reduced lung index, and protected lung tissue in PR8-infected BALB/c mice. Hemagglutination inhibition and neuraminidase inhibition assays suggested that the potential antiviral mechanism of the sangbaipi decoction operates through the inhibition of these proteins, highlighting its promise as a multifaceted anti-influenza agent. Hegazy et al. (2022) found that santonica flower extract (*Artemisia cina* Berg ex Poljakov, Asteraceae) exhibited potent anti-H5 N1 activity, with a high safety profile (CC_{50} > 10 mg/ml) and strong efficacy (IC_{50} 3.42 µg/ml). The extract also demonstrated robust anti-influenza activity against human influenza A/H1N1, comparable to its effect on H5N1. Further analysis of its major component, santonin, revealed significant antiviral potential against both influenza A/H5N1 (IC_{50}1.7 µg/ml) and A/H1N1 (IC_{50}2.9 µg/ml).

Figure 8 illustrates the various antiviral activities of phytochemicals derived from medicinal plants against different strains of the avian influenza virus, highlighting their effectiveness in inhibiting viral replication, reducing viral load, and enhancing host immune responses. This research presents promising avenues for the development of natural antiviral agents to combat avian influenza H5N1 and H9N2 infections in humans, noted for their safety, compatibility, efficacy, and minimal side effects.

Perspectives and Future Directions

The utilization of herbal medicines for human infections with avian influenza A (H9N2 and H5N1) viruses presents

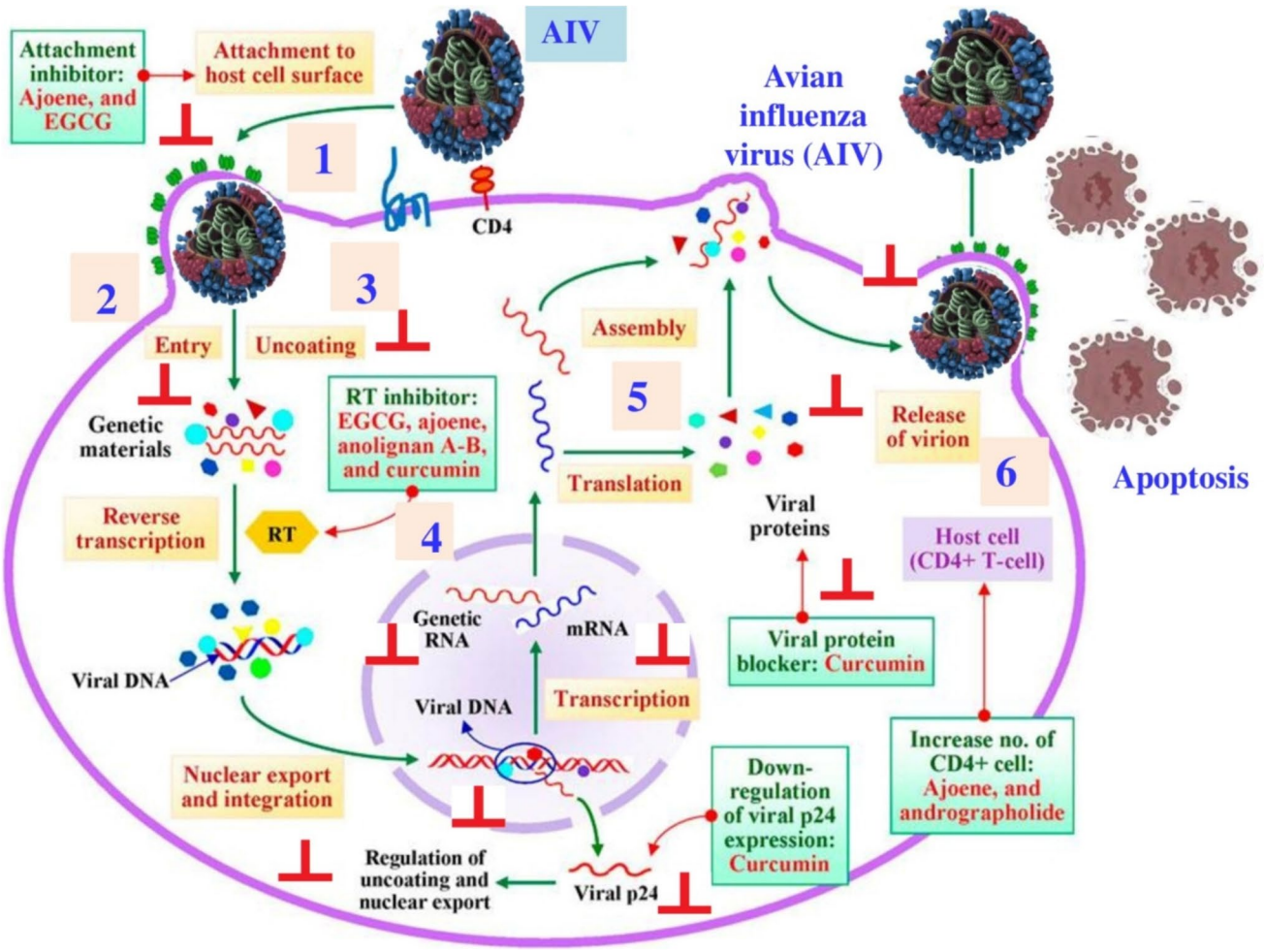


Fig. 8 Antiviral activities of active principles from medicinal plants against avian influenza virus strains. This diversity of antiviral activities highlights the effectiveness of secondary metabolites in inhibiting viral replication, lowering viral load, and boosting host immune responses, thus representing promising pathways for developing natural antiviral agents

a range of challenges. Firstly, the effectiveness and safety of herbal remedies in treating viral infections such as avian influenza have not been extensively studied or clinically validated, resulting in uncertainty regarding their efficacy. Additionally, the standardization of herbal formulations, quality control, and determining appropriate dosages present significant obstacles. Furthermore, there is an absence of thorough comprehension regarding the process by which herbal compounds (Abareethan et al. 2024) act against specific viral strains, which limits their targeted application. Despite these obstacles, herbal medicines show promising potential for fighting avian influenza A viruses. Ongoing research efforts aim to identify potent antiviral compounds in herbs, develop innovative formulations, and integrate traditional knowledge with modern medicine. By promoting collaboration among traditional healers, scientists, and healthcare professionals, it is possible to identify effective herbal treatments for avian influenza A infections, providing a complementary approach to conventional antiviral therapies.

Conclusion

In conclusion, natural remedies show promising anti-avian influenza properties, emphasizing the need for ongoing research to create commercially viable products. Different natural ingredients have proven to be effective against different phases of the virus replication process, indicating the potential for combination treatments in managing the disease. Nevertheless, additional research is crucial to produce products that can fully maximize the therapeutic advantages of these remedies. This shows the significance of continuous research endeavors to unlock the potential of natural medicines as efficient remedies for avian influenza, providing hope for improved treatment options in the future.

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Author Contribution MM and VKN: conceptualization, writing original draft, visualization, data curation, formal analysis, writing, review, and editing; MM, VKN, PRS, and HHS: visualization, data curation, writing, review, and editing. All authors have read and agreed to the published version of the manuscript.

Data Availability The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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