Chapter 07

Use of Nanotechnology to Treat Avian Influenza

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ABSTRACT

Avian influenza virus infection is a crucial challenge being faced by the poultry farmers in this day and age. The high rate of mortality and morbidity caused by this disease has resulted in a huge downturn in the economic situation of the poultry industry. Especially, recently there has been a rise in incidence of avian influenza virus strain that is highly pathogenic. Invasion of this strain leads to a higher mortality rate than the low pathogenic strain of AIV. Similarly, cases to zoonotic AIV infection from birds to humans have been also seen in recent years. This situation makes this virus a formidable foe for not only poultry birds but also human populations. This mandates proper research and analysis of viruses through new technological solutions like nanotechnology to formulate effective vaccines and better diagnostic tools. Once properly developed these tools can be used to control the spread of AIV hence preventing the economic and health losses it may cause.

KEYWORDS
Mortality, Morbidity, Pathogenic, Avian influenza virus, AIV

Received: 19-May-2024
Revised: 12-Jul-2024
Accepted: 08-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Naeem MI, Hussain F, Aslan ES, Nousheen J, Nisa QU, Sarwar M, Fatima M, Khanim A, Younis W and Murtaza G, 2024. Use of nanotechnology to treat avian influenza. In: Ahmed R, Khan A, Abbas RZ, Farooqi SH and Asrar R (eds), Complementary and Alternative Medicine: Nanotechnology-II. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 47-54. https://doi.org/10.47278/book.CAM/2024.225

INTRODUCTION

A key role is attributed to poultry products in the production of food items and reduction in poverty status in case there is a shortage of other types of food products that are nutrient-rich (Hedman et al., 2020; Desta, 2021). Various crucial factors will determine the poultry industry's upcoming growth rate. The list of factors is comprised of but not limited to the immunity of poultry birds, health status and production capacity of birds being reared (Hafez and Attia, 2020). Diseases of poultry keep emerging continuously at a global level and are the main topic of concern for the stakeholders of the poultry industry (De Boeck et al., 2015). The most common and widespread diseases of poultry, all over the world, include Infectious bronchitis (IB), avian influenza (AI), Newcastle disease (ND), and Gumboro disease (Nkukwana, 2018; Yadav et al., 2019).

The disease of Avian influenza virus (AIV) is caused by a very notable virus of poultry birds belonging to the Orthomyxoviridae family. The infection of AIV leads to huge economic losses for the poultry farmers at global scale (Dhama et al., 2005; Parvin et al., 2018). The structure of AIV is made up of a segmented negative eight piece, single-stranded RNA encoding bases for around 11 proteins (Chen and Deng, 2009). Additionally, the Avian Influenza Virus is divided into subgroups depending upon the proteins found on the surface of the viral agent. These proteins include hemagglutinin (HA) and neuraminidase (NA) which assist the attachment and release of viral agent to the target surface, in the same order (Ducatez et al., 2008; Yang et al., 2016). The rearrangement of hemagglutinin and neuraminidase with various subgroups may result in severely rampant pandemics such as H1N1, H2N2, and H3N2 in humans (Blagodatski et al., 2021). AIV is classified depending upon the severity of clinical signs it may cause in its victim. This classification includes highly pathogenic avian influenza virus (HPAIV) and low pathogenic avian influenza virus (LPAIV) (Luo et al., 2021; Soda et al., 2021).

Vaccination failure in during production phase of poultry birds is quite common due to the co-circulation of the

existence of various strains of AIV. These subtypes include H5, H7, and H9 (Mansour et al., 2017). Hence it is essential to strive for the advancement of a polyvalent vaccine that can be used for inducing immunity against various serotypes simultaneously. When taken into account such factors indicate that there is a high risk for emergence of novel infectious diseases and serotypes for the human and livestock populations (Mohamed et al., 2019). Such an example from the past is the inclination of poultry production systems towards intense rearing systems for battling the losses caused by the rise of highly pathogenic H7N9 AIV. The increase in poultry stocking density and rise in populations has led to an increase in the transmission rate of the disease between humans and birds (Astill et al., 2018). Furthermore, the increase in the rate of evolution and immense pressure on the immunity of birds are limiting factors against the effectiveness of vaccination (Gilbert et al., 2017). Additionally, the utilization of antimicrobial agents as feed additives has increased the problem of drug residues and consequently antibiotic resistance. This is the main reason that led to the ban of antibiotic utilization at the sub-therapeutic level in all European countries since January 2006 (Manyi-Loh et al., 2018).

Nanotech

Classification of Avian influenza viruses (AIV) is partitioned into two classes one is the low pathogenic viruses and the other is of highly pathogenic viruses. The low pathogenic avian influenza also known as LPAI is a less virulent strain of viruses that produces mild clinical signs after infection and has low chances of affecting the reproductive system and affecting egg production capacity (Gonzales et al., 2012), other hand HPAI or high pathogenic avian influenza virus infection lead to cause massive outbreaks of influenza with high death rate in birds (Tiensin et al., 2005). However, the actual pathogenicity of low pathogenic capability Avian Influenza virus is determined by various internal and external factors of the hosting individual (França and Brown, 2014). In regions where both types of this virus are prevalent among poultry birds, the use of inactivated whole unit and vectored viral vaccines is preferred to minimize the risk and occurrence of Avian Influenza Virus (Swayne, 2012; Suarez and Pantin-Jackwood, 2017). The parenteral administration of these vaccines induces the immunity at systemic level and provides partial to full protection against the progression of disease. Still, these vaccines provide no assurance of preventing viral invasion and release of viral agent from already diseased birds (Costa et al., 2011; Kapczynski et al., 2016). This marks the requirement for researchers to look into immunogenicity and efficacy improvement methods for existing vaccines against AIV. Such a goal can be obtained through the selection of adjuvants having greater capabilities regarding the stimulation of innate and adaptive immunity (Gutjahr et al., 2016; Pizzolla et al., 2017). This adjuvant can be used effectively through the exploration of efficient vaccination routes (Hasegawa et al., 2007) and by adopting optimized methods of vaccine delivery (Vyas and Gupta, 2007; Jain et al., 2011; Singh et al., 2016).

Linked directly with profound sciences of physics, chemistry. biology, materials and medicine, nanotechnology is a fairly recent and under-development field of applied sciences. It includes several types of cutting-edge technological tools and applications that utilize the properties of nanomaterials form the physicochemical aspect to regulate their surface area, size, and shape to produce various types of nanomaterials with of different properties. Nanoparticles have been vastly utilized for development of nanoparticle-based drug carriers with a targeting nature, test kits for rapid pathogen detection or bio-molecular sensing systems and antiviral agents that with mechanism of action relying on their interference with viral infectious agents, especially during their attachment to cell surface and entry in the host cell (Miranda et al., 2010; Cao et al., 2011; Falanga et al., 2011).

Influenza

The last twenty years have proven to be a nightmare for avian health as the rise of highly pathogenic type A avian influenza virus (AIV) strains was witnessed. The emergence of this strain led to have development of disease with severe and incurred heavy losses causing an economic crash in the poultry industry. The victims of this strain included chickens and turkeys, but humans were also affected as a number of avian-human transmissions cases were observed. The highly pathogenic AIV strains were found to be the main reason behind high morbidity and mortality rates in poultry post-infection. This led to breakouts and epidemics with significant economic downturns. For instance, in early 2006, an infection with highly pathogenic H5N1 AIV at a poultry farm in Egypt resulted in high mortality of birds. Afterwards, this breakout the first human case of AIV was detected. Since that, the WHO has recorded more than a hundred cases of AIV infection in humans from birds and several deaths have also occurred due to this infection in Egypt (Cattoli et al., 2011).

The diversity in genotype and phenotype diversity of influenza viruses along with their divergence capabilities pose a significant threat to the technological development of diagnosis and therapeutic tools and techniques. AIVs are classified for diagnosis based on their subtypes according to their haemagglutinin (HA, H1-H16) decided upon their antigenic properties and through testing of surface glycoproteins neuraminidase (N1-N9). The only strains that are avian and have been reported as an etiologic agent in humans include H5, H7 and H9. The H5N1 is the very well-identified and highly pathogenic avian influenza virus strain (Leong et al., 2008). Currently the recent reporting subtype of AIV, H7N9 has gained attention from the researchers. On the basis of evidence obtained through genetic research most of the strains belonging to the influenza virus are found linked to the aquatic birds. The wild birds usually show little or no disease in case of infection with AIV hence they are assumed to serve as ‘reservoirs’ for these viruses. The appearance of genetic mutations or re-shuffling of these viral genes has led to high pathogenicity in these strains making them extremely virulent and adaptable to new species of hosts, such as birds (chicken), livestock (pigs) and human populations. Poultry birds and

livestock pigs have been reported to play their role as 'mixing vessels' for various subtypes of avian influenza virus. This mixing facilitates shuffling genetic material among the highly pathogenic subtypes of avian influenza. This shuffling ultimately led to the development of strains that caused severe disease outbreaks among human populations (Bengis et al., 2004; Sakoda et al., 2012; Jones et al., 2013; Beaudoin et al., 2014). Alterations in the situation of hosting individual, environmental conditions, or transmission agent can lead to rise in occurrence of virus invasion rate. Several viral maladies that emerged in the last few tens of years have recently become entangled among the population of humans all across the globe. Many important instances of these viral attacks include Chikungunya virus, Hantavirus, monkey-pox virus, Hendra virus, Zika virus, Nipah virus and SARS coronavirus, and the challenge of avian influenza virus pandemic from bird or pig sources. Climate change and the effects of activities of humans on the ecosystem are the main factors contributing to the dispersal of pathogens. Especially the presence of high genetic biodiversity among wild birds along with the lower genetic biodiversity level of the domestic birds leads to the encouragement of the quick spread of infections in densely populated farms and live poultry markets (Loth et al., 2010; Jones et al., 2013; Wang et al., 2014; Wu et al., 2014).

Diagnosis

Viral agents of Avian Influenza have been mostly distinguished through detection and assessment of particular proteins and nucleic acids and by the use of analysis techniques like polymerase chain reaction (PCR) (Esposito et al., 2010; Heger et al., 2014), enzyme-linked lectin assay (ELLA) and enzyme-linked immunosorbent assay (ELISA) (Westgeest et al., 2015). Although effective, these methods require a set of specific expensive tools and equipment under special controlled laboratory conditions only to be performed by expert personnel (Sun et al., 2001; Park et al., 2010; Esfandyarpour et al., 2013; Qasim et al., 2014). Generally, influenza virus infection was diagnosed through a series of tests starting from Western blot, protein and DNA microarrays or PCR which later on led to analysis through DNA sequencing. The AIV typing microarray tests can be used for detection purposes but are also helpful in the provision of supplemental information regarding the subtype identified in the symptomatically positive samples as compared to the ones detected with real-time PCR (Lung et al., 2012). Techniques of Lab-on-a-chip and full integration methods have been optimized for identification and differentiation of pathotypes, and characterization of the influenza A viruses, isolated from actual field samples, phylogenetically (Charlton et al., 2009).

Several types of ELISA tests including strip tests like immune-chromatographic tests (Watanabe et al., 2015) along with double antibody sandwich enzyme-linked immune-sorbent assay (DAS-ELISA) (Moulick et al., 2017), have been mainly utilized for the quick identification of H9 influenza virus subtypes and the specificity of attachment of receptors in various sample types. DAS-ELISA employs the use of two monoclonal antibodies with a lofty specificity value of 99.1% in its results and it has a 93.1% sensitivity percentage. The type of ELISA test that employs the use a special type of blocking that is dual-function with high sensitivity and a perfect 100% specificity in its results for a quicker confirmation of avian influenza virus invasion as compared to other time-taking tests like PCR. These diagnostics techniques are useful methods for AIV diagnosis besides the traditional approach through the haem-agglutination inhibition (HI) test. HI test is primarily used for the sorting of numerous samples. However, these tests have evidently more sensitivity and specificity in their results as compared to the HI test while also being quicker and more convenient for implementation of automatic systems (Comin et al., 2013; Li et al., 2013). Another method reported for the identification of AIV in samples is through immunofluorescence assay of magnetic nature. This test can be performed by a spectrometer with optical fibres and a chip of microfluidics with portability options (Zhang et al., 2013). A technique has been formulated to identify the zoonotic pathogen strain of avian influenza A/ H7N9 using the real-time PCR test in a set of limited detection range starting from 3.2×10^{-4} to 6.4×10^{-4} haem-agglutination units (HAUs) for the genes of H7 and N9, respectively (Fan et al., 2014; Kang et al., 2014). An idea of a polydimethylsiloxane-made microfluidics chip with the capability to detect real-time fluorescence for the quick detection of AIV H5 has been presented (Zhu et al., 2014). Microarrays of DNA and protein and DNA can be utilized for the multiplexed detection, sorting and typing of Avian Influenza Viruses that have been recently categorized as the H16 and N9 subtypes. These microarrays have opened a new channel of possibilities for diagnosis applications. However factors like practicality and economics still limit their use in diagnostic laboratories at large scale (Rodrigo et al., 2014; Zhao et al., 2015).

Nanotechnology-based Solutions

Various types of nano-sized materials are now being utilized as the appliances of interactions between the materials and the viral agents. This interaction enables the researchers to build bio-sensing analyzers that work effectively in theory based on the application of electro-analysis with a portable nature. It can perform nearly perfect identification of influenza virus (Moulick et al., 2017). The utilisation of vaccines based on nano-materials has several benefits that include but are not limited to increased storage viability time, the stabilisation of vaccines by encapsulating with nanoparticles of a polymeric nature that stay solid at room temperature, the provision of the possibility to administer the vaccine through an alternate route, and obtaining ability of precise discharge. Nanomaterial-based vaccines can also be used to release soluble antigens that can assist in the induction of two forms of immunity, i.e., humoral and cellular (Chen et al., 2017). In the same way, nanoparticles formulated from the chitosan derivatives are utilized for delivering an immune response upon administration through the mucosal entry sites of birds. Post-vaccination a reduction can be observed in the morbidity and mortality rates of infection. The viral load was also found reduced in chickens that were infected with IBV and AIV (Renu and Renukaradhya, 2020).

Nanobeads also known as magnetic beads are considered nanoparticles and are utilized at amplifion for the

identification of signals along with quartz crystal microbalance (QCM) apta sensors, the magnetic nano bead-amplified QCM immune sensors. These beads can be utilized for the detecting presence of the H5N1 proteins (Brockman, 2013). Magnetic nanoparticles composed of silver nanoparticles (AgNPs) and carbon-derivative materials are often used for the analysis and identification of various influenza virus subtypes. These particles are prepared on the well-researched methodologies readily available in reports of past researchers. (Mokhtarzadeh et al., 2017; Boroumand et al., 2021). Furthermore, the knowledge of well-known methods like the electrode-based well array, on-chip nano-membrane tubular sensors based on full integration and electrochemical quantitative systems, also assists the research and development of such nanoparticles (Krejcova et al., 2012; Cha et al., 2013).

Mesoporous nanoparticles like that of silica can perform various functions due to their amino group and being naturally attached to probiotics like quercetin and shikimic acid. These nanoparticles have developed into a novel formulation of antiviral nanoparticles that target the identification of highly pathogenic avian influenza H5N1 virus. These nanoparticles also induce a strong response from the immune system. These particles limit the cytokines (IL-1β and TNF-α) and nitric oxide (NO) production by half. When tested on a critical carrageenan-induced rat model these nanoparticles served an extremely efficient role in inducing the anti-inflammatory effect and then continued it in vivo (Neethirajan, 2017; AbouAitah et al., 2020). Thus, nano-scaled technology through the utilization of several types of NPs and as the nano-vaccines, nano-bodies and nano-medicine, along with the utilization of adjuvants, has a significant role in future as a biomedical application for controlling avian infectious diseases.

Conclusion

Avian Influenza Virus has been the arch-nemesis of the poultry production industry since it was reported. Infection of Avian Influenza virus spreads rapidly and has severe clinical signs with a high rate of mortality if the infecting agent is the highly pathogenic strain of AIV. These factors make it a major risk for the progress of the poultry industry. Additionally, the recent discovery regarding the zoonosis potential of this disease has led to a rise of concern among public health researchers. This situation called for immediate action so now a number of researchers are exploiting cutting-edge innovations to counter AIV. One such innovation is the nanotechnology. Nanotechnology is being researched for its use for effective vaccination against AIV, its control and proper diagnosis. These advancements in nanotechnology have given mankind hope that this pandemic can be controlled. Control over AIV will not only reduce poultry losses but it will also bring a sense of security for public health.

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