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Recombinant Vaccines against Newcastle Disease: Current Trends and Research Agenda

Amir Ghaffar Shahriari[1], Maziar Habibi-Pirkoohi[2]*

[1]Department of Agriculture and Natural Resources, Higher Education Center of Eghlid, Eghlid, Iran. [2]Zist Pajoohan Baran, Afzalipour incubation, Shahid Bahonar University of Kerman, Kerman, Iran

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***Corresponding Author:**
Maziar Habibi-Pirkoohi;
Zist Pajoohan Baran, Afzalipour incubation, Shahid Bahonar University of Kerman, Kerman, Iran.
Email: maziar.habibi.p@gmail.com
Tel/Fax: +989178967220

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A B S T R A C T

Decades after the production of recombinant vaccines, the production of large scale and commercial use of such vaccines has become an important issue in the academic community. Newcastle disease (ND) is an infectious and highly contagious viral disease that causes diseases with different virulence and high infectivity in birds, especially chickens. ND imposes severe economic losses on the poultry industry, and as a result, tackling it is always a priority for all countries of the world. In this regard, many vaccines have been produced, some of which are commercialized and some of which are in the testing phase. Given the economic importance of controlling ND, the production of recombinant vaccines against the disease has been one of the major concerns in the history of recombinant vaccines. Over the past three decades, many studies have been conducted to produce recombinant vaccines against ND on various platforms, which in many cases have yielded promising results. This article reviews the literature on the production of recombinant ND vaccines. In this regard, while introducing ND and its causative agent, the basics of producing recombinant vaccines and production platforms are explained. The main objective of the article is to highlight the effectiveness of recombinant herbal vaccines against ND.

Citation:

INTRODUCTION

The poultry industry plays a significant role in meeting a large portion of today's human food needs. The extent of this industry and the high percentage of production in a short period of time as well as the low cost of fowl meat production can be considered as the major advantages of this industry [1]. Viral diseases are one of the most important causes of disruption in the production of poultry industry, due to reduction of the production and the increasing mortality rate, the industry suffers from considerable economic losses. Among such viral diseasesa is Newcastle disease (ND) which is an infectious and highly contagious viral disease that causes disease with varying severity and high infectivity in birds, especially poultry [2]. The disease is listed in The World Organization for Animal Health (OIE) and imposes severe economic losses on the poultry industry, and as a result, tackling it is always a priority for many countries [3]. In this regard, many vaccines have been produced, few of which are commercialized and a few are in the testing phase. Killed or attenuated viruses are currently used as ND vaccines [4]. Although these vaccines have often been associated with positive and effective results, the high cost of vaccination, side effects such as reduced egg count, high labor cost, and stress that reduce spawning frequency or increase susceptibility to microbial infections put limits on their application [5].

To overcome these limitations, many efforts have been made in recent years to produce novel types of vaccines with lower costs and high efficiency. One of such strategies is the use of green plants to express disease-causing antigens. This approach, which is a part of recombinant vaccine production technology, has been widely acknowledged by the scientific community and extensive research has been conducted in this field [6]. A recombinant vaccine, often referred to as a subunit vaccine, is an antigen produced by genetic engineering in an appropriate expression system [7]. Since vaccines produced by green plants are most often given orally, they are called recombinant oral vaccines. Theoretically, the genes encoding each protein could be cloned and expressed by recombination techniques in bacteria, yeasts, or mammalian cells. A number of genes encoding surface antigens of viruses, bacteria, and protozoan pathogens have been successfully cloned in cellular expression systems, and the expressed antigens have been used as vaccines [8]. However, plant systems have a unique place among the various expression systems used to produce recombinant vaccines [9]. Transgenic plants that express

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foreign proteins of industrial or medicinal value are a good alternative to fermentation systems.

Various vaccines have been produced temporarily or permanently in plants and it has been shown that these vaccines can maintain the spatial structure necessary to induce immunity in the human or animal body [10]. The main advantage of recombinant herbal vaccines is that in addition to ease of production and use, they stimulate the mucosal immune system, creating a high level of safety for the host. The mucosal immune system is the body's first and most important defense barrier against a variety of pathogens, and most animal pathogens enter the body of livestock and poultry by interacting with this defense system located in the respiratory and gastrointestinal tracts [11]. Moreover, transgenic plants can be produced at low cost and easily stored with no need for cold chain during the transport. In addition to their fast harvest, the simultaneous production of several vaccines is also possible. [12]. In terms of their effectiveness and scalability features, plant-based recombinant vaccines (in both stable transformation and transient expression systems) have been also suggested to combat COVID-19 [13-14].

Given the importance of ND as a limiting factor in the poultry industry and considering the significant advances in the field of recombinant vaccines, this article reviews the principles, advantages and limitations of production of recombinant vaccines against ND in transgenic plants.

ND

ND was first reported in 1926 in Java, Indonesia and Newcastle, England. In the UK, the disease was controlled by establishing quarantine and mass slaughter of the infected poultry, followed by disinfecting the infected nests. However, in Indonesia, the struggle was waged in such a way that the main source of the disease was not destroyed and it can be claimed that the origin of the spread and infection of the disease in the world is from this area. As a result, ND is currently considered worldwide as a limiting factor in poultry production [15]. ND attacks the respiratory system, gastrointestinal tract and the nervous system. Chickens, roosters, turkeys, ducks and other birds could also be affected. The ND virus (NDV) causes mild disease in humans that causes swelling of the conjunctiva. Newcastle virus is sensitive to heat, sunlight and disinfectants. However, it stays in the infected litter for 2 months and in the carcass of a dead poultry for one year [16].

ND symptoms vary depending on the type of the virus, the health and age of the bird, and the host species. The general symptoms include respiratory symptoms such as shortness of breath and coughing, neurological symptoms such as depression, anorexia, fluttering of the wings and paralysis, dizziness of the head and neck, dizziness, tremors, swelling of the eyes and throat, watery and green diarrhea, and abnormalities [17]. Regarding symptoms that depend on the type of the virus, the following should be considered. There are generally three strains of the virus, namely, mesogenic, velogenic, and lentogenic. The virus is transmitted through food poisoning and airborne while aerosol transmission does not usually occur. Symptoms observed after autopsy include swelling of the respiratory tract, inflammation and bleeding in the gastrointestinal tract, the presence of purulent cysts and cheese case in the tracheal mucosa, and exudative discharge at the beginning and along the trachea, especially the tracheal branch. There is no drug treatment for this disease, like most viral diseases and cure is only supportive [18].

NDV

The causative agent of this disease is the paramyxovirus which grows and multiplies well in the egg embryo. Six weeks after the disappearance of clinical signs of the disease, the virus cannot be found in feces and internal organs. There is a risk of transmission of the virus by carcasses, secretions and mucous membranes of the infected poultry's eyes which are sources of the virus. Newcastle virus is extremely sensitive to heat. Wild birds are the source of infection and spread the virus while the virus may pass part of its evolution in the body of such wild birds [19]. NDV is a coated, relatively spherical virus with 8-12-nanometer glycoprotein spikes. The genome of the virus is a single-stranded RNA with a negative polarity and a molecular weight of 5,700 kDa that is fully amplified in the cytoplasm of the host cell. The virus genome contains 15186, 15192, or 15198 nucleotides, depending on the genomic class, encoding six proteins, namely, nucleoprotein, phosphoprotein, matrix protein, fusion protein, hemagglutinin-neuraminidase protein, and a large polymerase protein (Fig. 1) [20].

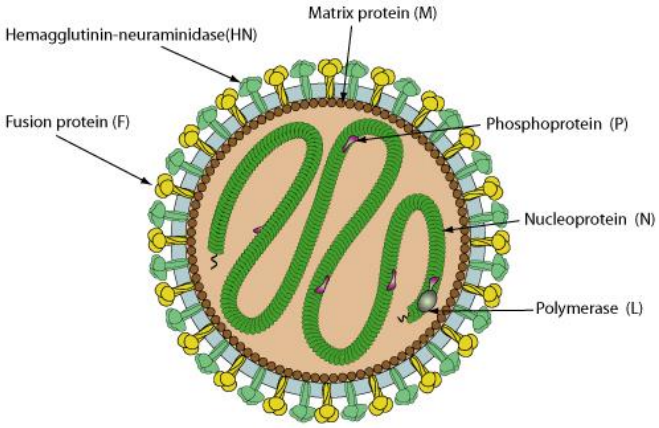

Fig. 1. Schematic representation of NDV (retrieved from expasy.org)

The fusion (F) and hemagglutinin-neuraminidase (HN) proteins are glycoproteins that are important for infectivity and pathogenicity, and both can stimulate the immune system [21]. Amino acids residues 65-81 of protein F and 346-353 of HN protein are known to be the most important immunogenic sites for antibody stimulation [18]. The F and HN proteins form spike-like projections on the outer surface of the viral envelop and are the neutralizing and protective antigens of NDV. The F protein is synthesized as an inactive precursor (F0) that is cleaved by the host cell protease into two biologically active F1 and F2 subunits. The cleavage of the F protein is a prerequisite for the virus entry and cell-to-cell fusion. The sequence of the F protein cleavage site is a well-characterized, major determinant of NDV pathogenicity in chickens. A homotypic interaction between the F and HN proteins is necessary for initiation of the fusion process [22]. The F glycoprotein belongs to the class I fusion protein group [23]. It undergoes a large, irreversible conformational change/refolding event which promotes the merger of the viral and the cellular bilayers to open a pore for delivering the viral genome into the cytoplasm [23].

The HN protein of NDV is a multifunctional protein. It possesses both the receptor recognition and neuraminidase (NA) activities associated with the virus. It recognizes sialic acid-containing receptors on the cell surfaces and promotes the

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fusion activity of the F protein, thereby allowing the virus to penetrate the cell surface. It acts as an NA by removing the sialic acid from the virus progeny particles to prevent self-agglutination of the virus progeny [24]. Thus, the HN protein plays an important role in the viral infection. Although the functions of the HN protein during NDV infection have been well studied, its role in NDV pathogenesis is not known at present. It has been shown that the cleavability of the F protein alone does not convert an otherwise nonpathogenic strain into a highly virulent pathotype [25].

Recombinant Vaccines

A recombinant vaccine is an antigen that is produced using genetic engineering and gene transfer technology in a suitable host, such as bacteria, yeast and plants. Recombinant products, including recombinant vaccines, have emerged after the advent of biotechnology [26]. Benefiting from this technology, many vaccines that have not been possible to be produced economically before have reached the stage of production and application. Fortunately, the technology of making such materials is not too complex and is attainable with moderate expertise and expenditure [27]. Recombinant vaccines are the result of using a part of a pathogen that has antigenic properties and is capable of stimulating the immune system. In fact, the body of the pathogen or its unnecessary parts are removed from the contents of the vaccine. Even in this case, the problem of dealing with the pathogenic organisms remains. Therefore, the target proteins or antigens are produced in other expression systems instead of being extracted from the pathogen. This provides immunization while making the production procedure economically viable [28; 29].

Biotechnology has made it possible to use multiple areas of biology to produce an economical product. For example, recombinant vaccines can theoretically be produced in plants or their fruits which can indirectly transfer a substance to the body by eating the fruit. In fact, with this approach, injectable vaccines can become oral vaccines that are easier to use and more acceptable by the population. Of course, such approaches have not yet been commercialized in the scope of human and animal applications [30].

The process of producing a recombinant vaccine is very long and complicated. Researchers must first identify the most immunogenic component of microorganisms. These are usually membrane proteins or glycoproteins. They should then identify the locus and sequence of the gene within the genome and then transfer the recombinant plasmids to a host cell, suitable for protein production [31]. If considered successful in terms of economic production, a candidate protein for a vaccine, a cell bank, and a plasmid bank of the recombinant cells will be created and used for later steps. Many steps must be taken to confirm that the vaccine is effective, efficient, and harmless to humans or a range of people over several years. A large amount of investment is needed for the industrial and commercial production of a vaccine. Part of this investment should be considered to create a completely standard environment in accordance with Good Manufacturing Practice (GMP) [32].

Recombinant Vaccine Production Platforms

The choice of expression system to produce recombinant subunit vaccines depends on the characteristics of the protein to be produced. In this regard, several issues should be considered, such as the level of expression, the need for post-translational changes, considerations regarding mass production and production costs [33]. The host may affect the immunogenicity and protective power of the product. For example, an antigen may be highly expressed in a bacterium; however, it may not be properly folded. Or the antigen's immunogenicity may be highly dependent on post-translational modifications. Before the use of green plants, four main biological systems were used to produce recombinant subunit vaccines: 1. Bacterial expression system, 2- Yeast expression system, 3- Insect cell expression system, and 4- Mammalian cell expression system. Each of these systems has advantages and disadvantages, as summarized in Table 1.

Bacterial expression systems are the easiest to use. The expression level of recombinant proteins in bacteria is also very high. The use of these systems is desirable when the recombinant protein does not require post-translational modifications. Rapid growth, ease of cultivation, fast protein expression and high production rate are the most important advantages of this system. However, the inability of this system to produce proteins with complex structures, the presence of bacterial endotoxins along with the manufactured products, the need for the necessary equipment and skilled labor are among the disadvantages of this system [34]. Escherichia coli is one of the first and most widely used hosts for the production of recombinant proteins. Prokaryotic expression systems using different strains of E. coli have been used to express a large number of commercially available proteins [35].

Yeast systems are another potential source of recombinant vaccines. Ease of working with them, ability to implement many post-translational changes, extensive knowledge of genetics and physiology and their performance in industrial fermentation processes, high speed and relatively low cost in the production of recombinant proteins are among the advantages of this system [36]. Yeast as a eukaryotic expression system can make post-translational changes including glycosylation; however, their glycosylation pattern is different from that of higher eukaryotes, and as a result, their products are affected with respect to the solubility, temperature stability, and half-life, causing safety problems for the consumers. Therefore, if glycosylation is an important issue in relation to production of an antigen, then another host, such as mammalian cell culture, must be considered [37].

The insect expression system, most-commonly known as the baculovirus system, is another way to make a recombinant vaccine. The advantage of this expression system is that it achieves a very high level of foreign gene expression, compared to the mammalian cell culture systems. Insect cells can also make a variety of post-translational changes; however, the glycosylation pattern of insects also differs from that of the mammalian cells [38]. The baculovirus expression system is a safe method because baculoviruses cannot infect vertebrates. Also, the precursors used in these systems are not active in mammalian cells [39].

The use of mammalian cell lines is an alternative versatile system for the production of recombinant proteins, and so far a variety of therapeutic proteins have been produced by such systems. The implementation of appropriate post-translational changes such as glycosylation, phosphorylation and addition of fatty acid chains as well as secretion of proteins into defined and serum-free media can enhance the safety of the final product and thus facilitate the ensued purification processes [40]. However, culturing animal cells and producing transgenic animals to produce recombinant proteins can only be done on a very limited scale due to its high costs and time consumption [41]. As a result, although different types of viral proteins have been produced using mammalian cell cultures, none of the

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vaccines produced in mammalian cells have yet been licensed for mass production and consumption. Another factor that increases the production costs of recombinant proteins in mammalian cells is the need to confirm that the products are free of viruses and carcinogens that could be originated from the cells used to produce them [42].

Table 1. Comparison of recombinant protein production systems and vaccines.

Platform	Cost	Time	Capacity	Quality	Glycosylation	Contamination risk
Bacteria	Low	Short	High	Low	No	Endotoxin
Yeast	Moderate	Moderate	High	Moderate	Inaccurate	Low risk
Mammalian cell	High	Long	Very low	Very high	Accurate	Virus/prion
Transgenic animals	High	Very long	Low	Very high	Accurate	Virus/prion
Plant cell culture	Moderate	Moderate	Moderate	High	Slight difference	Low risk
Transgenic plants	Very low	Long	Very high	High	Slight difference	Low risk

In recent years, transgenic plants have been considered by many scientists as a suitable candidate for the production of recombinant vaccines. Recombinant plant vaccines are those vaccines in which genes encoding viral and bacterial antigens are genetically engineered into transgenic plants [8]. With the advent of plant genetic engineering, efforts have been made to add plants as vaccine factories. Here, the goal is to produce plant organs, including fruits, leaves, or to use crude extracts or purified proteins as an immunizing agent [43]. The production of vaccines in plants can many benefits such as the ease of supply of raw materials such as sunlight, water and minerals which them inexpensive tools for the proper expression and processing of complex proteins. The expression of vaccines in plant tissues reduces the risk of infection with animal pathogens and provides a stable environment against heat. Moreover, by enabling the oral administration of the vaccine, the risks associated with needle injections would be reduced. Expression of the A antigen protein of Streptococcus mutans in tobacco plant in 1990 was the first case of a vaccine production in plants. Furthermore, Hepatitis B (HBsAg) surface antigen, enterotoxin responsible for diarrhea, Norwalk virus coat protein and rabies virus glycoprotein have also confirmed. Plant-produced proteins are shown to stimulate mucosal specific IgA and serum IgG antigens when administered orally as vaccines in humans and mice [26].

Among the various systems used, systems based on the use of transgenic plants have higher advantages over yeast and bacterial systems. The use of plants for the production of vaccines has the following advantages: 1- Plant vaccines can stimulate the blood immune system, the cellular immune system as well as the mucosal immune system 2- Due to the plant cell wall, the plant produces antigen against the plant which protects it and is gradually released in the lymph and then in the blood; 3. Viral antigens in plants bind exactly as they do in humans during a disease and become a subviral particle [12]; 4. The cost of producing vaccines by transgenic plants is much lower than conventional methods since there is no other costs than the usual cost of planting and harvesting the crops; 5- Storage of products or plant extracts containing an antigen can be done at room temperature without the need for any special equipment; 6. Plants are not host to animal viruses; therefore, there is no risk of such viral infections; 7. Vaccines produced in plants can be used as a supplement in livestock and poultry diets [44].

Reviewing the Literature on Anti-ND Recombinant Plant Vaccines

Yang *et al*. [45] developed a recombinant ND vaccine in rice. According to these researchers, transgenic plants are suitable bioreactors for the production of various medicinal proteins, including recombinant vaccines. In this study, two gene cassettes (pUNDVF and pGNDVF) contained an NDV fusion protein gene under the control of maize ubiquitin promoter and rice glutenin in rice. Agrobacterium was used for the gene transfer and 12 transgenic lines were obtained. Using PCR tests, it was determined that the F fusion gene was integrated in the rice genome. Moreover, Western blotting and ELISA indicated that the gene was produced in rice leaves and seeds. The results of experiments on mice showed that the obtained recombinant vaccine has proper immunogenicity proved by subcutaneous injection of the recombinant vaccine into the mice and detection of specific antibodies against the antigen. In another study by Berinstein *et al*. [46], the researchers transferred the genes producing the F and HN proteins of NDV to a potato plant and after feeding the mice with it, they observed mucosal immunity against NDV has been developed in the animals.

Hahn *et al*. [47] were able to express NDV-causing HN protein in tobacco plants using Agrobacterium EHA105. Using PCR and Southern blotting, the integration of the gene in the tobacco genome was confirmed. Transgene expression was also confirmed in transgenic lines using Northern blot. Recombinant HN protein was also detected in transgenic lines using Western blotting. The highest expression level of this protein was about 0.069 of total soluble protein in transgenic tobacco leaves. The results of ELISA showed that the recombinant protein extracted from the transgenic plant had normal immunogenic activity. The researchers then used the recombinant protein to study its immunogenicity in 6-week-old chickens and showed that it had a high potential to induce immune responses, indicating the high potential of tobacco plant to produce recombinant vaccines.

Sandhu *et al*. [48] used A. tumefaciens genus GV3101 for a transgenic tomato to express glycoprotein F as a recombinant oral vaccine. The immunogenicity of the recombinant vaccine was evaluated by feeding 25 mice with the transgenic tomato fruits over a period of 28 days. The results showed that the transgenic fruits containing glycoprotein F induced blood and mucosal immune responses in the treated mice. Among 25 mice studied, strong humoral response was observed in 22 and among these, IgA mucosal antibody was observed in 18 mice. However, no IgA antibodies were produced in any of the control mice. The researchers then concluded that immunization of mice through oral administration of the recombinant vaccine was an effective way to build immunity against severe respiratory distress.

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Lai *et al*. [49] used the medicinal plant *Centella asiatica* to express HN which is the most important target protein of NDV. To do this, the complete HN gene was inserted into a plant expression gene construct under the control of 35S promoter and a *GFP* reporter gene. Callus particle bombardment method was used for the gene transfer. Transgenic plants were screened using *GFP* in a culture medium containing hygromycin. Transcripts of this gene were detected in transgenic lines using RT-PCR. Dot blot analysis also confirmed the expression of the gene in transgenic lines. This was the first time a medicinal plant had been used to make a recombinant vaccine.

Guerrero-Andrade *et al*. [50] used the expression of the F protein-encoding gene in maize to produce the recombinant ND vaccine. Transgenic maize plants were regenerated and protein F expression in them was confirmed by Western blotting. The ability of the recombinant vaccine to induce an immune response in poultry was then investigated. For this purpose, 45-day-old healthy chickens were fed with the transgenic corn extract as well as wild corn. The production of specific antibodies in the tested chickens was assessed by ELISA. The results showed that in all cases, specific anti-F antibodies were produced in the treated chickens. A challenge test was also performed to evaluate the efficacy of this recombinant vaccine in protecting chickens against ND. Three groups of chickens were used for this purpose, namely, chickens injected with the transgenic corn extract, chickens injected with non-transgenic corn extract, and chickens injected with the common ND vaccine. ND pathogen was then injected into all three groups. All chickens in the first and third groups were fully protected against the disease while all members of the second group became infected and showed symptoms within 3 days.

Zhao and Hammond [51] studied the production of a recombinant ND vaccine using the epitope display of cucumber mosaic virus. To do this, a peptide fusion of cucumber mosaic virus capsid protein was designed to express a 17-amino acid epitope of F protein or an 8-amino acid epitope of HN protein. Protein extensions including F, HN and HN2 (double HN replication) were then transferred to tobacco leaves (Nicotiana benthamiana) using Ixora strain of cucumber mosaic virus. Once the epitopes were in the internal motif, the modified virus was contagious and both proteins were identified using anti-Newcastle serum. However, in some plants, one or more amino acids were removed. The use of duplicate HT epitope doubled the infectivity and survival of the virus.

The United States Department of Agriculture (USDA) has issued the first license for a plant cell to produce ND Vaccine by Dow AgroSciences LLC in 2006. The chicken vaccine is the first fully-licensed plant-cell-produced vaccine for animals in the United States and the first plant-made product to be licensed by USDA's Animal and Plant Health Inspection Service. The vaccine contains the major immunogenic protein of NDV and does not contain any whole NDV, live or killed. Once the chicken's cells take up the protein in the vaccine, they trigger a protective immune response [52].

Conclusion and Future Research Agenda

Among the various expression systems used to produce recombinant vaccines, plant systems have been considered advantageous by many researchers for reasons such as their eukaryotic nature, relatively low production costs and lack of contamination with human and animal pathogens. Doing a transgenic plant project without a clear purpose and proper design of the gene structure is nothing but a waste of time and assets. In this regard, the design of the gene structure should ensure that the recombinant protein has effective immunogenicity while large amounts of the recombinant protein are produced in the transgenic plant tissues.

In general, there are several considerations to further improve the production of the recombinant ND vaccine. Therefore, the following are suggested as potential strategies for obtaining an effective recombinant vaccine against ND:

- Evaluation of the immunogenicity in chicken by oral and injection routes.
- Including a challenge test of chickens treated with a recombinant vaccine and evaluating whether the vaccine prevents the occurrence of symptoms of the disease.
- Evaluation of producing a recombinant NDV vaccine in plants such as corn that can be used as raw poultry feed.
- Production of recombinant ND vaccines in microorganisms that can be used as probiotics.
- Inclusion of secretory peptides to facilitate the purification of the recombinant protein in capillary root culture.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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