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REVIEW

Status updates of Newcastle disease and amelioration effects of medicinal plants against Newcastle disease virus: A review

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Summary. – Recently, medicinal plants are achieving great interest because of their use in ethno medicine treatment of different common diseases and also other medicinal assertions are now reinforced by comprehensive scientific evidence. Almost 82 research articles and abstracts published, so far, were screened for evaluating antiviral efficiency of various plant samples and 23 different plants were found to be traditionally used against Newcastle disease (ND). ND is a most transmissible viral disease of avian species caused by virulent strain of Avula virus from the *Paramyxoviridae* family. The first epidemic of ND was perceived in Java, Indonesia and England in year 1926. ND causes great economic loses to the commercial poultry farmers around the world. Medicinal plants are traditionally used in the control of viral or other diseases and infections. Plants have been found useful in treating many microbial diseases in man and animals caused by bacteria and viruses. The ability to synthesize compounds retaining antiviral potential by secondary metabolism makes plants a vital source of pharmaceutical and therapeutic products, which can reduce chemotherapeutic load in birds. Current studies signify that the natural products posses a rich potential source of new antiviral compounds. Further ethnobotanical studies and laboratory investigations are established to identify species having potential to improve ND control.

Keywords: Newcastle disease; poultry; medicinal plants; antiviral efficacy; phytochemicals

Contents:

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Abbreviations: ECE = embryonated chicken eggs; ND = Newcastle disease; vNDV = velogenic NDV; NDV = ND virus; vvNDV = viscerotropic velogenic NDV; nvNDV = neurotropic velogenic NDV; OIE = Office International des Epizooties

1. Introduction

Newcastle disease (ND) is an important viral disease of poultry and other avian species regardless of their age and sex (Yune and Abdela, 2017). ND is often called Ranikhait as vernacular name in Pakistan (Narayanan *et al.*, 2010). First it was identified in Indonesia, Java and England in 1926 by Office International des Epizooties (OIE, 2012). However, there was an earlier report of same outbreak in Central Europe. ND was not reported in poultry before the year 1926. The name "Newcastle disease" (after the first outbreak) was professed by Doyle as a temporary measure to avoid confusion with other diseases (Doyle, 1935). ND is critical health problem in avian industry due to high mortality and morbidity worldwide (Khan *et al.*, 2010). Due to the severe nature of ND and the related consequences, NDV is counted in "listed" agents (reportable disease) by OIE (Boynukara *et al.*, 2013). OIE has the duty of ND epidemics notification (Cao *et al.*, 2013), when it meets certain criteria of virulence (Munir *et al.*, 2012).

1.1 Etiology of NDV

Newcastle disease virus (NDV) is a non-segmented, single-stranded, negative-sense, enveloped RNA virus belonging to the *Paramyxoviridae* family, the *Paramyxovirinae* subfamily and the genus *Avula virus* (Ashraf *et al.*, 2016). The virus exists in ten serotypes APMV-1 to 10 and NDV is synonymous with avian paramyxovirus type 1 (APMV-1). Only diseases with the virulent type APMV-1 are accounted as ND (Waheed *et al.*, 2013). NDV viral particles are observed by electron microscopy as pleomorphic, varying from roughly spherical to filamentous with varying lengths (Catroxo *et al.*, 2011). Spikes of approximately 8–12 nm are present on the viral surface. The "herring bone"-like nucleocapsid (about 13–18 nm in diameter) can be seen either free or emerging from disrupted viral particles (Alexander, 1997). Genome with length of around 15.2 kb (Zhang *et al.*, 2012) encodes for six structural and two non-structural proteins (Choi *et al.*, 2010). Six proteins, nucleoprotein, large RNA polymerase (L), fusion protein (F), hemagglutinin-neuraminidase, matrix protein (M) and phospho-protein, are encoded in 3' to 5' direction (Al-Habeeb *et al.*, 2013). NP is most important protein which forms the nucleocapsid helical core of NDV and induces antibody production in chickens. HN and F proteins are most significant in identification and pathogenecity of the virus. F protein is important for pathogenic and virulence properties. HN is vital for attachment and penetrating the host cell (United States Animal Health Association-USAHA, 2008). On the basis of their pathological index NDV is divided into three pathotype groups, which are lentogenic, mesogenic and velogenic pathotypes. Lentogenic strains cause mild respiratory infections. Mesogenic strains cause nervous and respiratory signs with mortality rates dependent on age of susceptible species. Velogenic NDV (vNDV) is virulent strain which causes severe mortality. The velogenic strains may be divided into neurotropic velogenic NDV (nvNDV) or viscerotropic velogenic NDV (vvNDV) types (OIE, 2012). According to field studies in Pakistan, the incidence of velogenic type was 5%, mesogenic type 55% and lentogenic type 40% (Waheed *et al.*, 2013). In severe cases the morbidity and mortality may reach up to 100%.

1.2 Epidemiology of NDV

Newcastle disease is endemic to various parts of the world. NDV affects more than 250 species of 27 orders of birds. ND, the most serious poultry disease kills in average 70 to 80% of the unvaccinated rural poultry flocks every year. Many evidences show that all avian species are susceptible to NDV including cormorants, pigeons, chickens, turkeys, parrots, migratory waterfowl, penguins and shorebirds (Institute for International Cooperation in Animal Science – CFSPH, 2016). Cormorants, pigeons, and imported psittacine are most susceptible to this virus and are also the major transmitters of NDV in poultry (Patti, 2014). Chickens are very vulnerable while the aquatic birds are the most resistant. Tame and exotic birds are mostly resistant (Erickson *et al.*, 1977). Virus shedding is short in *Galliformes* and different song birds while long lasting shedding is seen in *Columbiformes* (pigeons and doves) and *Passeriformes* with damaged kidneys (Kaleta and Baldauf, 1998).

Humans are also susceptible to NDV. NDV causes conjunctivitis in individuals highly exposed to virus for a long time. Mostly, laboratory workers and vaccinators are infected by this virus. In humans mild or self-limited influenza like symptoms with fever and headache have been diagnosed (Alexander, 2000; OIE, 2012).

1.3 Clinical signs

The clinical signs are dependent upon age and species of the host, viral strain, immune status of the host and environmental conditions (Al-Habeeb *et al.*, 2013). The clinical signs of ND are categorized into reproductive, respiratory, nervous and enteric signs.

Clinical signs of reproductive organ infection include: drop in egg number, misshapen eggs, rough or stumpy shelled eggs, and decrease in albumen quality. Sometimes egg production returns to normal level after 3–4 weeks (Yan *et al.*, 2011).

The respiratory infection signs include mild sneezing and gasping for air. More serious signs are sneezing, coughing, nasal discharges and respiration distress with open beak breathing. Inhaling can be accompanied by a rattling sound. Head shaking, with dislodged mucus form the respiratory airways and sometimes mucopurulent conjunctivitis may appear (Fig. 1). Nervous infection symptoms are tremors, paralyzed wings and legs, twisting and circling of neck (Fig. 2) (Bhaiyat *et al.*, 1994). In critical cases, death occurs immediately without the appearance of any signs (Ashraf and Shah, 2014). The enteric infection is accompanied by greenish diarrhea (McFerran and McCracken, 1988).

Viscerotropic velogenic (extremely virulent type) type of disease may appear suddenly, with high mortality with absence of other clinical signs (Beard and Hanson, 1984). Mortality is up to 100% in virulent forms of the disease (Martin, 1992). More often death occurs within 4–8 days preceded by weakness and fatigue. Varying levels of depression and inappetence are observed. Sometimes abandonment of egg laying may occur. Eggs display an altered shape, color and watery albumen of egg. Other signs as edema of head and tissues around the eyes, increase in respiration rate, watery greenish diarrhea, sometimes with blood may be observed. The common symptoms begin with loss of appetite, thirst, dehydration, emaciation with high body temperature. Somnolence, fluffed feathers, listlessness, huddling, progressing to complete depression, change of voice, diffuse cyanotic coloration of the skin especially in comb and wattles may be seen after infection by this virus type (Fig. 3) (McFerran and McCracken, 1988).

In the mesogenic type, mortality is up to 50% with acute respiratory disease and decline in egg production with low quality which may occur for about 1–3 weeks (Hadipour *et al.*, 2011). Respiratory signs of coughing, sneezing, but no gasping and rale is present in low virulence infections.

Fig. 1

Respiratory clinical signs of Newcastle disease of chickens
Conjunctivitis (Lucas and Jamroz, 1961).

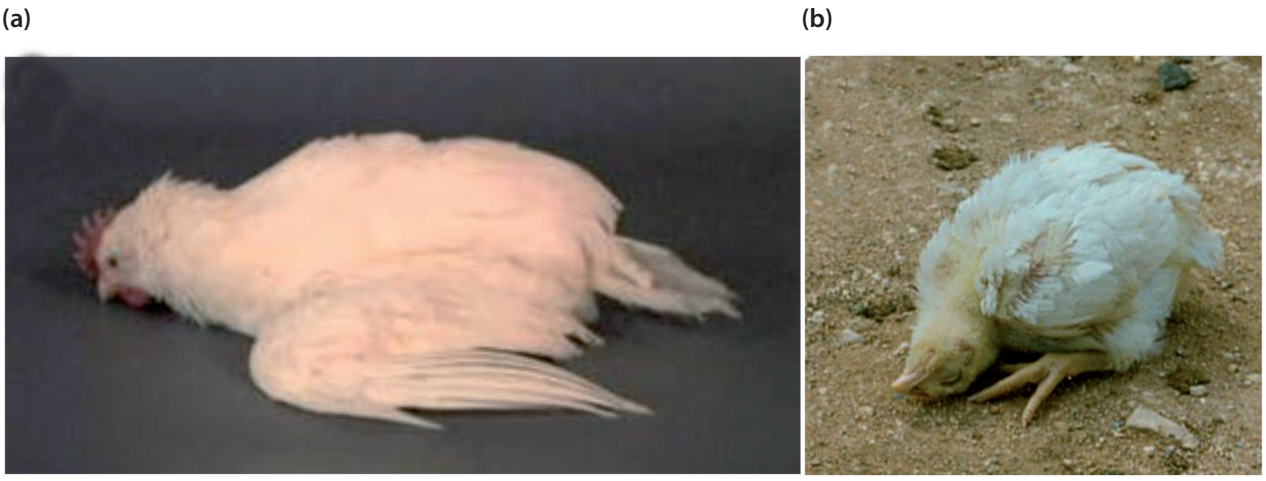

Fig. 2

Nervous clinical signs of Newcastle disease of chickens
(a) Paralysis (neurotropic); **(b)** twisted neck (nervous disorder) (http://partnersah.vet.cornell.edu/avian-atlas/taxonomy/term/562).

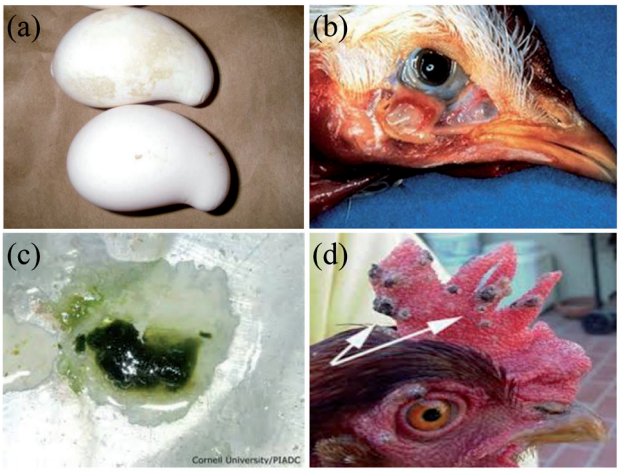

Fig. 3

Velogenic infection clinical signs of Newcastle disease of chickens
(a) Misshappen eggs (Piller, 2010); **(b)** internal and external hemorrhage (Herenda and Chamber, 1994); **(c)** green watery diarhhea (Lucas and Jamroz, 1961); **(d)** comb cyanosis (Admin, 2017).

Nervous symptoms are not common (Jordan, 1990). Death is usually rare in fowl, except in very young and vulnerable birds, or in worsened conditions (Alexander, 1993).

In lentogenic disease, adults are generally not harmed. In young birds, severe respiratory disease complications can be seen, often resulting in death. Vaccination or infection of broilers infected by these viruses can progress to septicemia (Alexander, 1993).

Shedding of the virus mostly occurs in birds before and after the clinical sign appearance. Virus shedding appears anywhere from one week to a year depending upon the species of the bird, e.g. chickens are more prone to infection than ducks (Kapczynski *et al.*, 2013). The pigeons infected by variant of paramyxovirus (PMV1) can cause morbidity up to 80%. Ducks and geese are usually resistant to NDV with morbidity less than 10%. Canaries are susceptible, showing a mild disease, although the mortality varies from 20% to 30% (Canadian Food Inspection Agency – CFIA, 2014).

1.4 Transmission

The disease is spread by direct contact with feces, droppings, respiratory secretions, egg shells and feathers of infected birds. It can also be transmitted from smuggled birds from area where NDV is endemic (Perozo *et al.*, 2008). Movement of contaminated people, clothes, trays and vehicles can also transmit the virus (Hitchner, 2004). Air borne transmission is most common way of infection (Li X, 2009). Transmission from infectious feces occurs by insects, rodents, fleas, dogs or scavengers (Ullah *et al.*, 2004).

The vaccination of NDV is helpful to prevent the disease but not infection and excretion of the virus. However, vaccination may significantly reduce the time of virus shedding (Alexander *et al.*, 1999). Vaccines and antibiotics result in the development of resistance in birds against these allopathic medicines, and residues of drugs in both eggs and meat, are detrimental to human health. The practice with different medicinal plants to control this virus is considered as a compatible approach, because nowadays plants have been involved in control of various infectious and non-infectious ailments. Secondary metabolites present in plants have been considered as innovative antiviral agents, and can lessen chemotherapeutics load in birds. Therefore, the search for highly selective and non-toxic antiviral plant compounds is urgently needed in view of spread of ND throughout the world (Ocazionez *et al.*, 2010).

2. Global distribution of Newcastle disease

Since in 1926 form its recognition, ND is regarded as being highly prevalent in many countries and occurs worldwide. Virulent NDV is endemic to Asia, Africa, South and North America, most parts of Mexico, Europe, Canada, and USA (Naveen *et al.*, 2013). All continents of the globe continually document the presence of ND (Munir *et al.*, 2012). About 20 years after its recognition it becomes a panzootic (Fig. 4).

The first epidemic outbreak in Java, Indonesia and in Europe from Newcastle-upon-Tyne, England occurred in 1926 and spread very slowly across the globe until late 1950s (Qiu *et al.*, 2011). ND outbreak in Middle East began in late 1960s and spreads to other countries untill 1973 and in 1981, ND reached also Europe (Mase *et al.*, 2002). The third drastic outburst appeared in Middle East during late 1970's. Then disease progressed until late 1980s in Far East, Europe and South Africa (Qiu *et al.*, 2011). In early 1990's incidence of this disease increased in Western Europe culminating with 239 occurrences in European Union countries in 1994.

ND has been reported in 1995 in wild birds in Canada, and in 2002–2003, an epidemic outbreak in California resulted in great losses that were estimated at 5 billion USD and the death of more than 3 million birds. Currently, in the United States, Western Europe, and Canada the disease is under control, however it endures in some regions of Asia, South America and Africa. The risk of reappearance of an outbreak is still high, since wild birds are asymptomatic carriers of the virus (CFIA, 2014).

3. Economic losses in Pakistan

Geographically, Pakistan is situated (33°40'N and 73°10'E) at the crossroads of the central areas of Asia. From 2009 to

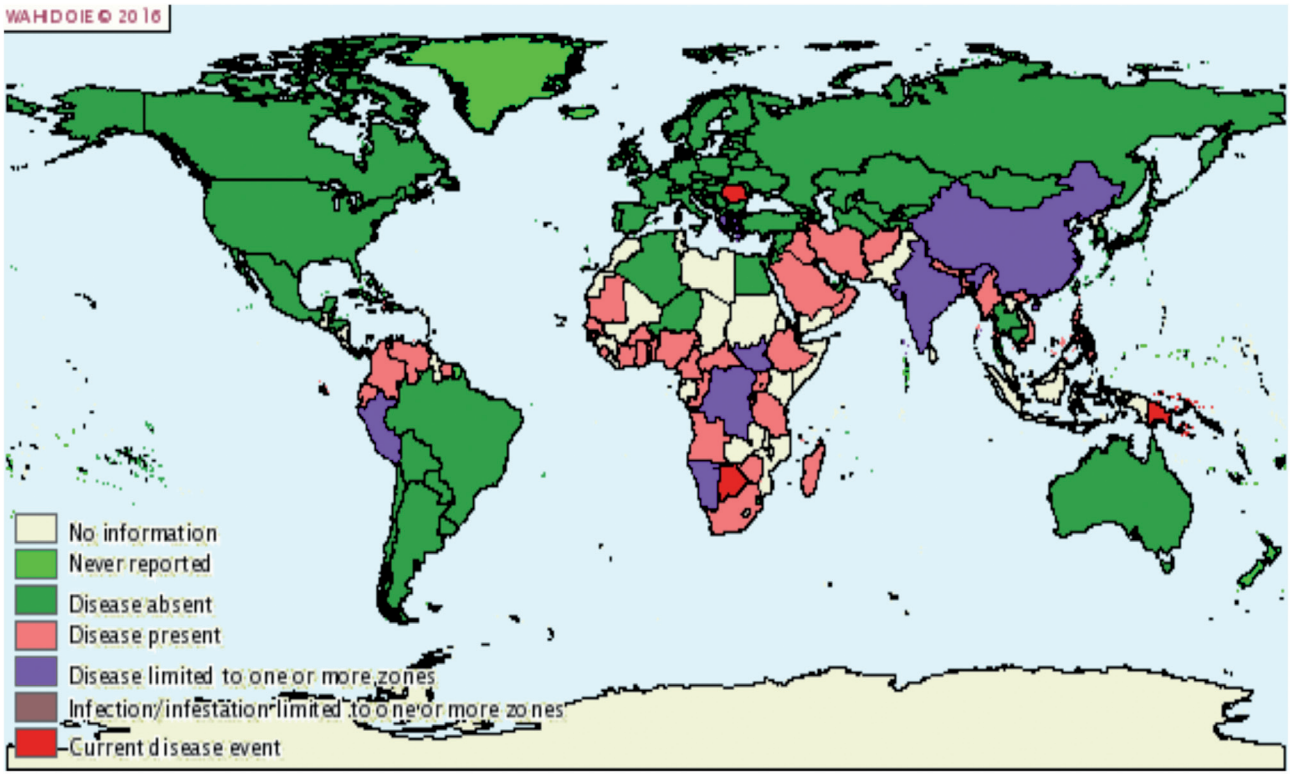

Fig. 4

Prevalence of Newcastle disease in 2015

World Animal Health Information Database (WAHID Interface), Version 1 Copyright © World Organization for Animal Health (OIE); www.old.caribvet.net/en/diseases/newcastlediseases/geographical-distribution.

mid 2012, high amount of ND outbreaks have been documented (OIE, 2013). ND causes massive economic losses to commercial poultry. In Pakistan a periodic form of ND appears throughout the year; however only a limited number of epidemics are reported (Munir *et al.*, 2012).

In the period of inadequacy, poultry eggs and meat are valuable protein source in Pakistan. Poultry industry is the back bone of rural as well as commercial economy in Pakistan. In Pakistan there is around 1105,91 millions of poultry, among which rural poultry is about 152,44 millions. It contributes to an energetic part of the village economy with the participation of up to 3,611 million eggs and 100,41 metric tons of the total poultry meat (Khan *et al.*, 2010). This sector is source of work and income for about 1,5 million people. Its abundance in agriculture is 56.3%, while the livestock forms only 11.5%. Poultry had a 28.5% share in meat production and in GDP at constant cost factor of 11.8 %. Fast growth of about 8–10% every year in poultry sector, indicates its inherent prospective. According to currently conducted survey, the present investment in the Pakistan poultry industry is about 200 billion USD (ESP, 2015–2016).

In Pakistan ND is the top ranking infection of rural poultry (Khan *et al.*, 2011). ND is reported as main respiratory distress causing agent in different areas (Ahmed *et al.*, 2009). Velogenic NDV and influenza with secondary bacterial infection were involved in epidemics in Smaundari, Kamalia, and Gojra in province Punjab. Incidence of ND in Faiyumi chickens and native breeds of rural poultry in district Sheikhupura has been estimated to 40.33% (Mustafa and Ali, 2005). In Faisalabad, the seroprevalence of NDV antibodies in broilers was 98.07% and in layers 100% (Numan *et al.*, 2005). According to Mustafa Kamal, convener of the disease control committee of the Pakistan Poultry Association, farmers in this country have faced losses of more than five million USD since an outbreak of NDV in 2011. Mortality ratio still occurs at 10–20% in the cities of the provinces of Punjab and Khyber PakhtunKhwa, Quetta and Karachi (Kamal, 2013). During 2012, in Jallo Wildlife Park Lahore, Pakistan the virulent velogenic strain of NDV took lives of 190 peacocks, and caused 100% mortality in other birds (Munir *et al.*, 2012) (Fig. 5).

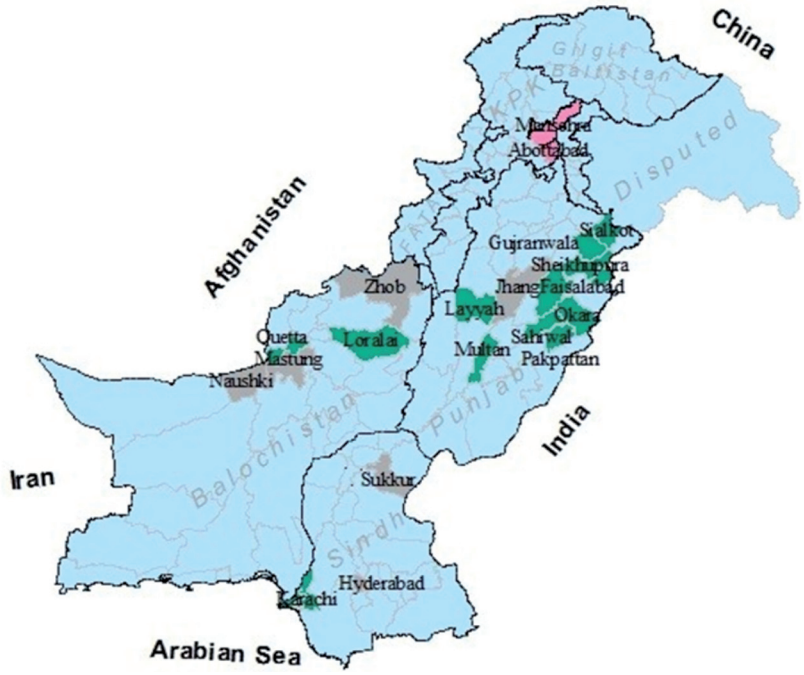

Fig. 5

Geographical sites of NDV in Pakistan (Shabbir *et al.*, 2013)

Plants were used as traditional medicine and petition for natural and herbal products since early civilization and recently their use has been reintroduced. Approximately 70–95% of the people in world depend on herbs for primary dealing of ailments (Robinson and Zhang, 2011). It was observed that 25% of total drugs used in the world contain antivirals from plants. The 60% of anticancer and 75% of infectious disease drugs are the derivatives of natural ingredients which are more suitable, less toxic, and less expensive than synthetic drugs. Investigation conveyed that potential antiviral components from plants are present in crude extracts, essential oils or purified compounds from which secondary metabolites like flavonoid, phenolic and anti oxidising compounds are used as antiviral agents for NDV (Newman and Cragg, 2007).

4. Pathophysiology of NDV

The virus enters the organism by respiratory or intestinal tract. In trachea the virus spreads by cell-to-cell infection or ciliary actions. Subsequent spread is largely governed by strain virulence. While lentogenic strains are present only at low titers in the circulation, mesogenic strains spread to kidney, lungs, bursa, and spleen. Virulent virus can be found within 22 to 44 h in practically all tissues, with highest titers in the thymus, and lowest in muscles and brain. During second multiplication, the virus is released into blood circulation again and the clinical symptoms appear. The virus is excreted into environment by feaces. Some viruses reach the target organs very fast and the birds die without showing any symptoms of disease (Kouwenhoven *et al.*, 1993). Incubation period depends upon the host species, age and strain of the virus. The OIE (2013) gives 21 day period duration for ND. After natural exposure to vNDV, incubation from 2–5 days or longer has been reported, with an average of 5–6 days (Alexander and Senne, 2008).

Replication, transcription and translation of NDV takes place in cytoplasm of the host cell, viral constituents accumulate at the plasma membrane and the virus is released by budding (Zanetti *et al.*, 2003). The NDV particles contain precursor glycoprotein F0, which is an important pathogenic marker for NDV (Madadgar *et al.*, 2013). F0 is cleaved into F1 and F2 proteins. Two pairs of basic amino acids of F0 protein are cleaved by host proteases (Pham *et al.*, 2005). Trypsin is responsible for cleavage of F0 and infectivity induction in non-infectious viruses (Nagai *et al.*, 1976). Cleavage of the F0 molecule was associated with the virulence of viruses *in vivo.* Viral particles containing F_0 molecules are highly contagious for chickens. F_0 can be cleaved by host's protease present in wide range of cells and tissues. This cleavage allows viruses to spread in the hosts' body and damage vital organs. Low

Table 1. Antiviral activity of plant specific parts used against viruses

No.	Plant name	Part used	Study attentive	References
1.	*Azidarachta indica*	leaves, stem	NDV	Waafa *et al.*, 2007
2.	*Acacia nilotica*	stem, leaves	NDV	Saeed, 2007
3.	*Adansonia digitata*	bark	NDV	Sulaiman *et al.*, 2011
4.	*Anthocleista nobilis*	root	NDV	Ayodele *et al.*, 2012
5.	*Aloe secundiflora*	gel	influenza virus, NDV, HSV-1, HSV-2	Waihenya *et al.*, 2002
6.	*Aloe hijazensis*	flower, leaves	NDV	Abd-Alla *et al.*, 2012
7.	*Artemisia annua* L.	flower, leaves, fruits	NDV	Liu and Genqiang, 2009
8.	*Curcuma longa*	aerial parts	MDV, NDV, immune response	Madbouly *et al.*, 2011
9.	*Commiphora swynnertonii*	bark, leaves, resin, stem, root	NDV	Bakari *et al.*, 2012
10.	*Cladosiphon okamuranus*	cell wall	NDV	Elizondo-Gonzalez *et al.*, 2012
11.	*Capsicum spp.*		variety of viruses	Lans *et al.,* 2007
12.	*Cucumis metuliferus*	ripe fruit	NDV	Chen *et al.*, 2010
13.	*Cassia tora*		NDV	Lans, 2003
14.	*Euphobia ingens*	branches	NDV	Lans *et al.,* 2007
15.	*Echinacea purpurea*	aerial parts	improve resistance against NDV, food uptake, decrease of mortality	Fard *et al.*, 2010
16.	*Glycyrrhiza glabra*	root	inhibition of virus gene expression, replication, attachment	Omer *et al.*, 2014
17.	*Momordica balsamina*	fruit pulp, leaves	NDV	Chollom *et al.*, 2012
18.	*Moringa oleifera*	seeds	NDV	Chollom *et al.*, 2012
19.	*Nauclea latifolia*	leaves	NDV	Onu *et al.*, 2014
20.	*Ocimum sanctum*	leaves	NDV	Jayati *et al.*, 2013
21.	*Psidium guajava*	leaves	NDV	Chollom *et al.*, 2012
22.	*Thymus vulgaris*	oil	NDV, HSV-1/HSV-2	Rezatofighi *et al.*, 2014
23.	*Withania somnifera*	leaves, roots	NDV	Mustaq *et al.*, 2012

virulent strains show low sensitivity towards host proteases so damage is not so severe and it is restricted to only certain types of cells.

Lysine (K) or arginine (R), and phenylalanine (F) localised at the position 113–116, 117 are important amino acids of virulent NDV. In virulent strains, existence of basic amino acids at these sites means that cleavage can be affected by proteases present in host tissues (OIE, 2012). OIE accepts the cleavage sequence of F protein as key factor for virulence identification.

5. Prevention and mechanisms in the treatment of NDV

Standard precautionary procedures are necessary to avert ND in flocks. Birds from commercial farms should be separated from the domestic birds, pet birds and wild birds. Workers should also evade contact with any birds outside the farm. Birds should be kept in special proof houses with minimized movement, they should be provided with sterilised food and water supplies and clean medical kits are used before entering the farm. Pests like insects and mice must be controlled and employees if possible, should change clothing before entering the farm (Ashraf and Shah, 2014).

Vaccines are used to prevent the ND all over the world (Shim *et al.*, 2011; Xiao *et al.*, 2013). The vaccination can prevent the birds from clinical signs but cannot stop the main source of infection which is virus replication and shedding (Chukwudi *et al.*, 2012). Anti-NDV antibody concentrations significantly maintain the anti-NDV maternal antibody titers of progeny which protect the chicks from illness in first week of life. Outbreaks are constantly occurring despite of extensive vaccination (Shabbir *et al.*, 2012). Poultry producers are using different combinations of live and inactivated vaccines in a flock to overwhelm this problem.

5.1 Plants used in NDV treatment

World Health Organization (WHO, 2008) estimated that 80% of the world depends on traditional methods as their primary health care according to geographical restraints in Asian and African countries (Meneses *et al.*, 2009). Based on knowledge, experience and indigenous cultural beliefs in traditional medicine is used to prevent, treat and diagnose

physical and mental illnesses and maintain human health (WHO, 2008). Today there is a huge collection of medicinal plants with broad spectrum of antiviral activity. Crude drugs from a variety of plants have been formulated and used for centuries against several human illnesses and diseases. Plants indeed provide an enormous source of novel compounds that may have the potential to treat diseases (Newman and Cragg, 2007).

6. Overview of plant species used in anti-NDV treatment

The use of herbs and plants as medicine to cure the ailments is very popular throughout the world, as they usually have no harmful effects. The successful studies document that the medicinal plants of different species have antiviral efficacy and can be used against NDV.

6.1 Azidarachta indica

Azidarachta indica is a hardy plant and member of the *Milaceae* family. It is native to Pakistan (throughout Sindh, lower Baluchistan, and Southern Punjab and Southern North-West Frontier Province (Durrani *et al.*, 2008) and India and also found in some parts of Africa. It is commonly known as Neem and a fast growing tree with final length of 15–20 m, growing in tropical and semi-tropical regions.

A. indica has many biological compounds (Senthil *et al.*, 2006). Different parts of *A. indica* has been demonstrated to contain more than 140 compounds, like nimbin, nimbindin, azadiractin, and quercetin (Makeri *et al.*, 2007), which have antihelminth, antiprotozoal, antioxidant, antifungal, antimicrobial, spermicidal, and insecticidal properties (Bonsu *et al.*, 2012). However, as observed by virus inhibition methods, its antiviral compounds are insufficient for some viruses (Rao *et al.*, 1969). Research revealed that it's methanolic extract of leaves and seed extracts in chloroform and hexane act as antivirals, however with obvious host cytotoxicity. Samples with concentrations exceeding 3–4 μg/egg significantly subdue NDV. In chicken embryos, inhibitory concentration (IC_{50}) and toxic concentration (TC_{50}) for *A. indica* were 4 μg/egg and 300 μg/egg, respectively (Wafaa *et al.*, 2007).

6.2 Acacia nilotica

Acacia nilotica is a single stemmed plant, widespread in tropical and subtropical areas of Asia (from Pakistan and India), Africa, Australia and Kenya. It is commonly termed as Kikar which is tannin rich medicinal plant.

The extract of plant in methanol has high antiviral activity against fowl viruses (Mohamed *et al.*, 2010). Hemagglutination assay was used to calculate the reduction of viability in the viral growth in presence or absence of the extract. The cytotoxicity of each extract was determined by the presence of the CPE. The methanol extract of *A. nilotica* in Vero cells showed non-cytotoxic concentration and significant inhibitory effect against the tested virus at the concentration of 40 μg/ml. These results indicated that *A. nilotica* has significant inhibitory effect on the replication of NDV (Saeed, 2007).

6.3 Adansonia digitata

Baobab tree is regional name of *Adansonia digitate*. It belongs to the *Malvaceae* family and it is native to Africa. It is used as medicinal plant in Africa to cure many infectious diseases (Vimalanathan and Hudson, 2009). Its parts like bark, fruit pulp, leaves and seeds have medicinal as well as nutritional usages.

Methanolic extract of rootbark of *A. digitate* was checked for its antiviral potential by treating it against 175 specific antibodies in embryonated chicken eggs (ECEs) infected with NDV strain. After 2 h exposure of the virus to eight concentrations of the extract and after 24 h incubation the mortality was observed. The 100 EID_{50} concentration of the virus and the highest concentration of the extract were inoculated as positive and negative controls, respectively. All eggs inoculated with the virus alone as well as 5 and 2 mg/ml extract/virus suspensions, died after 72 h post inoculation, while no mortality was observed amongst those inoculated with 250 and 200 mg/ml virus/extract suspensions as well as those inoculated with the extract alone. This study showed that methanolic rootbark extract of *A. digitata* has antiviral activity against NDV *in ovo*, particularly when used at dose rates of 200 and 250 mg/ml (Sulaiman *et al.*, 2011).

6.4 Anthocleista nobilis

Anthocleista nobilis, also called candelabrum or cabbage tree (in English) belongs to the *Loganiaceae* family. The root is pharmacologically the most active and it is mostly used as a purgative and dietary supplement, or a poison antidote. Ethanolic extract of *A. nobilis* was considered as good for the dealing with ND in fowl. Results indicated that the biochemical components present in this extract had significant effect in remedy of poultry caused by NDV (Ayodele *et al.*, 2012).

6.5 Aloe secundiflora

Aloe secundiflora reduced the mortality rates of NDV infected birds. Treatment or pre-treatment with *A. secundiflora* can reduce mortality to 21.6–31.6%. The gel of *A. secundiflora* contains polysaccharides with antiviral efficacy and the outer sap contains bioactive compounds as anthraquinone

glycosides. Anthraquinones have potential to damage the envelope of viruses like influenza virus, NDV, HSV-1, HSV-2 (Waihenya *et al.*, 2002).

6.6 Aloe hijazensis

Aloe hijazensis belongs to the *Aloe vera* family. Its different parts were examined for antiviral activity against NDV. Root, leaves, flowers, and flower peduncles posses many bioactive molecules. Flowers and peduncles contain 13 different compounds while roots and leaves contain chromones, anthrones, anthraquinones and flavonoids. Pathogen free embryonated eggs were used for evaluation of *A. hijazensis* flowers, peduncles, leaves, and roots against NDV. It was proved that extracts of leaves and flowers had better antiviral activity against NDV than roots and peduncles (Abd-Alla *et al.*, 2012).

6.7 Artemisia annua L.

Afsanteen (*Artemisia annua* L.*)* is the member of the *Asteraceae* family. It is native to temperate Asia and some parts North America. There is only limited information about the antiviral activity testing of *A.annua* however its anti-NDV activity was proved. The extracts of compounds were prepared by decoction methods and results revealed that due to presence of bioactive components, ethanolic extracts inhibit NDV propagation in embryos and show no side effects (Liu and Genqiang, 2009).

6.8 Curcuma longa

Curcuma longa (Turmeric), a primeval coloring spice, is traditionally used as a remedy worldwide (Araújo and Leon, 2001). Turmeric contains curcumin as important derivative which has efficient antiviral activity against different viruses (Dairaku *et al.*, 2010). Hubbard chicks divided into six groups (control group, group of chicks vaccinated with NDV, group of chicks vaccinated with MDV Rispen strain, group of chicks vaccinated with MDV and NDV, group of chicks vaccinated with MDV and treated with *C. longa* and group of chicks vaccinated with NDV and treated with *C. longa*) were used in the experiment for antiviral activity of *C. longa*. The results indicated that the powder of *C. longa* increased the immune response against the infection (Madbouly *et al.*, 2011).

6.9 Commiphora swynnertonii

Commiphora swynnertonii is found in tropical and subtropical areas of Asia and north Eastern Africa. *C. swynnertonii* species are characteristic for shrub appearance with spines, pale grey bark and brownish resinous exudate (Moshi *et al.*, 2010).

Different parts of *C. swynnertonii* as root, bark, leaves, resin and stem were tested to cure NDV by *in ovo* assay in ECEs. The eggs were divided into 7 groups in which five groups were treated with extracts of different parts of *C. swynnertonii* and two groups were left as positive and negative controls. Embryos were checked daily and weighted 5 days after inoculation and some eggs were left to hatch. For hemagglutination and hemagglutination inhibition assay, allantoic fluid from tested eggs and serum from hatched chickens were used. Results showed that mean weight and survival was higher in extract treated eggs than in infected control group. The presence of extract also lowered the virus titre. Moreover, no virus was detected in allantoic fluid of eggs treated with resin extract. Further, bark and root extracts were assumed to be efficient in virus clearance since no antibodies were observed in the blood of chicks (Bakari *et al.*, 2012).

6.10 Cladosiphon okamuranus

Cladosiphon okamuranus is type of edible seaweed, which is naturally produced in Okinawa, Japan. Research indicates that presence of fucoidan in this species has antiviral potential against NDV (La Sota strain) and restricts replication mainly between 0–60 min after infection. Reduced HA and NP protein expression was found in 48% of viral infections (Elizondo-Gonzalez *et al.*, 2012).

6.11 Capsicum spp.

Capsicum spp. is widely used to treat variety of diseases, often in combination with other plants. Capsaicin, one of the constituents of *Capsicum spp.*, is thought to improve resistance to viral disease in poultry (Lans *et al.,* 2007).

6.12 Cucumis metuliferus

This plant is also known as horned melon or kiwano and belongs to the *Cucurbitaceae* family. Ripe fruit is similar to cucumber but with yellow to orange skin and lime green, jelly-like flesh with a sour taste. Various phytochemicals present in this plant account for its different medicinal characteristics. Alkaloids present in fruit pulp of *C. metuiferus* have antiviral properties. The chickens infected with NDV were treated with extracts of kiwano to show the antiviral efficiency. The results revealed that alkaloids of this plant have strong anti-viral effects and reduce the signs of disease at concentration of 60 mg/kg (Chen *et al.*, 2010).

6.13 Cassia tora

Cassia tora is a dicot legume found mainly in South-East Asia. It contains sufficient quantities of anthraquinones and

has anti-NDV activity. Other species with anti-ND virus activity include *C. auriculata* and *C. fistula* (Lans *et al*., 2007).

6.14 Euphorbia ingens

Euphorbia ingens belongs to the *Euphorbiaceae* family and is indigenous to dry ranges of South Africa. It is also called the candelabra tree. The crushed and soaked (overnight in water) branches of *E. ingens* given to NDV infected chickens in drinking water decreased the mortality by 38.4% (Lans *et al.,* 2007).

6.15 Echinacea purpurea

Echinacea purpurea is known as purple coneflower belonging to sunflower family (*Compositae*). Its ethanolic extract contains set of essential amino acids such as isoleucine, lysine, glutamic acid, proline, serine, phenylalanine, and threonine which have significant effects in NDV clearance. Investigational studies stated that use of *E. purpurea* enhanced resistance against virus and significantly improved food uptake rates and amended rates of mortality in infected fowl (Fard *et al.*, 2010).

6.16 Glycyrrhiza glabra

Glycyrrhiza glabra is generally known as licorice, Malathi (in Punjabi) and sweetwood, is a native plant of some regions of Asia and Europe. It is used as flavour in tobacco products, drinks and candies. Its medicinal properties are found in the main taproot which is soft and fibrous.

Hemagglutination inhibition test of ECEs showed that 60 mg/100 ml of aqueous extract of *G. glabra* exhibited anti-viral activity against the virus (Omer *et al.*, 2014). It contains more than 20 tri-terpenoids and about 300 flavonoids. But only two triterpenoids, glycyrrhizin (Wang *et al.*, 2015) and 18-β-glycyrrhetinic acid (Feng *et al.*, 2013) have been reported to have antiviral effects. They can ablate virus activities by inhibiting virus gene expression and replication, reducing attachment force and stress, and reducing HMGB1 binding to DNA. They can also improve host cell activities by blocking the degradation of IκB, activating T lymphocyte proliferation and decreasing host cell apoptosis (Omer *et al.*, 2014).

6.17 Momordica balsamina

It is herbaceous climber plant, a member of *Curbitacae* family endemic to Northern Nigeria (Bokhari and Ahmed, 1980). Phytochemical analysis revealed that its fruit, leaves and seeds contain lectins, steroids, saponins, glycosides and tannins. Presence of alkaloids, flavonoids, saponins and tannins considers them as innovative antiviral mediators (Jassim and Naji, 2003). To prove the antiviral ability of fruit and leaf extracts of *M. balsamina*, fibroblastic cell lines from chicken embryos were used. Results revealed that both extracts inhibited the infection at concentration of 10 mg/ml and 20 mg/ml correspondingly. Further detailed investigations revealed the ability of the extract to avert the adhesion of virus on host cell surface (Chollom *et al.*, 2012b).

6.18 Moringa oleifera

Moringa oleifera also known as "miracle tree" has all essential amino acids, vitamins, calcium and all nutrients required concentrated in its leaves (Shirin and Hitesh, 2016). It is also known as Sohanjana, a member of the *Moringacea* family. Plant is endemic to Pakistan and India. Southern Punjab is considered as origin of *Moringa* plant. Aqueous seed extract of *M. oleifera* was analysed for anti-NDV activity in *in ovo* assay. Antibody production and virus clearance decreased in concentration dependent manner. The extract also enhanced the immunity efficiency (Chollom *et al.*, 2012a).

6.19 Nauclea latifolia

Nauclea latifolia is a shrub or evergreen small tree found in tropical forests of Africa. The dried powdered material of *N. latifolia* has been shown to have antiviral effects against wild type of ND. EID_{50}/ml was determined by end point analysis. In literature, test for toxicity demonstrates that three different concentrations of hot aqueous and ethanolic extract of *N. latifolia* were able to minimize virus loads. Both extracts with concentrations of up to 125 mg/ml were toxic for chicken eggs. Ethanolic extracts had better antiviral activity than hot water extracts (Onu *et al.*, 2014).

6.20 Ocimum sanctum

Ocimum sanctum called also Holy basil (English) and Tulsi (Hindi) cultivated primarily in India and tropical and subtropical regions is regarded as scared. It has therapeutic representations in primeval cultures of many countries. Antiviral efficiency of *O. sanctum* was studied by administration of hot aqueous leave extract of *O. sanctum* to chicken embryo fibroblast monolayer culture. Hemagglutination assay was used for estimation of viral concentration in medium, while examination of cytopathic properties of NDV was done on chicken embryo fibroblast monolayer. Results indicated that concentration of 10 mg/ml or less of hot aqueous leaves extract prevents the NDV cytopathic effect and restricts NDV replication in fibroblasts (Jayati *et al.*, 2013).

6.21 Psidium guajava

Psidium guajava or common guava is commonly present around the globe. It is a common shade tree in yard gardens

in the tropical areas. The pharmacologically beneficial substances such as alkaloids, tannins, flavonoids, saponins and other compounds in the leaves are accounted for the diverse claims and applications of parts of the plant in local treatment of diseases. Antiviral efficacy of *P. guava* leaf extract against NDV was performed by *in ovo* assay. Extracts prevented viral replication in ECEs at concentration of 250 mg/ml and 200 mg/ml. Embryo survival improved in dose dependent manner and the presence of the extract inhibited the antibody production in hatched chicks (Chollom *et al.*, 2012).

6.22 Thymus vulgaris

Thymus vulgaris is known as Thyme. It is indigenous to Mediterranean countries, North Africa and Asia. It grows to the height of 50 cm with woody branched stems. The flowers are purple to pink. It has essential oils and bioactive substance that possess antioxidant and antimicrobial activities. These substances can be active against microorganisms such as fungi, yeasts, viruses and bacteria. *T. vulgaris* was found to be effective against HSV-1/HSV-2 and NDV. Essential oils of this plant were able to disrupt viral envelopes and prevented attachment of the virion to the host cell (Rezatofighi *et al.*, 2014).

6.23 Withania somnifera

Withania somnifera is used as medicinal plant worldwide, belonging to the *Solanaceae* family. It is commonly known as Asgandha or asgund. The major compound in roots and leaves of *W. somnifera* are alkaloids, which are responsible for its boosting efficiency. It has been demonstrated that this plant enhanced production of the white and red blood cells (Senthilnathan *et al.*, 2006). *W. somnifera* aqueous extract administered to chickens in drinking water, improved the hemoglobin, body weight and total lymphocytes count. *W. somnifera* induced healthier food uptake, body weight, haematological profile and better immune status of chickens (Mustaq *et al.*, 2012).

7. Conclusions

Data presented in this review highlight the incidence of ND worldwide and medicinal plants used as a source for combating of ND. Here, 23 plants are discussed with their various parts and different extracts used against NDV. To find more active and less toxic anti-NDV remedies it is essential to utilize the novel antiviral drugs from bioactive components of the plants. Consequently substantial attention was paid on prospective abilities of plants with active components that exhibit antiviral virtues against NDV. In addition, *in vivo* and *in vitro* testing was followed by toxicity assays. After optimization and appropriate approach, promising compounds of novel antiviral products against NDV may be revealed. Drugs derived from medicinal plants around the continents, will be beneficial to individuals and also for nations. Although to utilize the antiviral compounds of plants, the facts of mechanisms of virus infection require to be understood in order to ease the exploration and advancement of most suitable drugs. Further investigation is desired to reveal how to target the proper regimens to avert the spread viral infections.

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