Chapter

Foot-and-Mouth Disease Virus (FMDV) and Its Treatment with Plant Extracts

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Abstract

Foot-and-mouth disease (FMD) is a contagious viral infection which is caused by *foot-and-mouth disease virus* (*FMDV*). The disease appears in cloven-footed animals. Symptoms of the disease are abrupt manifestation of sores on the mouth, nose, feet, etc. Nowadays the control and treatment of *FMDV* are becoming a worldwide economic problem and challenge for the society. Currently, there is no particular treatment available for *FMDV*, as well as the limitations and disadvantages in the use of vaccines divert the focus of researchers toward natural sources like plant extracts which possess potential antiviral activity. Various researches documented in the literature demonstrated various plant extracts with antiviral potency against *FMDV*. In the current chapter, we discussed about *FMDV* and its possible treatment with plant extracts.

Keywords: *FMDV*, treatment, plant extracts

1. Introduction

Foot-and-mouth disease (FMD) is a contagious viral infection [1] which is caused by *foot-and-mouth disease virus* (*FMDV*). The disease appears in cloven-footed animals. Symptoms of the disease are abrupt manifestation of sores on the mouth, nose, feet, etc. [2]. These symptoms can appear within 2–3 days postexposure and can take up to 7–10 days. *FMDV* belongs to genus *Aphthovirus* and family *Picornaviridae* and has seven species. In the year 2001, about 57 zones were previously influenced by dangerous FMD at the detection of *FMDV* for the first time in Britain. Later on about 43 animals were encountered with FMD just in a day. So estimate regarding the onset of FMD among animals may be biased [3].

For the prevention and elimination of *FMDV*, two methods could be adopted, that is, massacre and immunization [4]. The virus can last for an extended period of time especially in cool environment and neutral pH.

The foot-and-mouth disease virus (*FMDV*) belongs to genus *Aphthovirus* and family *Picornaviridae* [5]. *FMDV* has seven diverse serotypes O, A, C, SAT-1, SAT-2, SAT-3, and Asia-1. Serotype O is the most familiar in the world among all the serotypes. More than 60 strains are found among these serotypes. These serotypes differ

with each other in different topographic areas. Serotype O was accountable for that Asian epidemic which occurred in the year 1990 and influenced all over the world [1]. *FMDV* is a single-stranded RNA virus. It contains a protein coat comprising of four capsid proteins designated as VP1, VP2, VP3, and VP4 [4].

Foot and mouth disease (FMD) affects cloven-footed animals. The disease is very fast-growing and transmissible which usually affects pigs, cattle, goats, and sheep. The symptoms include vesicles/blisters on the hoofs, mouth, nose, feet, teats, etc. Ultimately these blisters result in skin erosions. Animals become unable to take food and thus become weak. Other symptoms include salivation, decrease in milk production, and weight loss. This viral problem occurs around the whole globe. *FMDV* epidemic occurred in different countries of the world like Europe, the United States, and Canada. In the year 1967, *FMDV* epidemic resulted in mortality of 400,000 pigs in the United Kingdom. Epidemic of *FMDV* in the United Kingdom causes death of about 70,000 pigs, cattle, and sheep in 70 areas [2].

Foot and mouth disease is a very dangerous communicable disease. It has affected different domestic animals in different areas with very lethal symptoms. Its breakthrough is especially notable in the United Kingdom. In the year 2001, about 57 zones were previously influenced by dangerous FMD at the detection of *FMDV* for the first time in Britain. Later on about 43 animals were encountered by this FMD just in a day. So estimate regarding the onset of foot and mouth disease among animals may be biased [3].

2. Plants for treatment of FMDV

Different plants were evaluated to prevent or eradicate *FMDV*. An experiment evaluated two parts of ginseng plant, stem and leaves, regarding susceptibility of mice to immunization to vaccine against serotype Asia-1 of *FMDV*. Ginseng along with its oil was also used to assess collective outcome regarding immunization against *FMDV*. This research showed that considerable high titer of various antibodies resulted when ginseng along with oil is given in combination. Important antibodies which were evaluated included IgG1, IgG2a, IgG2b, and IgG3.

In a study forty two plants were used to prepare 47 ethanolic extracts which were evaluated for their antiviral potential against KPS/005/2545 strain of type "O" *FMDV*. BHK-21 cell line was used in the experimental study. The virus was used at the rate of $10^{6.37}$ $TCID_{50}$. Transgenic plant (*Arabidopsis thaliana*) was used to synthesize VP1 with 135–160 amino acid residues. These antigens were found to provide immunization against viral disease [6]. Some plants showed significant antiviral activity against *FMDV* which included *Morinda elliptica* and *Morinda citrifolia.* Other plants failed to exhibit antiviral activity against *FMDV* [7]. This indicates that plants have antiviral potential and they can be used as antiviral agents against *FMDV*.

In another reported study, it was mentioned that FMD is a transmissible ailment of animals. Effective control of this disease needs sensitive, specific, and quick diagnostic tools at each tier of control strategy. Various pen-side tests, namely, lateral flow, RT-LAMP, immunostrip tests, and so forth, were also developed for the detection of the virus in field condition [8].

FMDV is transmissible, and to maintain protection against this virus, a study was conducted on guinea pigs and rabbits. The study suggested that immunization of animals with synthetic peptide 141–160 produces neutralizing antibodies that provide protection against *FMDV* [9]. Similarly, different synthetic peptide residues 141–158 and 200–213 of VP1 were synthesized from 01 Kaufbeuren strain of *FMDV*. These peptides were proved to provide protection against *FMDV* via acting on VP1 carboxyl terminal [10].

In the 1930s, the first vaccine was developed against FMDV. The vaccine was developed from live *FMDV* with formalin in combination with aluminum hydroxide gel. Treatment of animals with this vaccine reduced the outbreak of viral disease [11]. Later on, vaccines have been developed based on the virus capsid structure. These vaccines were synthesized from purified or recombinant DNA techniques, derived or chemically synthesized VP1 peptides, inoculation with DNA expressing VP1 epitopes or interleukin, and plant expressing VP1 [12]. Moreover, a vaccine was developed by deleting RGD receptor site on VP1, which resisted virus binding to the cell [13]. Similarly, a live attenuated vaccine was prepared that lack the L-coding in A-type A_{12} virus. The vaccine resulted in replication of cells but decreased the virulent factor of disease in cattle [14]. On the other hand, a swine inoculated with wild-type A_{12} in combination with oil led to neutralization of FMDV [15].

Different studies have been reported on targeted immunogens that lack infectious nucleic acid. In a reported study, mice were inoculated with active virus $3C^{pro}$ in empty capsules. This vaccine produced neutralizing response by producing antibodies [16]. Another study showed improved FMDV antibody response after coadministration of viral capsid along with porcine granulocyte-macrophage colony-stimulating factor [17].

Meanwhile some studies illustrated the recombinant and replication of vaccinia virus containing capsid-coding region of FMDV C1Oberbayern or C_3Argentina85 [18]. To prevent the outbreak, Ad5-vectored vaccine was prepared that reduced viral growth. Furthermore, porcine interferon omegas 7 and 8 have also been reported to reduce *FMDV* in vitro production in swine kidney cells [19, 20].

Nowadays the control and treatment of FMDV have become a worldwide economic problem and a challenge for the society. It not only affects the animals, but humans who eat these animals are also affected. Currently, there is no any particular treatment existing regarding the cure of FMDV. The conventional method involved the use of antibiotics, flunixin, meglumine, and mild disinfectants for treating infected animals. Traditionally for washing the lesions of infected animals, natural soda ash solution, honey, and finger millet flour are used [21].

Vaccination of animals is the first-line treatment for the control of the virus. However, vaccines take several days to elicit its response, and sometimes, a booster dose is required with repeated vaccination. There is no vaccine available which meets the ideal conditions like broad antigenic spectrum, high efficacy, low risk of FMDV release, and low production cost. Inactivated (traditional) and live attenuated (conventional) vaccines are used normally. Inactivated vaccines contain one or more cell culture-derived inactivated virus mixed with the suitable excipients. Inactivated vaccines may be categorized into standard or higher potency vaccines. Standard vaccines provide broad-spectrum coverage against the virus strains, while high-potency vaccine has rapid onset of action and wider range of protection. Live attenuated vaccines are not recommended for use as it reverts the chance of infection and also prevents the recognition of infection in vaccinated animals [22].

Azadirachta indica (*AI*), known commonly as neem, belongs to family Meliaceae and has possessed antiviral activity against different viruses [23, 24]. There is a study that reported the use of different concentrations (200, 100, 50, 25, 12, 6, and 1 μg/ml) of aqueous and ethanolic leaves extract of *Azadirachta indica* for evaluating antiviral activity against *FMDV* in farming animals on BHK-21 (baby hamster kidney) cell culture. Aqueous extract of the said plant showed considerable anti-*FMDV* activity between the concentration ranges of 12.5–50 and 50–100 μg/ml, whereas ethanolic leaves extract demonstrated strong antiviral activity at concentrations between 6 and 25 μg/ml. Antiviral activity was evaluated by examining cytopathic effects and determining cell survival percentages [25].

Moringa oleifera, local name is Sonjna, belongs to family Moringaceae and is an effective antiviral agent used against Epstein-Barr virus (EBV), herpes simplex virus (HSV), HIV/AIDS, and hepatitis B virus [26]. The anti-*FMDV* activity of ethanolic leaves extract of *Moringa oleifera* was evaluated at different concentrations, respectively (200, 100, 50, 25, 12, 6, and 1 μg/ml), on BHK-21 cell culture. Ethanolic leaf extracts of plant showed potent anti-*FMDV* activity between the concentration ranges of 12–100 and 50–300 μg/ml. However, in another study ethanol leaf extracts of plant showed significant antiviral activity at the concentration ranges from 1 up to 100 μg/ml with 50% cell survival rate [27].

Alhagi maurorum is a member of family Fabaceae, known by local name camel thorn and camelthorn-bush. The successful in vitro anti-*FMDV* activity of ethanolic, methanolic, and aqueous-acetic acid extracts of *A. maurorum* was reported at different stages of viral replication cycle, with the main compound found to be 1,2-benzenedicarboxylic acid, diisooctyl ester. Reduction in cytopathic effects (CPEs) and tissue culture infective dose (TCID50) values help in the evaluation of antiviral activity of *FMDV* on Razi bovine kidney (RBK) cells [28].

The *Withania somnifera* (*WS*), or Ashwagandha locally known as "Indian winter cherry" or "Indian ginseng," belongs to the family Solanaceae. Ashwagandha is a well-known South African herb used in the treatment of herpes simplex virus [29] and infectious bursal disease [30]. In literature in vitro activity of aqueous extract of Ashwagandha roots and leaves was reported against *FMDV* of livestock on BHK-21 cell line. Ashwagandha roots and leaves demonstrated effective anti-*FMDV* activity. The antiviral activity of the plant was confirmed by observing reduction in cytopathic effects when treated with Ashwagandha root and leaf extracts [31].

In literature in vivo anti-*FMDV* activity of Chinese herbal kombucha is reported against *FMDV* of swine on baby hamster kidney (BHK-21) cells. Chinese herbal kombucha is a combination of different herbal plants, i.e., *Radix Glycyrrhizae*, *Momordica grosvenorii*, Dendranthema morifolium, and *Camellia sinensis.* Study showed that Chinese herbal kombucha inhibited the replication of *FMDV* analyzed by using real-time quantitative reverse transcription-PCR (Q-RT-PCR) technique [32].

The ethanolic extract of *Spirulina platensis* demonstrated the presence of antiviral activity against different isolates of FMDV in baby hamster kidney (BHK) cell culture and in baby mice. The results of this study showed that at 50 μg/ml, *S. platensis* extract revealed 28.5, 31, and 35.7% reductions in *FMDV* titers type A, SAT-2, and O, respectively. At the same dose, 50% inhibition in *FMDV* was observed in infected baby mice [33].

Glycyrrhiza uralensis or Chinese liquorice is used to treat enterovirus 71 (EV71) and *Coxsackie* virus A16 (CVA16) of FMD. The essential antiviral component in plant is found to be glycyrrhizic acid, as the antiviral activity is directly dependent on the concentration of glycyrrhizic acid. At 1000 μg/ml concentration of plant extract, 1.0 log reduction in EV71 replication and 1.5 log reduction in CVA16 replication were observed. However, at concentration of 200 μg/ml, 1.7 and 2.2 log inhibition in EV71 and CVA16 replication is examined, respectively. Cytopathic effects were observed for determining antiviral activity [34].

Ocimum tenuiflorum (tulsi) of family Lamiaceae and *Curcuma longa* (turmeric) of family Zingiberaceae also possess potential antiviral activity for FMD. Aqueous extracts of both plants showed effective in vitro antiviral activity against *FMDV* of livestock on BHK-21 cell line at 1:2 and 1:1 dilutions [31].

Various plant crude extracts were studied for their in vitro antiviral activity against bovine *FMDV* on BHK-21. The immature fruit extract of *Morinda elliptica* L. showed *FMDV* inhibition at concentration of 0.39 μg/μl with TCID50 value of $1 \times 10^{3.65}$. The *Morinda citrifolia* L. extract also showed *FMDV* inhibition at 0.19 μg/μl, and TCID50

value was reported to be $1 \times 10^{3.35}$. Extract from leaves and stem of *Amaranthus viridis* L. has lowest FMDV inhibition at 0.024 μg/μl concentration ($1 \times 10^{2.44}$ TCID50). Extracts obtained from the rhizomes of *Boesenbergia rotunda* L., flowers of *Carthamus tinctorius*, and fruits of *Citrus reticulata* and *Elaeocarpus hygrophilus* showed inhibition of *FMDV* at concentration of 0.012 μg/μl of all extracts with $1 \times 10^{2.14}$ TCID50 [7].

3. Conclusion

Recently there is no particular treatment available for the treatment of *FMDV*, and the limitations and disadvantages in the use of vaccines divert the focus of researchers toward natural sources like plant extracts which possess potential antiviral activity. The various research works documented in the literature demonstrated various plant extracts with antiviral potency against *FMDV*.

4. Future prospects

The successful in vivo and in vitro anti-*FMDV* activities of plant extracts showed that they have the potential to be used to control the virus growth inside the body and also help in managing the lesions associated with these infections. In plant extracts, different chemical constituents are present which could be further isolated and effectively used in the development of powerful and potent antiviral drug against *FMDV*.

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