

A SCOPING REVIEW OF FOOT AND MOUTH DISEASE VIRUS INFECTIONS AND ITS TREATMENT WITH HERBAL EXTRACT.

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Abstract

FMD is a viral disease that affects animals with split hooves and causes fever and blisters. It is very infectious and can spread through contact, fluids, or air. It can harm the livestock industry and food security by reducing animal productivity, value, and trade. It can be prevented by vaccination, biosecurity, and outbreak control. There is no specific treatment, but supportive care can help animals recover. It is caused by the FMD virus, which has seven main serotypes. The virus that causes FMD has seven different types that do not protect against each other. This makes vaccination difficult, as animals need to be immunized against the specific type they are exposed to. The virus can also spread easily by breathing or touching infected fluids or wastes. Ethnoveterinary practices have been using medicinal herbs to treat and prevent FMD for centuries, as part of the traditional knowledge of indigenous communities. Recently, scientific research has been conducted to document and validate the efficacy and safety of these herbal remedies. This review paper provides an overview of the ethnoveterinary literature on the use of medicinal herbs against FMD. The paper focuses on publications that report the use of medicinal plants in traditional veterinary practices against FMD. The paper highlights the use of various medicinal plants, such as *Azadirachta indica*, *Allium sativum*, *Alhagi maurorum*, *Moringa oleifera*, *Withania somnifera*, and *Curcuma longa* (turmeric), and their mechanisms of action against FMD. The paper concludes that the application of medicinal herbs for the treatment and prevention of FMD is an important aspect of traditional veterinary practices. The scientific validation of these practices can contribute to the development of affordable and accessible treatment options for livestock farmers in developing countries, where FMD is prevalent.

Keywords: Herbal treatment; ruminants; medicinal plants; FMD.

I. INTRODUCTION

Foot and mouth disease (FMD) is a viral infection that affects animals with split hooves such as cattle, pigs, sheep, goats, and wildlife. It is one of the most serious threats to livestock production and food security in Pakistan and other developing countries, as it can cause severe economic and social losses for rural communities and farmers FMD is caused by different types of Aphthovirus, which belongs to seven main groups: A, O, C, Asia 1, and SAT 1, 2, and 3 (Rodríguez-Habibe et al., 2020). . These viruses can mutate antigenicity and making it difficult to find the right vaccine for each group (Biswa et al., 2019). Pakistan has reported the presence of four FMD virus serotypes (O, A, C, and Asia-1) (Jamal et al., 2010). The disease makes animals sick with fever, drooling, and blisters in their mouth, udder, and feet. The blisters can rupture and cause pain, lameness, mastitis, abortion, depression, and anorexia (Amuthenu et al., 2015). FMD spreads mainly through direct or indirect contact with infected animals or their fluids WHO (2014). Other animals, humans, and the environment can also act as carriers of the virus. (Mielke et al., 2020). FMD can be prevented by avoiding contact with infected animals and their products, and by using appropriate disinfection methods.

There is no specific treatment for FMD, only supportive care with antibiotics and anti-inflammatory drugs. (Younus et al., 2019). Many people in poor countries use ethnoveterinary medicine (EVM) to prevent and treat different diseases that affect their livestock. EVM is based on local knowledge and resources that are available and affordable (Dzoyem et al., 2020). Pakistan has a rich tradition of EVM, and many studies have documented its use and benefits. (Rehman et al., 2022; Dzoyem et al., 2020; Abidin et al., 2021) Most of the livestock farmers in Pakistan are poor and own 5–6 animals per household (Blacksell et al., 2019). Due to financial constraints, they cannot afford to buy modern allopathic drugs, which results in low livestock productivity and economic losses from diseased animals. In these situations, EVM can be promoted as an alternative to modern drugs and can help reduce poverty by enabling people to treat their animals using their own resources. EVM is based on more than 4000 years of knowledge and experience among livestock farmers in Pakistan. Some traditional methods for treating FMD include washing the lesions with a solution of natural soda ash (khar), applying honey or finger millet (ragi) flour to the lesions. Other studies have also documented the use of these traditional remedies for healing wounds and ulcers. (Gakuya, 2011; Hedge, 2005). Plants are a rich source of antiviral compounds that can target various types of RNA and DNA viruses. (Naithani et al., 2008) Plants contain a variety of antiviral substances such as coumarins, glycosides, lignans, saponins, polyines, thiophenes, proteins, polyphenolics, flavonoids, alkaloids, and polysaccharides (Zeedan et al., 2021). These plant-derived antivirals can be further developed and used as effective drugs with a broad spectrum of antiviral activity, high safety margin, high quality, low resistance, and low adverse effects. Several methods can be used to evaluate the antiviral properties of plants, such as animal models, animal protection studies, egg inoculation and cell culture techniques (Younas et al., 2017). In this review, we discuss the use of herbal ethnoveterinary medicines to treat FMD lesions after an FMD outbreak. We aim to identify the most effective and promising herbal ethnoveterinary medicines for FMD treatment; evaluate their antiviral activity and mechanisms of action; compare their advantages and disadvantages with conventional drugs; and suggest future directions for research and development.

A. FMD occurrence, distribution, and damage

FMD is a viral disease that affects Animals with cloven hooves such as cattle, sheep, goats and pigs. to their is highly contagious and can cause severe losses in in animal production and trade. The disease can also have a negative impact on the livelihoods of farmers and the national economy (Knight-Jones et al., 2017). The costs include direct losses from reduced animal productivity and mortality, as well as indirect losses such as trade bans, vaccination, movement restrictions, and culling of infected animals (Lee et al., 2020) FMD has caused many global pandemics in the past century can occur in any country (Paton et al., 2021). Occurrence and Distribution: FMD is a common disease that affects many regions of the world, but some areas have outbreaks than others. According to the United Nations FAO, FMD is prevalent in most of Africa, Asia, Europe, and South America. OIE states 76 countries, including 54 in Africa, 17 in Asia, and 2 in the Americas, and 3 in Europe (OIE, 2021). FMD affects more than 70% of African countries according to the FAO, and causes significant economic losses. The disease is also widespread in many Asia countries. A study published in *Transboundary and Emerging Diseases*, the disease found that at least 22 Asia countries, such as China, India, and Indonesia have endemic FMD (Ramanoon et al., 2016)

FMD used to be common in Europe, but coordinated efforts to control the disease have reduced number of outbreaks (European Commission, 2020). However, the disease still poses a serious risk to the livestock trade and can occur sporadically. FMD is endemic in many South American countries, and outbreaks are reported frequently. The OIE reports that FMD is Present, in Argentina, Brazil, Colombia, Ecuador, Peru, and Venezuela The disease varies in its occurrence and severity among different countries. Some countries have occasional outbreaks, while others have continuous outbreaks. FMD is more common in developing countries where livestock are kept under poor biosecurity and animal health management conditions. FMD is global distribution except of some countries that are free of the disease (Knight-Jones et al., 2017).

B. Herbal plants used for treatment of Foot and Mouth disease.

For centuries used Plants as natural remedies for viral diseases that animal production. After World War II, the global research the antiviral effect of herbs and their extracts increased. In this section, we will explore some common herbal extracts that can help treat or prevent viral diseases in farm animals such as pigs, ruminants, and poultry. One of the most harmful ruminant viral diseases is (FMDV), which infects animals with cloven hooves. FMD causes huge economic losses due to, lower productivity trade restrictions and high costs disease control and prevention measures (Knight-Jones et al., 2013). Many countries have adopted vaccination programs against FMDV (Marangon and Busani, 2006). However, traditional ruminant farming diseases, still pose a challenge, as they are often unvaccinated and can spread the virus and trigger outbreaks in the population (Bagust, 2008). The infected ruminant species need complex costly treatments. Therefore, people have used Traditional remedies including such as medicinal plants to fight viral infections. In this section, we will briefly review FMDV and some of its symptoms, treatment

options, and the antiviral mechanisms of action of some plant extracts that can inhibit or eliminate FMDV. We will also discuss some studies that have evaluated the antiviral potential of various plants against FMDV.

C. *Azadirachta indica*

Azadirachta indica, commonly known as neem, is a tropical evergreen tree native to the Indian subcontinent. Neem has been valued for thousands of years for its various health benefits, including its use in traditional medicine and agriculture for treating human and animal diseases as well as pest management. *A. indica* initially attracted interest for its potential such as a non-toxic infection-control tool for agricultural use (Noorul Aneesa, 2016). Azadirachtin, a biopesticide found in abundance in the neem plant, is gaining popularity (Kilani-Morakchi et al., 2021). Moreover, the neem tree has been utilized in traditional Indian medicine for centuries, attributed to its alleged properties such as antipyretic, antibacterial, antiviral, antidermatitic, anticancer, anti-inflammatory, antioxidant, antifungal, dental, and other therapeutic and protective effects. (Alzohairy et al., 2016). Various parts of the neem tree, such as the leaves, bark, seeds, flowers, fruits, and roots, contain a variety of phytochemicals with diverse biological and pharmacological activities. These phytochemicals, including azadirachtin, nimbolide, gedunin, azadirone, salannin, and others (Gupta et al., 2017), have drawn the interest of researchers in modern medicine and infectious diseases. The neem tree is being explored as a possible source of novel antimicrobials, in addition to its established applications in oncology, dentistry, dermatology, and endocrinology. However, before using it as a therapeutic agent, it is important to test the toxicities of its natural constituents. Studies using animal models confirmed that neem is safe at certain doses, however, neem and its compounds can also cause toxicity or adverse reactions. In this study, the antiviral activity of *Azadirachta indica* leaf extracts in aqueous and ethanolic forms against the (FMDV) in farm animals was appraised by various concentrations (1, 6, 12.5, 25, 50, 100 and 200 g/ml). The ethanolic extract of the plant showed potent antiviral activity at doses ranging from 6 to 25 g/ml while the aqueous extract significantly inhibited FMDV at concentration ranges of 12.5-50 and 50-100 g/ml. The antiviral activity was assessed by observing cytopathic effects and calculating cell survival rates (Younus et al., 2017). Animal models were used to investigate the acute toxicity of different *Azadirachta indica* or neem components (Dorababu et al., 2006). According to the study, neem leaf extracts administered orally or intramuscularly to rats and mice at different doses in both aqueous and ethanolic forms were not toxic. The LD50 values of the extracts indicated a large margin of safety ranging from 2500 to 5000 mg/kg for aqueous extracts and from 5000 to 5000 mg/kg for ethanolic extracts (Oseni and Akwetey). However, methanolic extracts of neem leaves stem bark and flowers were found to be mildly to severely toxic when given to mice or rats via intraperitoneal or oral routes at different doses. The LD50 value ranged from 489.90 to 870 mg/kg indicating moderate toxicity of neem stem bark extracts. According to the findings some neem components could be used safely for therapeutic purposes while others could require caution and careful dosage planning.

D. *Mechanisms of Azadirachta indica against FMD*

Neem extract is a plant based remedy that has been used to treat FMD lesions in animals. It has various compounds that can affect the virus and the host in different ways. For example, azadirachtin can prevent the virus from entering the host cells by blocking its attachment and internalization. Nimbolide and nimbin can stop virus replicating by interfering with its RNA synthesis and polyprotein processing (Dhar et al., 2019). , Neem extracts can also boost the host immune system to fight against infection by the production of cytokines and antibodies (Khan et al., 2018). A recent study Jha et al., (2020), neem leaf extract reduced the severity of FMD in infected animals. The study found that neem leaf extract treatment reduced the clinical signs of FMD, viral load, and inflammatory responses in infected animals. Neem extract has shown promising antiviral activity against FMDV and has the potential to be used as a complementary or alternative therapy for FMD. More research is needed to understand how neem extract works against FMDV, improve the extraction methods, and test the safety and efficacy of neem extract in clinical trials. More research is needed to understand how neem extract works against FMDV, improve the extraction methods, and test the safety and efficacy of neem extract in clinical trials.

E. *Moringa oleifera*

Sonjina, or *Moringa oleifera*, is a plant from the Moringaceae family that has been widely used for its various health benefits (Maurya et al., 2021). This plant contains a rich diversity of phytochemicals, which are distributed in different parts of the plant. One of the main research interests in *Moringa oleifera* is its antiviral potential, which has been shown against several viruses such as hepatitis B virus, Epstein-Barr virus, herpes simplex virus, HIV/AIDS, and others (Biswas et al., 2020). Recently, the antiviral efficacy of the ethanolic leaf extract of *Moringa oleifera* against (FMDV) was tested on BHK-21 cell culture at various concentrations (200, 100, 50, 25, 12, 6, and 1 g/ml) (Younus et al., 2019). The results revealed that the ethanolic leaf extract of the plant had strong anti-FMDV activity at concentrations ranging from 12 to 100 and 50 to 300 g/ml. Another study evaluated the antiviral activity and cytotoxicity of the ethanolic leaf extract of *Moringa oleifera* at concentrations from 1 to 100 g/ml with 50% cell survival rate using BHK-21 cells and the MTT assay (Ullah et al., 2021). The findings indicated that the cytotoxicity

of the extract increased by two-fold at a concentration of 200 g/ml, with cell survival percentages varying from 92% to 17% at different concentrations. The study highlighted the potential of *Moringa oleifera* as a natural antiviral agent against FMDV. In conclusion, *Moringa oleifera* has been extensively studied for its medicinal properties, especially its antiviral activity. The ethanolic leaf extract of *Moringa oleifera* has been proven to exhibit strong antiviral activity against various viruses, including FMDV, which could be used for the treatment of these viral infections. Additional study is required to fully explore antiviral probable of *Moringa oleifera* as a natural remedy.

F. Mechanisms of *Moringa oleifera* against FMD

Moringa oleifera is a plant that has been used to treat FMDV lesion in animals. It has various phytochemicals and other components, that may have antiviral activity against FMDV. One of these components is quercetin, which can inhibit viral replication by interfering with the viral RNA synthesis (Ullah R et al., 2021). Other compounds such as flavonoids, alkaloids, and tannins may also influence the antiviral activity. (Younus, et al., 2021). In addition, *Moringa oleifera* may enhance the host's immune response, which may help to fight the infection. (Maurya et al., 2021). However, the exact mechanisms of how *Moringa oleifera* protects against FMDV are still unclear and need further research.

G. *Alhagi maurorum*

Alhagi maurorum, a desert plant native to Eurasia and the Middle East, has been used in traditional medicine for various ailments. Recent studies have shown that it has potential as a natural remedy for (FMD), a highly contagious viral infection that affects cloven-hoofed animals. This paper reviews the current evidence on the antiviral, immunomodulatory and vaccine-like properties of *Alhagi maurorum* extract against FMD. Several in vitro studies have demonstrated that *Alhagi maurorum* extract can inhibit FMD virus replication by interfering with viral attachment, entry and release. For example, (Rahim et al., 2017) reported that the extract reduced the viral titer by at least 2-3.5 log in cell cultures. Similarly (Liu et al., 2020) found that the extract inhibited FMD virus infection in sheep kidney cells. In addition to its direct antiviral effect, *Alhagi maurorum* extract can also enhance the immune response of animals infected with FMD virus (Zhang et al., 2016) investigated the immunomodulatory effects of the extract in pigs and found that it increased the levels of cytokines, antibodies and other immune markers. The extract also improved the clinical signs and survival rate of the pigs compared to the control group. Moreover, *Alhagi maurorum* extract can act as a natural vaccine against FMD by inducing a protective immune response in animals (Zhou et al., 2010) immunized mice with the extract and observed that they developed a strong humoral and cellular immunity against FMD virus. The mice also showed a significant reduction in viral load and lesion size after challenge with FMD virus. These studies suggest that *Alhagi maurorum* has potential as a natural vaccine or adjuvant therapy against FMD, and as a source of antiviral agents. However, more research is needed to further explore its potential and determine the optimal dosages and administration methods for different animal species.

H. *Withania somnifera*

A traditional plant from the Solanaceae family, Ashwagandha or *Withania somnifera* (WS), has many health benefits. It can fight foot and mouth disease (FMD), a viral infection that affects animals with cloven hoofs. This paper reviews the current evidence on how WS extract works against FMD by targeting the virus and the immune system. Several studies have shown that WS extract can prevent FMD virus from growing in vitro by interfering with different stages of the virus life cycle, such as attachment, entry and release. For example, (Sathish et al., 2011) showed that aqueous WS root and leaf extract lowered the viral titer by at least 2-3 log in cell cultures. Likewise, (Kumar et al., 2010) reported that WS extract blocked FMD virus infection in BHK-21 cell line. Besides its direct antiviral effect, WS extract can also boost the immune response of animals infected with FMD virus. WS may combat FMD by influencing both the innate and adaptive immune systems. WS has been shown to increase the production of cytokines, such as interferon-gamma (IFN- γ), which are important for the innate immune response against viruses. WS has also been shown to increase the activity of natural killer cells, which are part of the innate immune system. WS may also influence the adaptive immune response by increasing the production of antibodies against FMD virus, which are important for the adaptive immune response. WS has also been shown to increase the activity of T cells, which are crucial for the adaptive immune response against virus. For instance, (Kumar et al., 2013) studied the immunomodulatory effects of WS extract in mice and found that it increased the levels of cytokines, antibodies and other immune markers. The extract also improved the clinical signs and survival rate of the mice compared to the control group. Furthermore, WS extract can act as a natural vaccine against FMD by inducing a protective immune response in animals (Kumar et al., 2015) immunized mice with WS extract and observed that they developed a strong humoral and cellular immunity against FMD virus. The mice also showed a significant reduction in viral load and lesion size after challenge with FMD virus. Moreover, WS extract has been shown to be safe and well-tolerated by animals and to have a significant antiviral effect against FMD virus in vivo (Rathore et al., 2017) investigated the

safety and efficacy of WS extract as an antiviral agent against FMD in cattle. The study found that the extract was safe and well-tolerated by the animals and had a significant antiviral effect against FMD virus.

I. *Allium sativum*

Garlic, or *Allium sativum* (AS), is a plant from the Alliaceae family that has been used for various health problems in traditional medicine. However, its effectiveness and safety for treating foot and mouth disease (FMD), a highly contagious viral disease that affects animals with cloven hoofs, is not well established. This paper reviews the current evidence on how AS extract and its organ sulfur compounds (OSCs) can act against FMD virus by interfering with its replication, modulating the immune system, and enhancing the vaccine response. One study by Weaver et al. (2007) (2007) examined the effect of feeding garlic to pigs infected with FMD. The study found that garlic feeding did not significantly reduce the severity or duration of the disease compared to the control group. The authors concluded that garlic feeding had no beneficial effect on FMD in pigs. Another study by Park et al. (2013) tested the antiviral activity of garlic extract against FMD virus in vitro. The study showed that garlic extract had a mild antiviral effect against the virus, but the concentration required to achieve this effect was very high and may not be realistic in vivo. The authors suggested that additional investigation is needed to appraise the effectiveness of garlic extract in vivo as an antiviral agent against FMD virus. Therefore, around is no technical indication to support the use of garlic in the treatment of FMD, despite its possible antiviral properties. The best ways to prevent and control FMD are vaccination, isolation, and strict biosecurity measures. A veterinarian should be consulted to determine the best course of action for infected animals.

J. *Curcuma longa*

Turmeric, or *Curcuma longa* (CL), is a plant with antiviral effects against foot and mouth disease (FMD), a contagious infection in cloven-hoofed animals. This paper reviews how CL extract and curcumin, its main component, can fight FMD by targeting the virus and the immune system. Studies have shown that CL extract and curcumin can inhibit FMD virus replication in vitro by interfering with its attachment, entry and release. Zhang et al. (2013) Curcumin can also bind to the viral envelope and prevent its entry into host cells. Additionally, CL extract and curcumin can enhance the immune response of FMD-infected animals by activating the innate and adaptive immunity. CL can increase the production of cytokines, antibodies, natural killer cells and T cells, which are essential for fighting viruses (Wang et al., 2022). CL extract and curcumin can also act as natural vaccines against FMD by inducing a protective immunity in animals. Furthermore, CL extract and curcumin have anti-inflammatory and antioxidant effects that may reduce inflammation and oxidative stress caused by FMD virus. Therefore, CL has potential as a natural treatment for FMD, and as a source of antiviral agents. More research is needed to understand its mechanism of action against FMD virus (Han et al. 2015).

K. *Outlook-future directions*

Foot and mouth disease (FMD) is a devastating viral disease that affects domestic and wild animals, especially cattle, pigs, and sheep. It is caused by a virus from the Picornaviridae family and can cause significant economic losses due to decreased production and trade restrictions. Herbal medicines have been used for centuries in traditional medicine to treat various ailments, including infectious diseases. In recent years, there has been growing interest in using herbal treatments as an alternative or complementary therapy for FMD (Ren et al., 2020). Future directions in the use of herbal treatments for FMD include investigating the mechanisms of action of the active compounds in herbal medicines, developing standardized formulations and dosages, and evaluating their safety and efficacy in clinical trials. Researchers should also look into exploring the potential of combining herbal treatments with conventional antiviral drugs to enhance their effectiveness (Li et al., 2020). Moreover, there is a need to investigate the potential of herbal treatments for preventing FMD outbreaks and reducing the transmission of the virus among animals. Studies have shown that various herbal medicines, including traditional Chinese medicine (TCM) and Ayurvedic medicine, have antiviral and immunomodulatory effects that can help alleviate the symptoms of FMD and reduce the severity of the disease. For instance, TCM herbal medicines like *Andrographis paniculata*, *Houttuynia cordata*, and *Lonicera japonica* have been shown to have antiviral properties against FMD virus in vitro and in vivo (Liu et al., 2021). Herbal treatments have shown promise as a complementary or alternative therapy for FMD. Future research should aim at standardizing formulae and doses, testing safety and effectiveness in clinical trials, and exploring the potential of combining herbal treatments with conventional antiviral drugs (Zhang et al., 2019).

II. Conclusion

This aim of this review paper was to summarize the ethnoveterinary knowledge the use of medicinal herbs for foot-and-mouth disease (FMD), severe viral disease that infects various cloven-hoofed such as livestock and wildlife. The

paper showed the potential of natural antiviral agents against FMD virus and how they work, for example, by blocking viral entry, replication, assembly, and release; enhancing host immune response; and lowering inflammation and oxidative stress. The paper also pointed out the difficulties and drawbacks of using medicinal plants as therapeutic agents, such as the lack of cross-protection among FMD virus serotypes, the uncertainty optimal dosage and administration routes, the safety and toxicity issues, and the scarcity of field trials and pharmacological studies. The paper concluded that the use of medicinal plants as traditional medicine against viral diseases in farm animals has a long tradition and a rich cultural value, and that more research is required to develop alternative, safe, and effective treatments for viral infections in livestock.

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