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EXPLORING EMERGING TOMATO VIRUS INFECTION WITH FOCUS ON CLINICAL IMPACTS, PREVENTIVE MEASURES, AND PHARMACEUTICAL THERAPEUTIC

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ABSTRACT

The emergence of tomato virus infection in humans represents a novel and concerning development in the field of infectious diseases. Initially restricted to plants, this virus has shown potential cross-species transmission, raising significant public health concerns. The present review explores the clinical impacts, transmission dynamics, preventive measures, and pharmaceutical therapeutic potentials associated with emerging tomato virus infection. Clinical manifestations often include mild to moderate fever, skin rashes, fatigue, and respiratory symptoms, resembling common viral illnesses, which complicates early diagnosis. Transmission is believed to occur through direct contact with infected plant materials, contaminated food sources, or vector-mediated pathways. Preventive strategies emphasize hygiene practices, monitoring of agricultural produce, and early detection through molecular diagnostic tools. The review also highlights the potential role of antiviral and immunomodulatory pharmaceutical agents that may offer therapeutic benefits, based on similarities with other plant-origin viral infections. Furthermore, the necessity for interdisciplinary collaboration among virologists, clinicians, and pharmacologists is emphasised to develop effective management strategies. Overall, this review provides an integrated understanding of the human health risks posed by tomato virus infection and underscores the urgent need for research into safe, targeted pharmaceutical interventions.

KEYWORDS: Tomato virus infection, cross-species transmission, clinical symptoms, prevention, pharmaceutical therapeutics.

Objectives of the Study

1. **To examine the emergence and evolution of tomato virus infection in humans**, focusing on its origin, possible cross-species transmission, and global occurrence.
2. **To analyse the clinical manifestations and pathophysiological effects** associated with tomato virus infection, highlighting similarities and differences with other viral diseases.
3. **To identify the routes and mechanisms of transmission** from plant to human and among human populations, including environmental and vector-based pathways.
4. **To review preventive and control strategies** that can minimize infection risks through hygiene, agricultural monitoring, and early diagnostic approaches.
5. **To evaluate the potential of pharmaceutical and therapeutic interventions**, including antiviral agents, immunomodulators, and natural compounds that may help in treatment or prevention.
6. **To emphasize the importance of multidisciplinary collaboration** among medical, agricultural, and pharmaceutical scientists for the effective management of emerging plant-origin viral infections.

7. **To propose future research directions** for understanding the molecular biology, epidemiology, and drug development strategies related to tomato virus infection in humans.

1. INTRODUCTION

Emerging viral infections pose continuous public-health challenges, particularly in pediatric populations with developing immunity. One such infection that recently gained attention in India is the so-called *"tomato flu"* or *"tomato fever,"* first reported in Kerala in May 2022 (The Lancet Respiratory Medicine, 2022). Despite its name, tomato flu is not caused by a virus associated with tomatoes or plants; instead, clinical and epidemiological evidence suggests it is a variant of **Hand-Foot-Mouth Disease (HFMD)**, predominantly linked to **Coxsackievirus A16, Enterovirus A71**, or other related enteroviruses (World Health Organisation [WHO], 2022; Kumar et al., 2023). This illness was named for its distinctive, red, blister-like eruptions resembling small tomatoes that appear on the hands, feet, and oral cavity of affected children (Jacob & Mohan, 2022).

Tomato flu primarily affects children under the age of five years and is characterised by fever, painful vesiculobullous lesions, fatigue, irritability, and dehydration, closely resembling the clinical profile of typical HFMD infections (Kumar et al., 2023). Transmission occurs rapidly through direct contact with infected individuals, contaminated surfaces, respiratory droplets, and faecal-oral routes, highlighting its potential for community outbreak in early childhood environments (WHO, 2022). Although generally mild and self-limiting, the infection poses a significant public-health concern due to its high transmissibility, absence of specific antiviral therapy, and risk of misdiagnosis with dengue, chikungunya, and varicella during early presentation (The Lancet Respiratory Medicine, 2022).

Given the recent outbreak and questionable public understanding often misinterpreting it as a novel zoonotic disease a systematic review of available scientific data is essential. This paper aims to synthesise current knowledge on **epidemiology, transmission dynamics, clinical presentation, prevention, and therapeutic strategies** related to tomato flu. Such insight supports evidence-based public-health interventions and helps counter misinformation surrounding this pediatric viral infection.

2. Identification and Scope Definition

The present review focuses on the **emerging tomato virus infection in humans**, a newly recognised and potentially cross-species viral threat. Although tomato viruses, such as *Tomato flu virus* (TFV) and *Tomato brown rugose fruit virus* (ToBRFV), were originally identified in plants (*Solanum lycopersicum*), recent reports of human infection symptoms resembling viral fevers have raised growing public health concerns (Kumar et al., 2023; Raj & Nair, 2023).

The primary aim of this review is to **define the current understanding of the human health impacts** of tomato virus infection and to **summarise recent findings** on its clinical manifestations, transmission pathways, preventive strategies, and potential pharmaceutical interventions. The study intends to bridge gaps between plant virology and human epidemiology to highlight the **possibility of plant-derived viral adaptation to human hosts**.

The **scope** of the review includes

- Assessing the **emergence and evolution** of tomato virus infection and its potential zoonotic relevance.
- Understanding the **clinical effects** and possible diagnostic challenges in differentiating tomato virus symptoms from other viral infections.
- Evaluating **preventive and pharmaceutical strategies**, including antiviral agents, vaccines, and herbal or synthetic compounds showing therapeutic promise.

3: Review of Literature

A. National literature (India)

Beginning in May–June 2022, clusters of a febrile rash illness described in the media as "tomato flu" or "tomato fever" were reported from the Kollam district of Kerala and subsequently from other Indian states. Early clinical descriptions emphasised high fever and large, round, red vesicles described as "tomato-shaped" blisters on the hands, feet, mouth and sometimes buttocks of young children (Kerala reports, 2022). Clinical case correspondence and public-health reports from India rapidly suggested that these presentations were consistent with an atypical or variant presentation of hand–foot–and–mouth disease (HFMD), rather than a novel plant-derived virus (Tang et al., 2022; Rai et al., 2023).

Several Indian review and outbreak-analysis papers summarised the Kerala events and subsequent reports. These national reports highlight:
(1) The predominance of cases in children under five years of age;
(2) Clinical features overlapping with enteroviral HFMD (fever, oral ulcers, vesicles on acral sites, occasional gastrointestinal symptoms and dehydration risk); and
(3) Rapid person-to-person spread in household and childcare settings (Adesola et al., 2023; Ismail, 2023).

The Indian Integrated Disease Surveillance Programme and national advisory documents emphasised symptomatic management, hydration, isolation of affected children for several days, and hygiene/surface-sanitation measures to interrupt transmission (IDSP/MoHFW advisory, 2022). Case reports and short series from pediatric infectious disease clinics in India and neighboring regions reinforced that diagnostic testing, when performed, frequently identified common HFMD enteroviruses (for example Coxsackie A strains), supporting the interpretation that "tomato flu" represents

an unusual clinical phenotype of known enteroviral disease rather than a new zoonosis (Tang et al., 2022; Rai et al., 2023).

Despite rapid local reporting, national literature also pointed to important concerns: inconsistent terminology in media versus scientific reports, limited laboratory confirmation in many field reports, and limited systematic surveillance data to determine whether any change in viral types, virulence, or age distribution occurred. Several Indian reviews called for strengthened virologic surveillance and standardized case definitions to avoid unnecessary public alarm and ensure appropriate public-health responses (Adesola et al., 2023; Open Public Health Journal, 2023).

B. International literature

Internationally, the body of evidence on HFMD is large and well established. HFMD is a common childhood viral exanthem caused primarily by enteroviruses (most notably Coxsackievirus A16 and Enterovirus A71), with other serotypes (Coxsackie A6, A10, etc.) increasingly implicated in atypical presentations and outbreaks (StatPearls; WHO). Classic HFMD presents with fever, oral enanthem, and vesiculopapular lesions on palms and soles; severe complications (meningoencephalitis, polio-like paralysis) are uncommon but well-documented with certain strains (for instance, EV-A71) (WHO; Huang et al., 2024).

Recent international reviews and large systematic syntheses outline several points relevant to the Indian "tomato flu" experience: (1) enteroviruses readily generate clinical phenotypic variation some serotypes (e.g., CV-A6) produce more widespread or atypical skin eruptions; (2) HFMD transmission occurs via contact with respiratory droplets, vesicular fluid, and fecal–oral routes, which explains rapid spread among young children; (3) management is predominantly supportive, with no widely used specific antivirals; and (4) promising vaccine development (targeting EV-A71) and improved diagnostics are active areas of research but are not universally implemented (Zhu et al., 2023; Huang et al., 2024; Mayo Clinic overview).

International correspondence and commentary on the Kerala events placed them in context: similar scenarios elsewhere (atypical HFMD outbreaks with prominent cutaneous lesions) have been associated with known enteroviruses rather than new pathogens. This international perspective supports cautious interpretation of novel disease labels and emphasises laboratory confirmation and genomic surveillance when an unusual outbreak pattern is reported (Tang et al., 2022; The Lancet commentary, 2022).

C. Synthesis and knowledge gaps

Taken together, the national and international literature converge on the following conclusions:

The "tomato flu" events in India are best interpreted as atypical HFMD presentations (national case descriptions and testing) rather than a new plant-associated infection.

Clinical management remains supportive; prevention relies on standard infection-control practices (isolation, hand hygiene, surface sanitation).

Important data gaps persist in comprehensive laboratory typing and genomic sequencing of outbreak strains in affected regions, systematic surveillance to detect changes in age distribution or severity, and formal studies quantifying transmissibility in childcare settings.

Addressing these gaps requires coordinated surveillance, standardised case definitions, and investment in diagnostic capacity to differentiate true novel emergences from variant presentations of known pathogens.

4. Overview of the Tomato Flu Outbreak in India (2022)

The primary "tomato flu" outbreak was reported in the Kollam district of Kerala, India, in early May 2022, predominantly affecting children below five years of age. The illness was initially suspected to be a new viral infection due to its distinctive clinical presentation and rapid spread (MoHFW, 2022). However, subsequent clinical observations and expert reviews indicated that the disease represents an atypical manifestation of **Hand, Foot, and Mouth Disease (HFMD)** primarily caused by **Coxsackievirus A6 and Coxsackievirus A16**, which are members of the *Enterovirus* group (Tang et al., 2022; WHO, 2022).

4.1 Epidemiology and Spread

The first case was documented on **May 6, 2022,** in Kollam, Kerala. The disease later spread to other parts of Kerala and neighbouring states such as **Tamil Nadu, Odisha, Karnataka, and Maharashtra**, prompting state-level alerts to prevent transmission among children (IDSP, 2022). Although children were the most affected group—particularly those under five—sporadic cases were also seen among immunocompromised adults.

4.2 Clinical Presentation

The term **"tomato flu"** emerged from the characteristic **red, painful, tomato-shaped blisters** appearing on the hands, feet, mouth, and in some cases, on the buttocks. Along with these lesions, commonly reported symptoms included:

- Fever
- Joint pain and swelling
- Skin rash
- Fatigue
- Nausea, vomiting, and diarrhea
- Sore throat and dehydration

These symptoms closely mirror those seen in HFMD and certain arboviral infections such as dengue and chikungunya, contributing initially to diagnostic uncertainty (Ismail, 2023).

4.3 Severity and Clinical Management

Despite notable discomfort in affected children, the illness was generally **self-limiting**, with no significant complications or mortality reported. Recovery usually occurred within **7–10 days**. Management strategies emphasized **supportive care**, including:

- Isolation for **5–7 days** to prevent transmission
- Adequate hydration
- Paracetamol for fever and pain
- Rest
- Warm sponge baths to relieve skin irritation
- Strict hygiene measures and disinfection of personal items

No specific antiviral treatment was indicated, consistent with standard HFMD care protocols (WHO, 2022; Mayo Clinic, 2023).

4.4 Public Health Response

Authorities implemented surveillance, issued advisories to schools and parents, and encouraged hygiene practices such as frequent handwashing, avoidance of close contact, and surface disinfection. Laboratory confirmation of suspected cases was recommended to differentiate tomato flu from HFMD, dengue, monkeypox, and other vesicular illnesses (IDSP, 2022).

5. Pharmacological Relevance of "Tomato Flu" (HFMD Caused by Coxsackievirus A6/A16)

Although "Tomato Flu" was first thought to be a new virus, scientific studies confirmed that it is a clinical variant of Hand, Foot, and Mouth Disease (HFMD) caused mainly by Coxsackievirus A-6 and A-16, belonging to the Enterovirus group. There is no specific antiviral drug available for this infection; therefore, pharmacology plays an important role in understanding symptom management, supportive treatment, vaccine research, and preventive care.

Table 1: Pharmacological Management (Symptomatic Treatment).

Symptom	Medicine Used	Pharmacological Purpose
Fever & body pain	Paracetamol (Acetaminophen)	Antipyretic & analgesic
Mild inflammation & swelling	Ibuprofen (with caution in children)	NSAID, pain & swelling control
Skin irritation & blisters	Calamine lotion, zinc oxide cream	Soothing, reduces itching & irritation
Dehydration	ORS, electrolyte fluids	Maintains hydration, prevents fluid loss

5.1. Antiviral and Immunotherapy Research

Currently, there are **no approved antiviral drugs** specifically for Tomato Flu (HFMD due to Coxsackievirus A6/A16). However, several antiviral and immunotherapy agents are being explored in research, including:

- **Pleconaril** – a viral capsid inhibitor that may block virus attachment and replication.
- **Ribavirin** – a broad-spectrum antiviral with activity against RNA viruses.
- **Interferon-α** – an immune-modulating therapy that enhances antiviral defense mechanisms.
- **Intravenous Immunoglobulin (IVIG)** – used in severe or complicated cases to boost immunity.

These treatments remain **experimental** and are **not part of routine clinical management** for Tomato Flu.

5.2. Pathopharmacology: Tomato Flu primarily targets:
Skin and mucosal tissues, producing blisters on the hands, feet, and mouth.
Immune system cells, leading to fever, fatigue, and inflammatory responses.
Pharmacological management focuses on:
Reducing fever, pain, and inflammation (e.g., paracetamol/ibuprofen).
Supporting the immune system through rest and hydration.
Preventing dehydration, particularly in young children, with oral rehydration solutions and fluids. Thus, treatment is mainly **symptomatic and supportive**, rather than curative.

5.3 Vaccine Development

Vaccine research is a key pharmacological area for HFMD. At present:

- **China has licensed vaccines for Enterovirus 71 (EV-71)**, a major cause of severe HFMD.
- **No vaccine exists yet for Coxsackievirus A-6 or A-16**, the viruses associated with Tomato Flu.
  Current research efforts aim to develop **multivalent vaccines** capable of providing protection against multiple HFMD-causing viruses.

5.4. Public Health and Pharmacovigilance

Effective pharmacological practice involves:

- **Avoiding unnecessary antibiotic use**, as Tomato Flu is viral and misuse can cause antimicrobial resistance.
- **Ensuring safe administration of fever and pain medicines** in children to prevent overdose or adverse effects.
- **Promoting hygiene and isolation measures** (5–7 days) to minimise viral transmission.

Public health monitoring and rational drug use are essential components of outbreak control.

5.5 Traditional and Herbal Therapies

Supportive care measures often used in Indian households include:

- **Neem water** for bathing or skin cleansing to reduce irritation.
- **Turmeric paste** is applied for its anti-inflammatory properties.
- **Tulsi, ginger, and honey** for boosting immunity and soothing symptoms.

While these remedies offer **comfort and supportive benefits**, **scientific research is still required** to validate their antiviral efficacy. Pharmacognosy-based studies may help identify potential natural therapeutic agents in the future.

6.0 DISCUSSION

The emergence of "Tomato Flu" in India in 2022 sparked public health concern due to its rapid spread among children and similarity to earlier viral outbreaks such as chikungunya, dengue, and COVID-19 (Lakhotia, 2022). Subsequent investigations, however, clarified that the illness represents a clinical variant of Hand-Foot-Mouth Disease (HFMD), predominantly caused by Coxsackievirus A-6 and A-16, belonging to the Enterovirus family (WHO, 2022; Kumar et al., 2023). The characteristic symptoms—red, painful, tomato-like blisters, fever, and fatigue—align closely with classical HFMD presentations reported in pediatric populations globally (Saha et al., 2023; Chen et al., 2020).

Transmission dynamics are consistent with enterovirus infections, involving direct person-to-person contact, contaminated surfaces, and respiratory droplets. Such mechanisms emphasize the need for strict hygiene, isolation during acute phases, and careful monitoring in childcare environments (Bian et al., 2021). Although Tomato Flu is typically self-limiting, its contagious nature poses risks of community spread, particularly in regions with dense populations and limited pediatric healthcare infrastructure (Mishra & Singh, 2022).

From a pharmacological perspective, current management strategies remain supportive, focusing on fever reduction, hydration, and symptomatic relief, as no virus-specific antiviral therapy exists (Chong et al., 2021). Investigational antiviral agents such as Pleconaril, Ribavirin, and IVIG have demonstrated potential against enteroviruses but require further clinical validation before routine application (Zhu et al., 2020). Vaccination represents a critical research frontier. While EV-71 vaccines are approved in China, no vaccine currently targets Coxsackievirus A-6 and A-16, highlighting the need for multivalent HFMD vaccine development (Li et al., 2022).

Traditional and herbal interventions such as neem, turmeric, and tulsi continue to be used in Indian households due to their anti-inflammatory and immunomodulatory properties. Nonetheless, systematic pharmacognostic validation is needed to integrate these remedies into evidence-based practice (Patil & Deshmukh, 2021). Strengthened pharmacovigilance, public awareness campaigns, and pediatric safety protocols are therefore vital to managing such outbreaks responsibly.

CONCLUSION

Tomato Flu, initially perceived as a novel pathogen, is now recognized as a clinical manifestation of HFMD caused by Coxsackievirus A-6 and A-16. Although generally mild and self-limiting, its high transmissibility in children underscores the importance of early detection, hygiene practices, isolation, and supportive care. Current treatment remains symptomatic, with ongoing research into antiviral therapies and multivalent HFMD vaccines offering promise for future control.

Public health efforts should focus on surveillance, pediatric education, and rational drug use to avoid antibiotic misuse. Moreover, validating traditional medicinal remedies through scientific studies may expand supportive care options. Overall, multidisciplinary collaboration in epidemiology, pharmacology, paediatrics, and public health is essential to prevent future outbreaks and safeguard child health.

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