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Review Article

Revisiting the therapeutic potential of homeopathic medicine Rhus Tox for herpes simplex virus and inflammatory conditions

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ABSTRACT

Background: Herpes simplex virus type-1 and type-2 cause a viral disease named Herpes. Genital herpes is mainly caused by HSV-2 with symptoms of painful and itchy blisters on the vagina, cervix, buttocks, anus, penis, or inner thighs with blisters that rupture and convert into sores. The homeopathic remedy Rhus Tox has been widely used to treat herpes and has shown *in vitro* anti-inflammatory effects in previous studies.
Purpose: The presented review focuses on relapses and harmful effects caused by acyclovir in modern medicine and the probable antiherpetic activity of Rhus Tox on HSV infection based on its pathophysiology, preclinical findings, on primary cultured mouse chondrocytes, mouse cell line MC3T3e1 and a comparative study of Natrum Mur with Rhus Tox on HSV infection.
Study design: The design of the study focuses mainly on the descriptive data available in various literature articles.
Method: Databases such as PubMed, Google Scholar, Medline and ScienceDirect were used to search the articles. Articles are selected from 1994 to 2022 focusing solely on the competence of Rhus Tox against herpes. Keywords used for the study are antiviral, Herpes, Rhus Tox, *in vitro* and homeopathy.
Results: The review includes fifteen articles, including 4 full-text articles on HSV, 6 *in vitro* studies of homeopathic compounds performed on the herpes virus, and 5 articles based on the pathophysiology and effects of Rhus tox. The review article proposes the anti-inflammatory and antiviral action of the homeopathic remedy Rhus Tox which can be used in crisis conditions when the physician doubts the simillimum, as it prevents further outbreaks of HSV infection.
Conclusion: The homeopathic medicine Rhus Tox has no cytotoxicity observed under *in vitro* conditions and can be used to treat herpes infection. Further studies are needed to confirm the results under *in vitro* and in vivo conditions as well as in clinical trials.

1. Introduction

The Herpes simplex viruses 1 and 2 (HSV1 and HSV2), also recognised by taxonomical names Human alpha herpesvirus 1 and Human alpha herpesvirus 2 [1], are the most pervasive viruses of the Herpesviridae family. HSV 1 and 2 are noted by a ubiquitous prevalence globally, having raising digits of infected individuals with time. An estimated 491.5 million people are surging with HSV-2 infection, whereas HSV-1 has affected even more, with 3.7 billion infected individuals. In 2016, according to the WHO estimated prevalence, 13.2% of the 15–49 years of age group of the general population were infected with HSV-2 infection [2]. The Global Burden of Disease (GBD) research has also published estimates for HSV type 2 infection (identical to the WHO statistics), most recently in 2017 [3]. In 2019, it was observed that HSV-1, primarily associated with oral infections, is increasingly becoming a leading cause of genital herpes [4]. In African countries, the prevalence of HSV-2 in 2020 was significantly high, which greatly increases the chances of contracting HIV [5]. The global prevalence of HSV outbreaks is rapidly increasing, necessitating the development of HSV vaccine to combat this diseased condition [6].

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The infection is able to outspread when a person with the infection begins to shed the virus. HSV-1 infection is generally developed orally during adolescence, and it could be physically transferred by oral exchange of saliva while kissing (felatio) [7]. Whilst the HSV-2 is known to be very well transmitted by private contact making it perhaps the best-known sexually transmitted infection [8]. Alongside its efficient mode of transmission, establishment of latent infection and its reactivation pile-up to the significant hurdle posed by HSV against its elimination [9]. The recrudescence of HSV 1 & 2 is accompanied with influences such as immune system and physico−chemical reactions namely UV rays, menstruation, stress, and fatigue [10].

The pathophysiology of HSV-1 & 2 are canker sores and anogenital herpes viral infection which are individualized by the presence of vesicular cysts in the orofacial and sexual organs which progressively dry up in the outer layers and may persist for up to 14 days. The improvement in blisters is significant and commences with a prodromal stage showing erythema, pustules which may evolve into blisters that get separated causing ulcer development [11]. The skin portion that is exposed is more susceptible to HSV attack. The infection after reactivation of the virus follows a pathway from infected neurons to the semilunar ganglia (oral manifestations) or spinal ganglia (genitalia-related disease), to target attached fibroblasts and the epithelial cells, containing new cankers that will replicate the course of extra neuronal infectious state [12,13].

The herpes simplex virus can lead to various complications such as increased susceptibility for infection with HIV, Alzheimer's disease, Atherosclerosis, Meningitis, Neonatal Herpes Encephalitis, Cranial neuropathy, HSV-2 radiculopathy, etc (Fig. 1) [14].

Treatment in modern medicine typically involves the use of antiviral drugs that target viral replication. This approach helps to reduce the severity of ulcers effectively and minimize the transmission of the virus to other individuals. Heavy consumption of anti-herpetic drugs (acyclovir and valacyclovir) has shown good suppression of the symptoms but could not prevent relapses. Most antivirals have little to no effect on individuals who are immunocompromised or HIV-positive and acquire HSV-2 infections.

Topically applied acyclovir can shorten the healing time of blisters, but it does not impact the dormant infection within the host neurons and therefore cannot provide a cure for the disease. As the infection undergoes variations by acquiring changes in gene expressions, prolonged use of antiviral medications contributes to the development of drug resistance. Second-line antivirals like acyclovir are not sustainable to variations and they come up with secondary effects such as abdominal discomfort and skin dryness triggering chronicity of the symptoms with frequent relapses. ACV when given to renal disease patients experiences the ill effects of neurotoxicity as they can't discharge the drug.

Homeopathic treatment for herpes infection: Homeopathic philosophy and science are based on treating the patient than his ailments. Various remedies with different concomitant symptoms are quite effective in herpetic care. According to the law of cure by Herings [15,16], cure takes place from the centre to periphery, from top to bottom, from inside to outside and from more important organ to less important organ and in the reverse sequence of their appearance.

Skin eruption is a sign of the body's defence mechanism in presence of infection. Healing begins when the disease is removed from the skin. Application with allopathic drugs suppresses the disease whereas homeopathy acts on both the root and effect of the disease process thereby curing the patient.

Modern medicines target only specific organs at a time, but there is a risk of widespread infection which influence complications such as meningitis or HSV-2 radiculopathy which are not observed after the use of homeopathy as the disease progression does not involve vital organs and the disease level stays on the skin layer itself. Topical application with allopathy for post-herpetic neuralgia suppresses the disease and only focuses on a single part in modern medicine whereas simple homeopathic drugs can give relief from maximum maladies in the most painless way with little or no side effects.

There exists a potential association between HSV-1 and Alzheimer's disease, particularly in individuals who carry the APOE epsilon4 allele. This allele affects the sensory system and poses a risk of promoting the development of Alzheimer's disease. The virus attaches itself to the parts and receptors of lipoproteins, which could advance the worsening of symptoms in Alzheimer's disease [17]. Modified herpes simplex infection is considered a likely treatment for malignant growth and has been extensively tested clinically for its oncolytic (elimination of disease) ability [18]. Herpes simplex virus is furthermore used as a trans neuronal tracer essential in connections among neurons by virtue of traversing synapses [19].

2. Methods

The study design focuses mainly on the descriptive data available in various medical literature articles. The review was done from May to December 2020 and the articles were chosen from the duration of 1994−2022 focusing on the effect of Rhus Tox on herpes. Databases such as PubMed, Google Scholar, Medline, Complementary Medicine and ScienceDirect were used to identify the articles. Keywords used for the study are 'antiviral', 'Herpes', 'Rhus Tox', '*in vitro*' and 'homeopathy'. Relevant research papers were reviewed including case studies, clinical trials, observational studies, case control studies, different books on homeopathy and

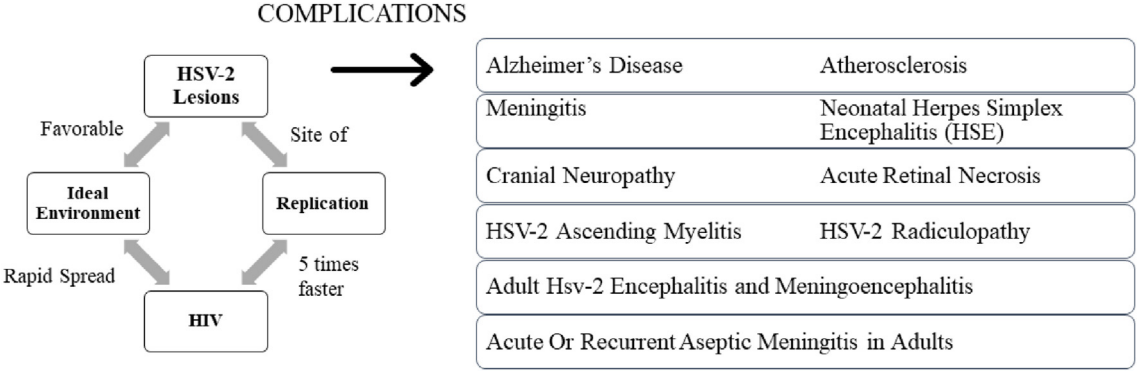

Fig. 1. Complications associated with Herpes infection.

pre-clinical experiments of homeopathic compounds. The review was confined to experiments based on herpes infection, the *in vitro* effects of homoeopathic medicines on herpes and the efficacy of Rhus Tox on herpetic management only. After the recognition of relevant studies, the review included 15 articles, including 4 full-text articles on HSV, 6 *in vitro* studies of homeopathic compounds performed on the herpes virus, and 5 articles based on the pathophysiology and effects of Rhus Tox. 15 publications which are relevant to the subject matter have been highlighted and discussed (Table 1 and Table 2).

2.1. Anti-herpes viral drugs and their mechanistic actions

Various drugs in allopathy are routinely administered against herpes, like Acyclovir (ACV, Zovirax (9 (2 hydroxyethoxymethyl) gauanine), Valacyclovir (VACV), penciclovir (PCV), famciclovir (FCV) Famvir). Antiherpetics add the analogue foscarnet pyrophosphate, the nucleotide analog of cidofovir [20]. The drugs used have severe side effects, durable action is not seen in various drugs and higher potency is needed for further action of the drug. These antiherpetics focus on the viral DNA polymerase and nucleotide analogue.

2.1.1. Mechanism of action of herpes virus

When an antiherpetic drug is induced, the main characteristics are absorption, distribution, metabolism, and excretion of the drug. Acyclovir (ACV) supports the anticancer activity of the nucleotide analogue, cytosine arabinoside, along with the antiherpetic activity due to the inhibition of adenosine deaminase. The recovery in the infected cell morphology notifies about the inhibitory activity of the drug against the virus and is a simple way of observing the mechanism of action. The selection of antiviral is mostly dependent on existing resistance as informed by the mutation sequencing in the targeted viral genes [20].

2.1.2. Antiviral target in early replication event

The potent inhibitor should stop the attack of a cell by the virus and arrest the spread of infection and assist as a protective agent. After replication events, the inhibitor should limit viral diseases and decrease inertial reactivation, for this immediate early gene (deleted IE). Antivirals act after the adsorption stage of HSV or CMV infections before viral DNA replication starts. The benzothiophene class interferes with the replication cycle of HSV type I by impeding rapid viral genomic expression, particularly the articulation of VP16 and ICPO [20].

2.1.3. Antiviral targets in HSV-DNA replication complex

Essential proteins (6–7) comprise the herpes viral DNA replication machinery that targets enzymatic targets for drug development and protein–protein interactions. The components are DNA binding protein (pUL29 and ICP8), accessory polymerase factor that is pUL42, helicase primase complex (pUL52, pUL8 and pUL5) and viral DNA polymerase that is pUL30. Antiviral action includes affecting protein recruitment and transport (post-translational modification), catalytic functions of enzymes in DNA synthesis process and ordered protein–protein binding events in replisome assembly [20].

2.1.4. Herpes virus DNA polymerase inhibitor

The Herpes virus possesses a multifunctional DNA polymerase enzyme which has both deoxynucleotide polymerizing activity and 3′-5′ exonuclease activity for proof-reading purposes. It has substrate recognition regions that are deduced by comparative modelling with the Klenow polymerase and by genetic investigation of mutants that are resistant to nucleoside or nucleotide analogues. The inhibitor can interrupt by binding either in the catalytic sites, or outside it such that it hampers the three-dimensional folding of the enzyme leading to the loss of enzyme function [20].

2.1.5. Herpes helicase-primase inhibitor

Herpes helicase-primase consists of 3 proteins that associate as a trimeric complex which unwinds the dsDNA in the 5′-3′ direction, RNA polymerase activity and ssDNA-stimulated ATPase activities. The gene elements of HSV are UL5, UL8, UL52 and ORF's. The mechanism of inhibition has stabilization constraints not only to enzyme progression through DNA unwinding reaction, but also to primase catalytic activity [20].

2.1.6. Inhibitors of DNA processing and packaging

Post herpes virus DNA replication, the concatemeric product is bundled into preformed capsids and cut into unit-length genomes by site-explicit cleavage. By similarity with DNA bacteriophage processing and packaging, a terminase complex ties to the capsid portal, further trims the concatemeric DNA at a particular

Table 1
Compilation of *in vitro* experiments of homeopathic compounds (Abbreviations: HSV 1 & 2 – herpes simplex virus type 1 and 2, ACV- Acyclovir).

Sr. No	Author	In vitro activity	Homeopathic medicine	Potency	Methodology	Conclusion
1.	A. V. Nefedchenko et al. (2001)	MDBK and KST cell line. Bovine HSV-1 & bovine viral diarrhoea virus-1	Euphorbium compositum, Nasentropfen S, Engystol & Echinacea compositum	Compo-sition	Virus neutralization test	Reducing virus concentration & the duration of nasal shedding in calves
2.	B. Glatthaar-Saalmuller et al. (2001)	Influenza A, HRV and HSV-1	Composition-Euphorbium resinifera, Pulsatilla P, *Luffa operculata*	Extracts	Plaque Reduction Assay	Considerable plaque reduction
3.	Silke Nolkemper et al. (2006)	RC37 cell; HSV-1, HSV-2, HSV-1 (ACV)	Aqueous extracts-Lamiaceae family	Extracts	Plaque reduction assay	Plaque formation significantly reduced; HSV-1 and HSV-2 by more than 90% and ACV by more than 85%
4.	Frenkel (2009)	MDA-MB-231 & MCF-7 cell line; breast cancer	Carcinosin, Phytolacca, Conium, Thuja	30C, 200C, 3C, 30C	MTT Assay & Western blot analysis	Modification in the expression of dephosphorylation of glycated Rb
5.	Sammader A et al. (2013)	Hela cell line; anticancer effect	Lyco Clavatum	LC-5C, LC 15C	Flow cytometry & fluorescence microscopy	Induced apoptosis in the form of early DNA damage
6.	Sayed Monavari et al. (2012)	Vero cell line; HSV-1	Chelidonium Majus	Extracts	Cytotoxicity, Yield reduction, antigenic expression test.	Significant reduction in first-pass protein synthesis preventing viral gene expression

Table 2
Summary of action of Rhus Toxicodendron.

Sr. No	Author	Rhus Tox activity	Potency	Methodology	Conclusion
1.	White K (1994)	Recurrent cutaneous HSV-1 clinical trial	Different potencies	Clinical trial	50% patients were prescribed Rhus Toxicodendron
2.	A L dos Santos et al. (2007)	Carrageenan-induced paw oedema in rats in vivo	6C, 12C, 30C & 200C	Writhing test in mice, Stress induced gastric lesions	Influence inflammatory processes-histamine, prostaglandins & inflammatory mediators
3.	Allahverdiyev A et al. (2013)	42 patients- Skin lesions caused by RT ingestion	–	Oral or parenteral contact	Pathophysiology and symptoms justify use of RT against herpes
4.	Huh, Yun Hyun et al. (2013)	Primary cultured mouse chondrocytes *in vitro*	4X, 30X, 30C and 200C	Quantitative (real-time) RTPCR or qRTPCR and immunoblot tests.	Increased cox2 mRNA expression, inhibited the expression of type 2 collagen.
5.	Lee, Kyung Jin et al. (2016)	Mc3t3e1 mouse cells *in vitro*	Different potencies	(RT-PCR) and immunoblotting	Increased PGE2 release with higher levels of COX2 expression

arrangement with distinct features, moves the DNA inside the capsid and lastly cleaves the DNA at a specific repeat of the sequence. This pathway provides the chance of finding extremely specific antiviral candidate agents [20].

2.1.7. HSV and existing antivirals

Current antivirals interfere with HSV disease where the lesions contain virions and invading leukocytes. Effective annihilation of these infections is not found in today's drugs from neurons [21]. Immuno-compromised or HIV-positive people who are infected with HSV-2 are unaffected by most antivirals. The elongation of the viral genome is observed during the replication which is executed by the viral DNA polymerase. Acyclovir when in its triphosphate structure turns into a substrate for viral DNA polymerase by interfering with DNA combining, limiting the combining of new duplicates of the popular genome which therefore has, at this stage, less developed infection by viral particles. It does not affect the inert infection in the host's neurons and is therefore unable to cure the disease. Infection variants are safe by obtaining changes in the gene coding viral thymidine kinase that reduces the enzyme expression or regulates substrate particularity by suppressing ACV phosphorylation.

3. Association of HSV and other maladies

3.1. Alliance of HSV-2 and HIV infection

The causal risk level of HIV with HSV-2 infection was extended to 80% HSV-2 infection in 47% of the population [22]. An increased risk of acquiring HIV among HSV-2-positive heterosexual men and MSM (bisexual men) is found in cohort and case—control studies. In agricultural countries, there is a higher indicator of relative risk for control cases and cross-sectional surveys. The danger of HIV is higher when the patient suffers from genital herpes or recurrent genital ulcers since the site of ulceration is the objective passage point for the infection to enter the body through the mucosal surfaces. HIV virions are widely visible (>95%) at the site of genital herpes. HSV-2 canker sores are an ideal environment for the rapid progression of HIV infection. Other sexually transmitted diseases can set up a similar cellular atmosphere favourable for HIV infection. In accordance with the study, tissue developed from the sites of healed HSV-2 sores replicate HIV 3 to 5 times more rapidly than tissue cultured from control sites [22].

3.2. Reactivation of genital HSV-2 infection

Symptomatic individuals have a higher possibility of viral reactivation than asymptomatic individuals. A probable report of genital spread of HSV infection in 53 subjects who had antibodies but had no incidental symptoms suggest the pattern of viral spread compared with 90 symptomatic subjects. 62% of females and 64% of men without genital herpes developed sores and ulcers during the development of the infection. 37 selected patients without genital disease with HIV, underwent antibody testing and 16 subjects underwent HSV-2 immunization testing but were randomly confirmed to carry HSV-2 antibodies. The results stated that seropositivity for HSV-2 is related to viral shedding in the anogenital area [9].

3.3. Link to HSV disease and atherosclerosis (AS)

In the subgroup analysis of 17 studies, increased risks for AS was observed in the group with myocardial ischemia, the group with a male proportion >60%, and the age group ≤60 years [23]. Herpesvirus is involved in inflammatory atherosclerotic interaction where constant occurrence of irritation from the virus is assumed to advance atherosclerosis and thrombosis. It has been explained in 1991 why HSV-infected VSMCs accumulated more impregnated cholesterol esters and triacylglycerols than uninfected cells. According to Key et al. HSV can worsen the thrombus on atherosclerotic plaques and start coagulant degradation by reducing thrombomodulin's activity and enhancing tissue factor mobility [24].

Much research has detailed the identification of HSV-1 DNA in human vascular tissues from various sites and is also represented in the tissue of the coronary artery. HSV-1 DNA was discovered in carotid artery occlusive plaques by Chiu et al. and it was also discovered in the atherosclerotic tissues of six different types of Shi and Tokunaga atherosclerotic lesions [25]. The adverse effects of androgen on the plasma lipid and lipoprotein profile result in thrombosis and cardiac hypertrophy which have all the potential of being connected to an increased likelihood of coronary disease.

4. Critical perspectives of homeopathy

Homeopathy is derived from a Greek word homoios whose meaning is “like” and pathos means “suffering” [26]. It is a system of alternative medicine that states that any substance that produces disease in a person can cure it in diseased individuals which are based on the “law of similars”. It is based on the principle “like can be cured by like” called **“Similia Similibus Curentur”**. A German physician named **Samuel Hahnemann** (1755—1843) developed this method. After allopathy and Ayurveda, homeopathy is the third most popular medical treatment in India. According to a nationwide health study conducted in 2014 in India, 3% of people take homeopathic medicines [27].

It is said that high medication dosages of the drugs that have triggered similar symptoms can only worsen the disease, and therefore extreme dilutions are used. A technique was invented with dilution and succussion of diluted homeopathic dilutions beyond Avogadro's number which preserve the biological activity of the substances while suppressing its harmful effects. The most potent and deep-acting drugs are those that are more diluted and have a higher potency [26]. The dilution process enhances the hidden dynamic energy of the medicinal raw materials which is aroused into activity [28]. Different homeopathic remedies used to treat herpes are Rhus Tox, Ars Alb, Natrum Mur, Mezereum, Calendula ointment, etc.

4.1. Homeopathy based In vitro studies

Homeopathic preparations are tested at the cellular level in the studies conducted for the *in vitro* effects of homeopathic medicines. A normal part of tissue development and regeneration is apoptosis, which can be caused by homeopathic remedies. During the growth and development of the foetus, the control of the immune response and in the removal of diseased and altered cells., apoptosis plays a crucial part although there is a chance of long-term viral infections in excessive apoptosis [29].

4.1.1. Anticancer impact of Lycopodium on Hela cells

Using a potent Lyco Clavatum preparation that has been significantly diluted, anti-cancer effects on HeLa cells were evaluated (LC-5C and LC 15C). Lycopodium had little impact on blood flow, however, it significantly induced apoptosis in the form of early DNA damage in Hela cancer cells. There is no cell death in cancer cells from Homeopathic medicines above and below Avogadro's number (Table 1) [30].

4.1.2. Anticancer effect of homeopathy on breast cancer cell lines

Carcinosin, Phytolacca, Conium, Thuja are homeopathic medicines that are tested on cell lines of breast cancer. The cell line used was MDA-MB-231 and MCF-7 acquired from preserved mammary epithelial cells. Cell death and cell cycle breakdown result from their toxicity to cells. In exposed cells, there was a modification in the expression of cyclins such as dephosphorylation of glycated Rb, and increased expression of the p27 CDK receptor (Table 1) [31].

4.1.3. Antiviral agents of homoeopathy upon viruses

Euphorbium compositum SN, a cure complex containing three parts have been utilized since 1984 for the treatment regimen of irritation of the nasal mucosa. The review investigates the antiviral activity of Euphorbium compositum SN, as well as its plant-determined components, with a focus on their activity against a set of human pathogen infections including both RNA and DNA infections, herpes simplex type 1 infection. The antiviral activity of examined substances against RSV resulted in considerable plaque reduction.

As Euphorbium compositum SN is a combination of several agents and compounds of plant origin, the clear efficacy against RSV is exhibited, demonstrating that these herbal compounds have antiviral properties that are equivalent to those of the treatment complex Euphorbium compositum SN (Table 1) [32].

4.1.4. Role of Lamiaceae family against HSV

The antiviral activity for Herpes simplex virus (HSV) is tested using Aqueous extracts of species of the Lamiaceae family. Extracts of lemon balm, peppermint, sloe, rosemary, sage and thyme are used for the study. The plaque reduction assay was employed utilizing RC37 cells to assess the inhibitory impact against HSV-1, HSV-2, and an acyclovir-resistant strain of HSV-1 (ACV). Plaque formation has significantly reduced HSV-1 and HSV-2 by more than 90% and ACV by more than 85%. There is no effect on intracellular viral replication but there is an effect on HSV (Table 1) [33].

4.1.5. Efficacy of Chelidonium on HSV-1

Chelidonium majus L. against herpes simplex virus type-1 for an in-vitro antiviral activity was initiated [34] using cytotoxicity, yield reduction test, viral infection and antigenic expression test. The impact of different concentrations of the phyto-extract on the vero cell lines is assessed post 72 h of incubation by neutral red staining method. Inhibition of viral yield shows that the first passage viral titre can be drastically reduced when cells are treated with the extract 1 h after infection. The inhibitory action of the extract was brought about by the prevention of protein expression of α genes or by the repression of the function of the integumentary protein VP16. This indicates that the extract can prevent viral gene expression at the transcriptional or translational level (Table 1) [34].

4.1.6. The action of different homeopathic compounds on bovine HSV-1

An *in vitro* and in vivo study of Euphorbium compositum, Nasentropfen S, Engystol and Echinacea compositum are used for tissue cultures measured by a decrease in viral concentration against bovine herpes virus-1 and bovine viral diarrhoea virus-1 [35] which is done by exposing the calves to these viruses. The results establish that the combination of above homeopathic remedies at 100 μL/mL show no toxicity for MDBK (Madin Darby Bovine Kidney) and KST cell cultures. The combination of homeopathic remedies has low toxicity for MDBK and KST cell cultures. Engystol plays a role in reducing virus concentration and the duration of its nasal shedding in calves (Table 1) [35].

5. Historic background of Rhus Toxicodendron

The botanical name is *Rhus Toxicodendron Linn;* drug of the Anacardiaceae family. Its common name is poison ivy, trailing sumac, pubescent and poison oak [36]. Its active principles are Toxicodendralis, Urushiol, Pheridic oil, Fisetin, Gallico and tannin with a pH between 5.20 and 6.00. The name of the genus is derived from the Greek words (toxikos) for “poison” and (dendron) for “tree”. It was introduced to England as a herb in 1640. In 1798 Duffresnoy of Vallenciences first used it as a medicinal plant. He was notified by the cure of a young man of a six-year-old herpes rash, due to coincidentally touching the plant. Hahnemann described it in 1816 under the traditional name Rhus in Allen's Encyclop. Mat. Med.-Vol.VIII, 330 [36].

Its origin is from the vegetable kingdom where the less juicy part is used for the preparation of the mother tincture. It has a deciduous shrub up to 1 m tall with reddish branching stems and ascending rootlets. The entire plant is exceedingly toxic, milky and contains acrid juice. Its sphere of action is mainly on the skin, nerves, tissues, lymphatic glands, etc. The tincture contains rhoitannic acid (C18H28O13) and toxicodendric acid which is harmful [37,38].

5.1. Pathogenesis and guiding features of Rhus Tox

The effects of Rhus Tox administration are many. Dizziness and a mild form of intoxication appear first, followed by redness and swelling of the afflicted area, along with terrible stinging and burning. Along with extreme agitation, discomfort, thirst, and fever; there is an infiltration of the face and eyes with clumping of the eyelids. After some time, confluent bullae appear on the skin's

surface. This is followed by erysipelas-like dermatitis, which can expand aggressively and finally affect the mucous membranes.

When applied topically it causes itching, blisters, pemphigus, and skin eczema that can spread to the mucous membranes. When ingested or inhaled, colicky abdominal pain, worse at night, tenesmus, bloody stools and urine, often typhoid-like or intermittent fever, rheumatoid pains relieved by heat and aggravated by rest. It also produces serous secretions in the form of oedema. It acts on the lymph nodes, causing inflammation [38,39]. Therapeutic indications are Cellulitis, Carbuncles, Chilblains, Dengue Fever, Eczema, Erysipelas, Herpes Zoster, Measles, Rheumatism, Sprains, Urticaria etc [38].

5.2. Rhus Tox as anti-inflammatory agent

Rhus tox is used in inflammatory states. It is compared with succussed ethanol controls and active controls. Rhus Tox dilution is used in 6C, 12C, 30C and 200C potencies using carrageenan-induced paw oedema in rats. RT 6C is more effective in the tests. Contractions of vascular permeability induced by peritoneal acetic acid have been observed *in vitro* and gastric lesions induced by stress. The dilution of Rhus Tox appears to influence inflammatory processes involving histamine, prostaglandins, and inflammatory mediators (Table 2) [40].

5.3. Application of anti-herpetic compound Rhus Tox

The dynamic binding that produces the responses is “urushiol”, its active ingredient. In the acute phase, oral or parenteral contact with certain allergens may result in an eczematous skin reaction [41]. In a study involving 42 patients having skin lesions with systemic contact dermatitis caused by Toxicodendron ingestion, 14 have a background characterized by sensitivity to the enamel, skin lesions are present, e.g., erythema multiforme-like lesions (7%), maculopapular rash (50%), vesiculobullous lesions (14%) and erythroderma (29%). Hepatic capacity irregularities occurred in some patients (5%). Clinical signs with Toxicodendron sensitivity for more than 10 years include maculopapular rashes (65%), erythroderma (19%), erythema multiforme (32%) with pustules and papules. The pathophysiology and symptoms of the drug support the justification for the use of the drug against the manifestations of herpes (Table 2) [37–39].

5.4. Analysis of RT on primary cultured mouse chondrocytes

A study on primary cultured mouse chondrocytes was done with Rhus Tox potency of 4X, 30X, 30C and 200C. An inducible enzyme chondrocyte marker protein, cyclooxygenase 2 (cox2) (cyclooxygenase (COX) 2 which is involved in the production of prostaglandins in inflammatory processes) was examined. Collagen type II and cox2 were tested using biochemical and immunological methods such as qRTPCR analysis and immunoblot tests. The results confirmed that RT of different concentrations increases cox2 mRNA expression. Rhus tox 30x showed the highest mRNA expression in qRTPCR. RT 30x increased PGE2 release (Table 2) [42].

5.5. Assessment of Rhus Tox on Mc3t3e1 mouse cells

The previous study explored the COX2 expression and prostaglandin E2 (PGE2) in primary cultured mouse chondrocytes stimulated with Rhus tox (Table 2). Rhus tox driven MC3T3e1 cells show increased expression of Cox2 mRNA [43]. Cox2 expression is generally increased in MC3T3e1 cells stimulated with 30X Rhus tox. It increased PGE2 release in Rhus-stimulated MC3T3e1 cells. 30X Rhus tox treated MC3T3e1 cells show more significant levels of PGE2 creation than control and homeopathic dilutions. Rhus-tox treated MC3T3e1 30C cells showed higher levels of COX2 expression. In view of these results, it can be concluded that Rhus Tox homeopathic dilution is directly linked to the expression of the COX2 gene and the inflammatory reaction in MC3T3e1 cells (Table 2) [43].

5.6. Clinical evidence of Rhus Tox on recurrent cutaneous HSV-1 infection

The justification for the review is to decide on the feasibility of similar and homeopathic treatments Natrum muriaticum and Rhus Toxicodendron on the treatment of cutaneous intermittent infection of herpes simplex 1 [44]. The impact of treatment on suffering time, scab shedding time with full recovery time in days, and several sores were observed in Natrum Muriaticum and Rhus Toxicodendron Group. Compared to the first recurrence at baseline, the duration of aggravation from the second recurrence to the fourth recurrence was reduced. The probability of loss of the outer mucosal layer of skin was reduced from the second to the sixth recurrence. It is found that the simillimum group shows a 21% safer treatment response than the NM and RT group. 42% of remedies prescribed as acute prescription are NM and 50% are RT (Table 2) [44].

6. Discussion

Protection with currently authorized antivirals (ACV, PCV and their prodrugs) is weak considering HSV isolates that cannot completely be eradicated by these drugs despite their widespread use. Most ACV-safe HSV infections (TK-lacking) fail to reactivate after inactivity, minimizing the possibility of transmission and hence an ACV-safe infection is seen. Compared to an immunocompetent person, an immunocompromised patient is considerably more likely to experience sickness, and the clinical consequences end up being a major challenge.

Acyclovir, when given to patients with kidney disease, experience the negative effects of neurotoxicity as they cannot offload the drug [45]. Topical acyclovir reduces the time of recovery by only 2 days of cold sores and 3 days of infection with genital herpes. Recovery time from skin blisters is long after the administration of modern medicine [46]**.** Risk assessments noticed in cross-sectional and case−control studies could be misleading because the proportion of probabilities and associated hazards may differ depending on the prevalence. A higher percentage worldwide can be caused by HSV-2 infection which then facilitates easy HIV infection [22]. Seropositivity for HSV-2 infection is linked to viral transmission in the anogenital part, even in asymptomatic people who do not show any symptoms [47]. The meta-survey confirms that HSV-1 and HSV-2 diseases may constitute the danger of AS. However, further massive, and highly planned investigations are needed to affirm these findings, including multiple geographic locations and careful coordination between cases and witnesses [23]. Inhibitory, virucidal and preventive effects of various homeopathic remedies are studied under in-vitro and in-vivo conditions.

According to all experiments, homeopathic remedies are advantageous in cell cultures against a wide range of microorganisms. All drugs are often used at the same dosage of 100 μL/mL, which is not harmful to cell cultures, to rule out a dose-dependent impact of antiviral activity [48]. The extracts of Lamiaceae have an antiviral effect on HSV and can be used for topical application for recurrent herpetic eruptions [33]. Chondrocyte dedifferentiation and inflammatory responses such as COX2 expression and PGE2 generation were caused by Rhus Tox in primary cultured chondrocytes [42]. According to homeopathy, a disease-producing power of the

medicine is the disease-curing power of that medicine (Law of Similars) [49]. Rhus tox of the Anacardiaceous family contains the active ingredient urushiol, which can cause severe allergic reaction when in direct contact with the skin [50]. Homeopathy treats patients holistically taking into consideration all the physical, mental and characteristic ailments of the patient. Rhus tox can effectively relieve all the symptoms of herpes infection, including pain, blisters, redness, restlessness, etc. Rhus Tox can effectively penetrate the capsid structure of the infected cells and cure the patient. Rhus tox in different potencies is currently being used to treat inflammatory and viral diseases. Rhus Tox is more likely to be used as a recommended "complex crisis" remedy in severe cases where a specific remedy (Similimum) is doubtful or by non-homeopaths [44]. Homeopathic remedies are safe and effective with minimum side effects [51]. More experimental investigations are needed to confirm the probable therapeutic benefits of Rhus Tox and other suitable preparations for the control of herpes infection.

7. Conclusion

There is a requirement for successful treatment that prevents or minimizes the recurrence of HSV-1 and HSV-2 episodes and further decreases the severity of exacerbations. In homeopathy, many treatments have been clinically proven to have some impact, and in individual cases a solution for herpes viruses. Homeopathy can prevent further outbreaks of herpes simplex infection. Simillimum, especially when used long-term, appears to be the most effective in managing the herpes simplex virus. It follows the individual in general, within the framework of homeopathic laws and standards, and considers the variety of explicit conditions of each patient.

Rhus tox when prescribed as a single simillimum individualized indicated homeopathic remedy can work on multiple organs such as skin, tissues, vital organs and digestive system at a time-alleviating almost all the symptoms. Lower potencies are recommended during acute stage of infection to prevent unintended aggravation of effect of Rhus Tox which can cause skin irritation in some cases. Higher potencies are more beneficial in conditions with repeated relapses and recurring symptoms. Hence there is no excessive exposure to other drugs as a single drug is sufficient to cure the patient.

Other homeopathic remedies which can be used for herpes infection are Natrum Mur, Hepar Sulph, Graphites, Arsenic Alb, etc. It is suggested to expand the sample size of clinical trials, which would help the acceptability of other reviews as small sample groups are inappropriate and the correlation within the clusters is not realistic due to different sample sizes. Similarly, the treatment time must be extended before the start of treatment by recording the number of lesions each month/year to choose a more similar set of recurring symptoms. Homeopathy strengthens immunity to fight infections and contributes to mental, physical, and social well-being, hence complementary therapies should be used along with the traditional antiviral drugs to give maximum comfort to the patient.

Author's contribution

MDS: Review of Literature and Manuscript Writing, Approving the final version.

SAP: Supervision, Manuscript Editing, Approving the final version.

AM: Supervision, Manuscript Editing, Approving the final version.

VN: Supervision, Manuscript Editing and revision, Approving the final version.

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Conflicts of interest

All authors declare that there is no conflict of interest between all authors and with any other person.

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References

[1] Cliffe A, Chang L, Colgrove R, Knipe DM. Herpes Simplex Virus. Reference Module in Biomedical Sciences 2014. https://doi.org/10.1016/B978-0-12-801238-3.00080-5. Elsevier.
[2] McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. NCHS Data Brief 2018:1–8.
[3] James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789–858. https://doi.org/10.1016/S0140-6736(18)32279-7.
[4] Durukan D, Fairley CK, Bradshaw CS, Read TRH, Druce J, Catton M, et al. Increasing proportion of herpes simplex virus type 1 among women and men diagnosed with first-episode anogenital herpes: a retrospective observational study over 14 years in Melbourne, Australia. Sex Transm Infect 2019;95:307–13. https://doi.org/10.1136/sextrans-2018-053830.
[5] Looker KJ, Welton NJ, Sabin KM, Dalal S, Vickerman P, Turner KME, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. Lancet Infect Dis 2020;20:240–9. https://doi.org/10.1016/S1473-3099(19)30470-0.
[6] Gottlieb SL, Giersing B, Boily MC, Chesson H, Looker KJ, Schiffer J, et al. Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization Consultation on HSV Vaccine Impact Modelling. Vaccine 2019;37:7336–45. https://doi.org/10.1016/j.vaccine.2017.03.074.
[7] Wald A. Genital HSV-1 infections. Sex Transm Infect 2006;82:189–90. https://doi.org/10.1136/sti.2006.019935.
[8] Schiffer JT, Mayer BT, Fong Y, Swan DA, Wald A. Herpes simplex virus-2 transmission probability estimates based on quantity of viral shedding. J R Soc Interface 2014;11:20140160. https://doi.org/10.1098/rsif.2014.0160.
[9] Wald A, Zeh J, Selke S, Warren T, Ryncarz AJ, Ashley R, et al. Reactivation of Genital Herpes Simplex Virus Type 2 Infection in Asymptomatic Seropositive Persons. New England Journal of Medicine 2000;342:844–50. https://doi.org/10.1056/NEJM200003233421203.
[10] Grinde B. Herpesviruses: latency and reactivation - viral strategies and host response. J Oral Microbiol 2013:5. https://doi.org/10.3402/jom.v5i0.22766.
[11] Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. J Am Acad Dermatol 2007;57:737–63. https://doi.org/10.1016/j.jaad.2007.06.027. quiz 764–6.
[12] Campadelli-Fiume G, Menotti L. Human Herpesviruses- Biology, Therapy, and Immunoprophylaxis; Basic virology and viral gene effects on host cell functions: alphaherpesviruses; Entry of alphaherpesviruses into the cell. Cambridge University Press; 2007.
[13] Verzosa AL, McGeever LA, Bhark S-J, Delgado T, Salazar N, Sanchez EL. Herpes Simplex Virus 1 Infection of Neuronal and Non-Neuronal Cells Elicits Specific Innate Immune Responses and Immune Evasion Mechanisms. Front Immunol 2021;12:644664. https://doi.org/10.3389/fimmu.2021.644664.
[14] Berger JR, Houff S. Neurological Complications of Herpes Simplex Virus Type 2 Infection. Arch Neurol 2008;65. https://doi.org/10.1001/archneur.65.5.596.
[15] Kent JT. Reprinted 4th ed. Lectures on Homoeopathic Philosophy; Lecture 35 Prognosis after observing the action of the remedy. New Delhi, India: B. Jain Publishers; 1997.

[16] Saha S, Koley M, Arya JS, Choubey G, Ghosh S, Ganguly S, et al. Hering's law assessment tool revisited. J Evid Based Complementary Altern Med 2014;19:260–6. https://doi.org/10.1177/2156587214543142.
[17] Middleton PJ, Petric M, Kozak M, Rewcastle NB, Crapper McLachlan DR. Herpes-simplex viral genome and senile and presenile dementias of Alzheimer and pick. The Lancet 1980;315:1038. https://doi.org/10.1016/S0140-6736(80)91490-7.
[18] Varghese S, Rabkin SD. Oncolytic herpes simplex virus vectors for cancer virotherapy. Cancer Gene Ther 2002;9:967–78. https://doi.org/10.1038/sj.cgt.7700537.
[19] Norgren RB, Lehman MN. Herpes simplex virus as a transneuronal tracer. Neurosci Biobehav Rev 1998;22:695–708. https://doi.org/10.1016/S0149-7634(98)00008-6.
[20] Karen Biron Affiliations AK. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Chapter 68 Candidate anti-herpesviral drugs; mechanisms of action and resistance. Cambridge University Press; 2007.
[21] Álvarez DM, Castillo E, Duarte LF, Arriagada J, Corrales N, Farías MA, et al. Current Antivirals and Novel Botanical Molecules Interfering With Herpes Simplex Virus Infection. Front Microbiol 2020:11. https://doi.org/10.3389/fmicb.2020.00139.
[22] Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. J Infect Dis 2002;185:45–52. https://doi.org/10.1086/338231.
[23] Wu YP, Sun DD, Wang Y, Liu W, Yang J. Herpes Simplex Virus Type 1 and Type 2 Infection Increases Atherosclerosis Risk: Evidence Based on a Meta-Analysis. Biomed Res Int 2016. https://doi.org/10.1155/2016/2630865.
[24] Key NS, Bach RR, Vercellotti GM, Moldow CF. Herpes simplex virus type I does not require productive infection to induce tissue factor in human umbilical vein endothelial cells. Lab Invest 1993;68:645–51.
[25] Shi Y, Tokunaga O. Herpesvirus (HSV-1, EBV and CMV) infections in atherosclerotic compared with non-atherosclerotic aortic tissue. Pathol Int 2002;52:31–9. https://doi.org/10.1046/j.1440-1827.2002.01312.x.
[26] Merrell WC, Shalts E. Homeopathy Medical Clinics of North America 2002;86:47–62. https://doi.org/10.1016/S0025-7125(03)00071-3.
[27] Rudra S, Kalra A, Kumar A, Joe W. Utilization of alternative systems of medicine as health care services in India: Evidence on AYUSH care from NSS 2014. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0176916.
[28] Elia V, Niccoli M. Thermodynamics of Extremely Diluted Aqueous Solutions. Ann N Y Acad Sci 1999;879:241–8. https://doi.org/10.1111/j.1749-6632.1999.tb10426.x.
[29] Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol 2007;35:495–516. https://doi.org/10.1080/01926230701320337.
[30] Samadder A, Das S, Das J, Paul A, Boujedaini N, Khuda-Bukhsh AR. The Potentized Homeopathic Drug, Lycopodium clavatum (5C and 15C) Has Anticancer Effect on HeLa Cells In Vitro. J Acupunct Meridian Stud 2013;6:180–7. https://doi.org/10.1016/j.jams.2013.04.004.
[31] Frenkel. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. Int J Oncol 2009;36. https://doi.org/10.3892/ijo_00000512.
[32] Glatthaar-Saalmüller B, Fallier-Becker P. Antiviral action of Euphorbium compositum and its components. Forsch Komplementarmed Klass. Naturheilkd 2001;8:207–12. https://doi.org/10.1159/000057223.
[33] Nolkemper S, Reichling J, Stintzing F, Carle R, Schnitzler P. Antiviral Effect of Aqueous Extracts from Species of the Lamiaceae Family against *Herpes simplex* Virus Type 1 and Type 2 *in vitro*. Planta Med 2006;72:1378–82. https://doi.org/10.1055/s-2006-951719.
[34] Seyed Hamidreza M. Evaluation of in vitro antiviral activity of Chelidonium majus L. against herpes simplex virus type-1. Afr J Microbiol Res 2012;6. https://doi.org/10.5897/AJMR11.1350.
[35] Nefedchenko AV, Glotova TI, Glotov AG. In vitro and in vivo activity of homeopathic drugs against bovine herpesvirus-1 and bovine viral diarrhoea virus 1. Bulg J Vet Med 2015;18:56–64. https://doi.org/10.15547/bjvm.846.
[36] The Names of Plants. Toxicodendron. Fourth Edition. Cambridge University Press; 2008. p. 382.
[37] Murphy R. Lotus Materia Medica. Rhus Toxicodendron. Third Edition. B. Jain Publishers Pvt. Limited; 2010.
[38] Garth WB. Boericke's New Manual of Homeopathic Materia Medica with Repertory; Rhus Toxicodendron. Third Edition. B.Jain Large Print; 2010.
[39] Leaders in Homeopathic Therapeutics. Rhus Toxicodendron. B Jain Pub Pvt Ltd; 2013.
[40] dos Santos AL, Perazzo FF, Cardoso LGV, Carvalho JCT. In vivo study of the anti-inflammatory effect of Rhus toxicodendron. Homeopathy 2007;96:95–101. https://doi.org/10.1016/j.homp.2007.03.001.
[41] Cardinali C, Francalanci S, Giomi B, Caproni M, Sertoli A, Fabbri P. Contact dermatitis from Rhus toxicodendron in a homeopathic remedy. J Am Acad Dermatol 2004;50:150–1. https://doi.org/10.1016/S0190-9622(03)01476-2.
[42] Huh YH, Kim MJ, Yeo MG. Homeopathic Rhus toxicodendron treatment increased the expression of cyclooxygenase-2 in primary cultured mouse chondrocytes. Homeopathy 2013;102:248–53. https://doi.org/10.1016/j.homp.2013.07.001.
[43] Lee KJ, Yeo MG. Homeopathic Rhus toxicodendron has dual effects on the inflammatory response in the mouse preosteoblastic cell line MC3T3-e1. Homeopathy 2016;105:42–7. https://doi.org/10.1016/j.homp.2015.09.004.
[44] White K. The homoeopathic treatment of recurrent cutaneous herpes simplex I. Durban University of Technology; 1994. https://doi.org/10.51415/10321/2021.
[45] Ryan L, Heed A, Foster J, Valappil M, Schmid ML, Duncan CJA. Acute kidney injury (AKI) associated with intravenous aciclovir in adults: Incidence and risk factors in clinical practice. Int J Infect Dis 2018;74:97–9. https://doi.org/10.1016/j.ijid.2018.07.002.
[46] Martinez V, Caumes E, Chosidow O. Treatment to prevent recurrent genital herpes. Curr Opin Infect Dis 2008;21:42–8. https://doi.org/10.1097/QCO.0b013e3282f3d9d3.
[47] Wald A, Zeh J, Selke S, Warren T, Ryncarz AJ, Ashley R, et al. Reactivation of Genital Herpes Simplex Virus Type 2 Infection in Asymptomatic Seropositive Persons. New England Journal of Medicine 2000;342:844–50. https://doi.org/10.1056/NEJM200003233421203.
[48] Cunningham AL, Diefenbach RJ, Miranda-Saksena M, Bosnjak L, Kim M, Jones C, et al. The cycle of human herpes simplex virus infection: virus transport and immune control. J Infect Dis 2006;194(1). https://doi.org/10.1086/505359. S11-8.
[49] Drofenik M. Homeopathy and Law of Similars. La Prensa Medica Argentina 2019:105. https://doi.org/10.47275/0032-745X-152.
[50] Aguilar-Ortigoza CJ, Sosa V, Aguilar-Ortigoza M. Toxic Phenols in Various Anacardiaceae Species. Econ Bot 2003:354–64.
[51] Dantas F, Rampes H. Do homeopathic medicines provoke adverse effects? A systematic review. British Homeopathic J 2000;89:S35–8. https://doi.org/10.1054/homp.1999.0378.