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Review Article

Effective Natural Drug Remedies against *Herpes Zoster*: A Review

Shinde Poonam R*, Patil Pankaj S, Bhambar Rajendra S

Department of Pharmacognosy, MGV'S Pharmacy College, Panchavati-422003, Dist: Nasik, Maharashtra, India

Abstract

Herpes zoster (HZ), also known as shingles, is a painful vesicular rash resulting from reactivation of the virus that also causes chickenpox – *Varicella zoster* virus (VZV). Typically, the rash runs its course in a matter of 4-5 weeks. The pain, however, may persist months, even years, after the skin heals. This phenomenon is known as postherpetic neuralgia (PHN). This review tried to provide more comprehensive and accurate data on the effects of different herbals on the VZV as a probable alternative treatment for VZV. Further clarification of the herbals interactions with VZV is required which could provide valuable information about the chemical nature and mechanism(s) of action of the potential anti-VZV molecule(s) and all the most potential plant extracts must undertake further analysis and purification steps with the aim of identifying the active elements existing in the herbals.

Key words: *Herpes zoster* (HZ), Shingles, *Varicella zoster* virus (VZV), Post neuralgia, Natural products

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*Address for Correspondence:

Miss. Shinde Poonam R, Department of Pharmacognosy, MGV'S Pharmacy College, Panchavati-422003, Dist: Nasik, Maharashtra, India.

Introduction:

Varicella-zoster virus (VZV) causes two distinct diseases, *varicella* (chickenpox) and shingles (herpes zoster). Herpes zoster (HZ) is the reactivated form of the *Varicella zoster* virus (VZV), the same virus responsible for chickenpox. HZ is more commonly known as shingles, from the Latin *cingulum*, for "girdle." This is because a common presentation of HZ involves a unilateral rash that can wrap around the waist or torso like a girdle. Similarly, the name zoster is derived from classical Greek, referring to a belt like binding (known as a zoster) used by warriors to secure armor. Annually, over 500,000 people in the United States experience a shingles outbreak [1]. Over 90 percent of the adult population in the United States has serological evidence of a prior VZV infection and thus are at risk for developing shingles [2]. There is no way to predict who will develop HZ, when the latent virus may reactivate, or what may trigger its reactivation. However, the elderly and those with compromised immunity – such as those who have undergone organ transplantation or recent chemotherapy for cancer, or individuals with HIV/AIDS – are at greater risk for developing HZ. Between 10-20 percent of normal (immunocompetent) adults will get shingles during their lifetime [3, 4].

Infection with *varicella zoster* virus (VZV) was first documented in the writings of ancient civilizations as a

vesicular rash of unknown causes. A relationship between herpes zoster and chickenpox was suggested in 1888 and was finally proven in the 1950s. Since then, much progress has been made in preventing and treating the disease with the introduction of a live attenuated vaccine in 1974, treatment with acyclovir (Zovirax, Valeant) in the 1980s, and complete DNA sequencing in 1986, all of which may ultimately lead to the eradication of VZV infection[5].

Etiology and Pathology

VZV is one of eight known herpes viruses that infect humans. Its structure is characterized by an icosahedral nucleocapsid surrounded by a lipid envelope. Double-stranded DNA is located at its center. The virus is approximately 150-200 nm in diameter and has a molecular weight of approximately 80 million [6]. Primary infection is clinically identified as *varicella* or chickenpox. VZV is ubiquitous and highly contagious, with initial exposure typically occurring during childhood. The virus enters the host via the respiratory system, replicates at an undefined site (presumably the nasopharynx), infiltrates the its way into the bloodstream. Evidence of viremia is manifested by the scattered nature of the telltale skin lesions on the body. The usual incubation period for varicella is 14-16 days, with communicability ranging from 10- 21 days after initial exposure. An individual can no longer transmit VZV once the final skin lesions have crusted. Indirect transmission (via an immune third person)

is not thought to occur [7]. Once the initial outbreak has subsided, VZV then retreats into the dorsal root ganglia where it can lie dormant for years until some excitatory factor triggers reactivation. The associated outbreak is then clinically identified as HZ or shingles. Microscopic examination of select dorsal root ganglia tissue during active HZ shows presence of hemorrhage, edema, and lymphocytic infiltration.

Lowered cellular immunity places an individual at risk for HZ, hence the susceptibility of immunocompromised individuals and the elderly. It has been proposed that one reason VZV may not recur as frequently as other herpes viruses, such as *Herpes simplex*, type 1 (HSV-1) or *Herpes simplex*, type 2 (HSV-2), is that genes involved in reactivation of HSV are missing in VZV [8].

Sign and Symptoms:

Skin inflammation occurs when the virus reaches the dermis and epidermis of the affected dermatome. This process of nerve damage and dermal inflammation continues from the neural pathways to the overlying dermis and epidermis,

resulting in the development of maculopapular lesions. These lesions quickly morph into vesicles filled with fluid that contains VZV itself (figure 1). When the infection nears the end of its natural course, the fluid-filled vesicles rupture and form crusts or scabs, becoming less contagious [9]. Within 3 to 5 days of the initial symptoms, an erythematous maculopapular rash erupts unilaterally in the nerves of sensory dermatomes adjacent to the involved ganglia. Over the next 7 to 10 days, the rash progresses to pustules and ulceration, with crusts, scabbing, or both, this can persist for up to 30 days in the acute phase. At the end of the healing process, altered (post-inflammatory) pigmentation may develop along the affected dermatome [10]. The herpes zoster rash usually occurs on the chest or face. Involvement of the seventh cranial nerve can result in weakness in facial muscles and dermatological eruptions in the external auditory canal (zoster oticus). This combination of facial-muscle weakness and zoster oticus is known as Ramsay-Hunt syndrome. Involvement of the seventh cranial nerve can also cause ringing in the ears, hearing loss, nausea and vomiting, vertigo, and involuntary eye movements [11].

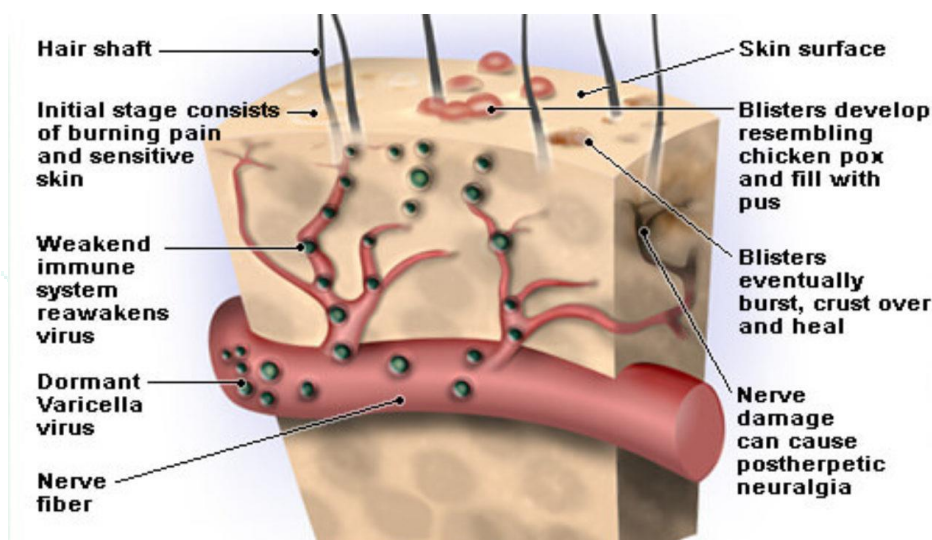


Figure 1: Symptoms of Shingles

Diagnosis

An appropriate diagnosis of HZ is aided by the appearance of a vesicular rash with characteristic distribution. When the presentation of skin lesions is not as clear, as may be the case with immunocompromised patients, laboratory confirmation is recommended. The polymerase chain reaction (PCR) technique is the most sensitive and specific diagnostic test, as it can detect VZV DNA in fluid from the vesicle. Availability of the PCR technique, however, may pose a challenge [12]. Viral culture is possible but typically has low sensitivity. VZV is labile, resulting in difficult recovery of an adequate sample from vesicular fluid. Use of direct immunofluorescence assay is a good alternative to PCR. It is preferred over viral culture, as it is more sensitive, of lower cost, and offers a more rapid turnaround time [13].

Mechanisms of action of established antiviral drugs

There are different approaches for antiviral control. To prevent viral entry into the cell, adsorption of the virus has to be avoided, e.g. by antibodies or specific ligands. Capsid stabilizing agents and blocking of endosomal ion channels inhibit viral uncoating after endocytosis. DNA or RNA replication can be suppressed by inhibition of DNA- or RNA-

polymerases, by endonucleases, or by nucleoside analogues. Nucleoside analogs are derivatives of nucleosides and interfere with virus replication. As false DNA precursors, they are not incorporated into DNA by the virus-encoded DNA polymerase. Nucleoside analogs inhibit this enzyme, resulting in chain termination. Neuraminidase inhibitors bind to neuraminidase. As a consequence, the budding virus budding remains bound to the cell receptors and the release of new viruses is inhibited. This interrupts the infectious process. Protease inhibitors prevent virus maturation and discharge. These substances are peptides that block protease substrates. This leads to suppression of maturation and interruption of the viral replication cycle [14].

Treatment

Acyclovir and other antiviral drugs have provided a major advancement in the treatment of HZ and PHN. However, of growing concern is the appearance of acyclovir-resistant HSV strains among immunosuppressed patients, such as organ transplant recipients and patients with HIV/AIDS. One study revealed seven percent of immunocompromised patients had acyclovir-resistant HSV infections. As with conventional protocols, the objective of natural therapeutics in the prevention and treatment of HZ and PHN is to facilitate healing of skin lesions, reduce pain, and prevent

complications. An underlying goal for employing natural therapies is to strengthen cell-mediated immunity, thereby allowing the body's natural defense mechanisms to control the virus and prevent recurrence. Natural therapies can provide solutions to effectively manage herpes viruses, prevent and treat complications, and minimize the risk of developing viral resistance [15].

Herbal Drug Regime

• Dietary/Multiple-Nutrient Effects :

Incidence of herpes zoster rises sharply after the age 50 years. One possible explanation is the potential decline in immune competence (immunosuppression). Maintaining adequate nutrition is one contributing factor to ensuring healthy cell-mediated immunity. A study by Thomas *et al.* in 2006 reviewed 243 cases of herpes zoster and concluded that individuals who ate less than one serving of fruit or vegetables weekly had a three-fold greater risk of zoster as compared to those who ate more than three servings daily [16]. Hence, it is thought that nutrients may act synergistically to maintain healthy immune function and consequently decreases the risk of herpes zoster. Vitamin A functions both as a fat-soluble vitamin and a hormone, contributing to the visual pigment rhodopsin and controlling gene transcription that allows normal proliferation and differentiation of epithelial cells. It is a key immune modulator, involved in the synthesis of lymphocytes, neutrophils, cytokines and immunoglobulin's. Its deficiency has also been associated with increased susceptibility to numerous infectious diseases including herpes zoster [17].

Citrus fruits are rich sources of natural vitamin C which helps in fighting inflammation and keeps your skin cells healthy. If you are suffering from shingles pain, eating citrus fruits is the best way to fight this infection. Oranges, lemons, cherries, tomatoes, mango and all other such fruits are beneficial as a natural cure for shingles pain. You can also have citrus fruits juices throughout the day.

• Enzyme Therapy

Prior to the introduction of acyclovir, pancreatic enzyme preparations were used effectively in Germany as a treatment for herpes zoster. Such historical application led researchers to conduct a comparison trial [18]. In a double-blind controlled trial two groups of 96 herpes zoster patients were given either acyclovir (800 mg) or an enzyme preparation (120 mg trypsin, 40 mg chymotrypsin, and 320 mg papain) five times daily for seven days and were followed for 14 days. During the course of the study, the intensity of pain and reddening of skin lesions were measured. No statistically significant difference was seen between the two groups either in pain intensity or reddening of skin lesions during the first seven days. However, on day 14 a significant decrease in skin reddening was noted in the acyclovir group while no other parameters revealed statistically significant differences. Overall the study concluded that the enzyme preparation was just as effective as acyclovir. The suspected mechanisms of action for the enzyme formula included stimulating breakdown of immune complexes and enhancing cell-mediated immunity [19].

Antiviral Molecules of Plant Origin

Natural products provide an unusual approach for the discovery of antiviral agents with remarkable pharmacological effects [20-21]. At present, approximately 25% of the drugs prescribed are of plants origin. Herbal practitioners use traditional plants since ancient times to heal several human and animal diseases especially in Asia. People still rely on traditional plants and their products for their health, living and primary health care in many parts of the world [22]. Polyphenols, alkaloids, flavonoids, saponins, quinones, terpenes, proanthocyanidins, lignins, tannins, polysaccharides, steroids, thiosulfonates and coumarins are prominent bioactive phytochemicals, which have been observed to combat viral infections [23-29].

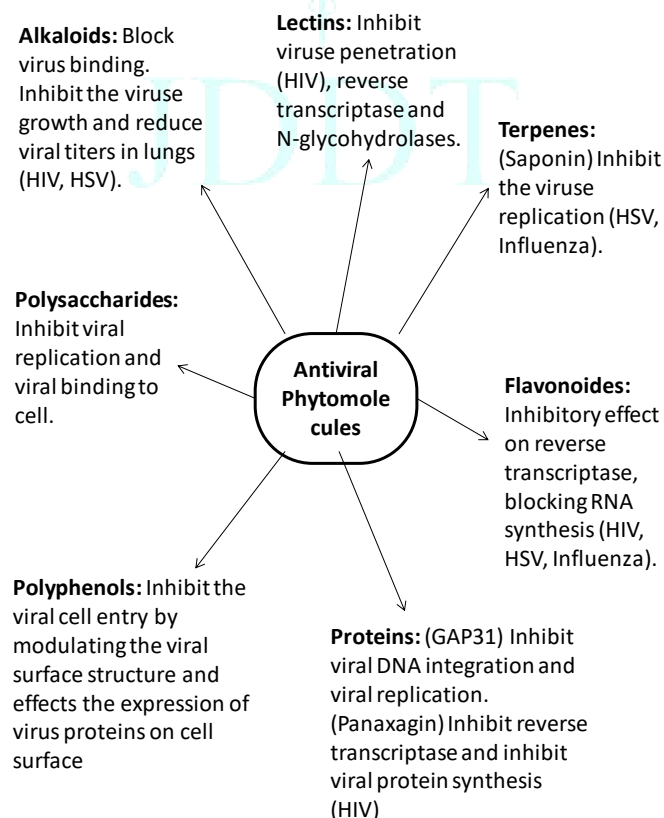


Figure 2: Major application of antiviral phytoconstituents

Gathering traditional information from local or indigenous people or using ethnomedicinally important plant(s) to extract bioactive molecules/phytochemicals for curing various diseases are quite challenging approaches. Many factors such as different solvents (polar, nonpolar) employed for the extraction of bioactive constituent(s), choice of plant part/tissue for extraction bioactive constituent(s) often play important roles in extracting the biologically active phytochemicals/natural constituents from plants efficiently. To appraise the antiviral activity of plants systematic approach to isolate and characterize the bioactive molecules/phytochemicals and virus replication inhibition assays in animals or mammalian cell system are indeed needed before such phytomolecules could actually be employed to treat viral infection [30]. Different methods for isolation, purification of bioactive molecules/phytochemicals from the extracts of plant to carry out biological activity such as their antibacterial, antifungal and antiviral properties are

requires to be established. A variety of biological assay such as antiviral properties such as cytopathic effect screen, neutralization assays, yield reduction assays and haemagglutination inhibition test have been successfully used to study the. Extraction of bioactive principle is an important first step in the analysis of plants to extract the desired bioactive molecules/phytochemicals. The traditional practices in isolation of these bioactive molecules/phytochemicals using different separation techniques such as TLC, column chromatography, flash chromatography, HPSCCC, HPLC, FTIR, NMR and MS have been extensively exploited to obtain and facilitate the identification of the bioactive molecules/phytochemicals. The ability to identify bioactive molecules/phytochemicals from large chemical libraries accurately and rapidly has been the ultimate goal in developing high throughput screening assays (Figure 3).

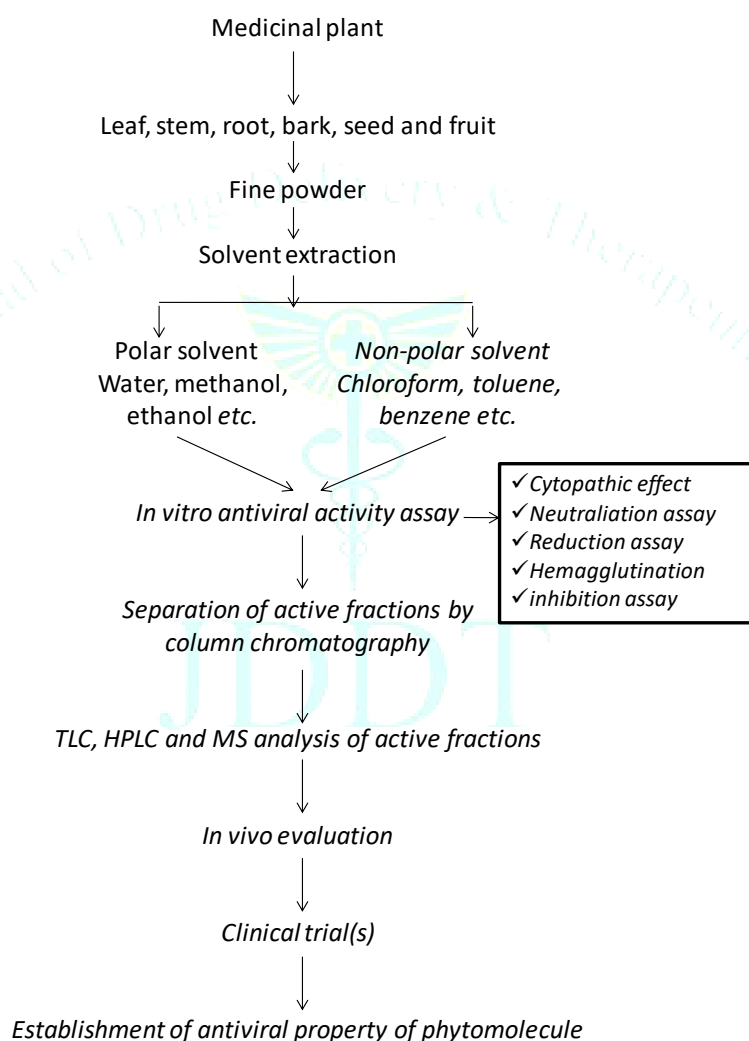


Figure 3: Isolation of antiviral phytochemicals from plants.

To firmly establish the antiviral activity and adverse reactions like reactogenicity or toxicity of the purified phytomolecules, appropriate *in vivo* studies (animal models) and subsequent clinical trials are necessary. A bioactive flavonoid 'Baicalein' isolated from Chinese medicinal plant *Scutellaria baicalensis* Georgi showed antiviral properties using high-speed counter-current chromatography (HSCCC) technique [31].

Botanicals with Specific Efficacy:

1. Capsaicin (from *Capsicum frutescens*)

Capsaicin is an alkaloid derived from cayenne pepper (*Capsicum frutescens*). Capsaicin causes an increase in the release of substance P. Eventually the substance P is depleted and further releases from the nerve ending are reduced [32]. Creams containing capsaicin have reduced post-

operative pain associated with mastectomy patients and for amputees suffering from phantom limb. Prolonged use of the cream has also been found to reduce the pain occurring because of shingles (Herpes zoster).

2. Licorice (*Glycyrrhiza glabra*)

Licorice is one of the most widely used herbs in traditional medicine spanning many generations and several continents. It possesses properties of an anti-inflammatory, mucoprotectant and antiviral agents. This suggested that it may have potential value in the treatment of herpes zoster [33]. One of its constituent named glycyrrhizin can inhibit viral growth and may also inactivate viral particles. It has demonstrated antiviral activity in vitro against various forms of herpes virus including *varicella zoster virus*.

3. Madonna Lily (*Lilium candidum*)

In northern Italy, traditional folk medicine has identified *Lilium candidum* as an herbal treatment for herpes zoster. Bulbs of cultivated *L. candidum* have yielded successful results when fried in olive oil and applied externally as a poultice on herpes zoster lesions. Healing properties are thought to come from the presence of eight spirostanol saponins and two furostanol saponins identified in the bulb of the plant [34, 35].

4. Reishi Mushroom (*Ganoderma lucidum*)

A few small studies have documented the effect of *Ganoderma lucidum* alone or in combination with other herbs for the treatment of herpes zoster or post herpetic neuralgia [36]. One case study on two patients with herpes zoster and two patients with post herpetic neuralgia demonstrated that administration of hot-water-soluble extracts of *Ganoderma lucidum* (36-72 g dry wt/day) had a dramatic effect on decreasing pain. In another small clinical trial, five patients with herpes zoster experienced almost complete pain relief within 10 days of treatment with an oral preparation consisting of *Ganoderma lucidum*, *Wisteria floribunda*, *Trapa natans*, *Miristica agrans*, *Coix lachrym-jobi*, *Elfungia applanata*, *Panax ginseng* and *Punica granatum* [37].

5. Bi Phaya Yaw (*Clinacanthus nutans*)

Clinacanthus nutans a small shrub found in Southeast Asia has long been used in Thailand as a traditional medicine for snake and insect bites and various other skin ailments. Several studies have documented its benefit for herpes zoster. One randomized, placebo controlled trial was performed on 51 herpes zoster patients using a topical preparation of *C. nutans* extract applied five times daily for 7-14 days. This was followed by resolution of the herpetic lesions [38].

6. Aloe vera (*Aloe barbadensis*)

Aloe vera possesses immense healing properties and is used as a natural cure for many skin conditions. It can be used to treat shingles pain effectively. Cut a leaf from *aloe vera* plant and apply the gel like liquid that is inside the leaf all over the affected areas. It will provide an instant soothing effect and help relieve the itching. Regular application will help in quicker healing of the blisters and rashes. Refrigerate the leaf and use it for three to four days. You can also apply aloe vera gel that is readily available in all health stores [39].

7. Plantain (*Musa paradisiaca*)

Plantain is a natural remedy for shingles that works wonders in relieving the pain and provides quick healing. Simply grind the plantain and mix with a little warm water to make a paste. Make a poultice using this paste and apply

on the painful areas of your body. It will soothe the pain and itching in the area. You can also add a few mint leaves to the plantain while making the paste. This gives even better results [39].

8. Turmeric (*Curcuma longa*)

Turmeric is used widely for culinary purposes, but this spice has also been used since centuries as a natural cure for many health ailments. It possesses strong anti-inflammatory and antiseptic properties, which makes it ideal as a natural cure for shingles pain. You can make a paste of turmeric powder and apply over the affected areas. This will provide relief from the shingles pain and also help healing by preventing infections on the site.

9. Cayenne pepper (*Capsicum frutescens*)

Cayenne pepper contains a compound called capsaicin that gives it the spicy property. These compounds bring relief from shingles pain as they block pain signals from the nerves that are just under your skin. Mix a little cayenne pepper with any moisturizing lotion and apply over the affected areas. It numbs the nerve endings and provides relief from pain due to shingles. You can also get a capsaicin ointment from the market and keep it handy.

10. Calendula (*Calendula officinalis*)

Calendula is an herb that is used to treat many skin conditions, especially wounds and burns. It is an effective natural cure for treating pain due to shingles as it has a numbing effect. You can apply some calendula lotion on the affected areas thrice a day to get relief from the pain and itching from shingles. It will also help heal the blisters effectively and prevent any infection at the site.

11. Olive oil (*Olea europae*)

A skin become harsh and rough when these rashes and blisters outbreak. Your skin needs healing and vitamin E is the most important enzyme which keeps your skin healthy. Ozonated olive oil is all about vitamin E. Rubbing some olive oil on the shingles blisters will reduce its size and promotes speedy treatment. The ozonated olive oil is another excellent natural treatment of shingles causing virus and also provide vitamin E blast to affected skin. Apply this home remedy for several days to reduce recovery time. Olive oil will also nourish the skin around the blisters.

12. Tea tree oil (*Melaleuca alternifolia*)

It is one of the oldest antiviral elements used in Ayurveda. Tea tree oil is another excellent home remedy for shingles recovery. This oil is used for making anti-bacterial and antiviral drugs. This is used to cure any airborne viral infections such as common cold and flu, fungal infection, and stomach flu treatment. The topical use of tea tree oil can cure skin disorders such as pimples, dermatitis, wart treatment, rashes, ringworm, and rough plaque skin patches.

13. Bayberry (*Myrica faya*)

Bayberry is a shrub that grows in Texas and the eastern US. The root bark and berries are used to make medicine. In folk medicine, bayberry has been used internally as a tea for its tonic and stimulant properties, and in the treatment of diarrhea. Natural herb, bayberry have astringent abilities which may account for wound healing and to treat skin disorders. Bayberry dried leaves are sometimes used as gargle element to treat cough and sore throat. Bayberry ointment can speed up the healing process of shingles [40].

14. Lemon balm (*Melissa officinalis*)

The other name for lemon balm is Melissa. The herb contains polyphenols. These are compounds that are anti-herpes in nature and are therefore considered the best treatment for shingles. Prepare lemon balm tea by adding 3 teaspoons of the herb in a cup of very hot water. Steep the herb in hot water for 5 minutes. Let the tea come down to room temperature. Dip a cotton ball in the tea and apply on the blisters. This treatment should be done at least 4-5 times during the day. In some western countries there is available an ointment that contains lemon balm leaves. This ointment is widely recommended in the treatment of shingles. The other herbs that are anti-viral in composition are oregano, thyme, sage and hyssop. However, the anti-viral agents in these herbs are not as abundant as they are in lemon balm.

15. St. John's wort (*Hypericum perforatum*)

St. John's wort is not a readily available herb but it is very effective in the treatment of shingles mainly because of its anti-viral properties. The herb is sold in pill form and the recommended dosage is 300 milligrams thrice a day to treat herpes zoster effectively. Combination of skullcap, St John's wort and oat straw is also used for treating shingles. Mix the three herbs in equal quantity and take a tablespoon of this herbal mixture four times during the day.

16. Oat-straw (*Avena sativa*)

Oat straw is an herb that belongs to the same family as oats. It is useful in the treatment of shingles as it helps calm down the sufferer. People with shingles are often stressed because of the intense itching and burning in the blisters. The herb is taken orally and is available in capsule form. Oatmeal powder is mixed in warm water bath to bring relief from inflammation and itching that is associated with shingles. Oatmeal bath also helps in reduction of scars that are left behind after the blisters dry up. Extract of this herb is often used in the treatment of patients suffering from depression, stress and anxiety because it helps calm down the nervous system [41].

17. Echinacea and goldenseal

Echinacea and goldenseal both have amazing healing and anti-viral properties. For this reason they are excellent for boosting the immune system which becomes very weak during shingles. The combination of these herbs acts powerfully on the immune system and protects it from further infections. To treat shingles drink tea prepared using Echinacea and goldenseal extracts three times during the day. Echinacea and goldenseal even add extracts of nettle and ginseng for extra boost to the immune system. This combination of herbs is sure to protect you from attack of any kind of infections in the future.

18. Alhagi (*Alhagi pseudalhagi*)

The genus *Alhagi* (*Camel thorn*) has various medical uses. Several studies across the literature have revealed the wide use of *Alhagi* plants in treating a wide spectrum of diseases including gastroenteritis, ulcers, fever, inflammations and angina pain, headache and toothache, rheumatoid arthritis, liver disorders, kidney stone and urinary tract infections, hypertension and cancer.

Ahed J Alkhatib [42] case study, it is the first time to report the use of crude extract of *Alhagi graecorum* in olive oil to treat HZ (shingles). After 10 days, she was advised to use the extract of *Alhagi graecorum* in olive oil. It was topically used over 10 days. The patient reported positive effects of its use after two days since itching became less painful and the lesion started to disappear slowly. After 10 days of using the

extract of *Alhagi graecorum* in olive oil, the lesion had been disappeared. The clinical presentation of shingles as vesicles was described to diffuse and become as one layer within the first 5 days, and this layer further completely disappeared. Finally, the patient and her husband expressed their happiness to successful treatment and improving their quality of life [42].

20. Passion flower (*Passiflora incarnata*)

Passionflower is considered to be one of the most effective herbs for the long-term treatment of recalcitrant and chronic insomnia. An active herb that contains alkaloids that specifically target insomnia, it favours deep and restorative sleep. Passionflower contains several active principles, flavonoids (apigenin, luteolin, quercetin, campherol, vitexin) and alkaloids (harmine, harmaline, harmalol and harmene). It has sedative, hypnotic, anxiolytic and antispasmodic effects. It is also used to fight pain (in the treatment of shingles and neuralgia) and to calm spasms (epilepsy and Parkinson's disease). Passionflower is often used with other herbs to direct and balance its action [43].

Others

Acupuncture

Acupuncture has long been regarded as an effective therapy for pain management. Several cases have been documented on its use in herpes zoster and post herpetic neuralgia. One study documented a case of a 52-year-old male with post herpetic neuralgia that was successfully treated after four treatments using a combination of acupuncture and moxibustion [44, 45].

Oatmeal baths

Oatmeal baths is soothing, especially when your skin feels itchy or irritated (such as during shingles blister outbreak or poison ivy rash). It is also beneficial if you are suffering from chicken pox it will soothe the pox and reduces the inflamed skin. You might have heard of various types of oatmeal bath.

Conclusion

Herpes zoster infection is an often painful condition which may progress to persistent pain. It is imperative to manage the symptoms early and aggressively. Evidence based management guidelines are useful for both the primary care physician and the specialist. The management of HZ may affect the patient's outcome including future quality of life. Future studies should address the effect of management on both pain and quality of life. This review has revealed rich source of medicinal and potential targets of many plant extracts. In addition of lacking the adverse side effects of pharmaceutical drugs, advanced herbal formulas tend to be inherently safer, more effective and less expensive than their synthetic counterparts. In the present scenario, a number of synthetic antiviral drugs are available which prove to be effective against virus but in specific manner. Then again the problem of anti-viral resistance makes most of the antiviral drugs ineffective. Therefore there is an urgent need for the development of new formulation having effective antiviral properties. Knowledge based on traditional system of medicines can be utilized in the development of various herbal formulations from different medicinal plants. The field of herbal medicines holds immense possibilities for research and development and various countries around the world are now relying on their research and development programs for formulation of effective drugs against various viral diseases based on the knowledge of traditional systems on medicines including Ayurveda.

Conflicts of Interest

All authors report no conflicts of interest regarding this manuscript.

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