

LongoVital- An Imminent Therapeutic Modality: An Unseen Drug Review with Advanced Features and Hypothesis

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ABSTRACT

Herbal medication still happens to be the backbone of the major world's population essentially because of the assumption that these drugs are free of any side effects and easily available. LongoVital (LV) is a herbal preparation with documented immune-modulatory and immune-stimulatory effects in man. Various studies conducted to date, have shown LV to have prolonged and beneficial impact in the treatment of orofacial diseases, when administered in recommended daily doses. With its combined antimicrobial and immunostimulatory effects, LV can be regarded as an emerging therapeutic modality in the treatment of orofacial diseases.

Keywords: Herbal, Immunostimulatory, Immune-modulatory, Orofacial diseases

INTRODUCTION

The majority of synthetic drugs that are used today have their basic origin from the plant kingdom. Our pharmacopeia was ruled by numerous herbal preparations almost 200 years ago. Herbalism almost diminished when Pharmacology was established as a leading branch in therapeutics. Developing countries like India, Japan and China, never abandoned medical herbalism [1]. World Health Organization (WHO) reported that the usage of herbal medications around the world is up to two to three times in comparison to the conventional drugs [2]. Numerous practicing doctors and people in today's practice are prescribing herbal and ayurvedic medications with the prescription and nonprescription drugs. A lot of these herbal medicines can probably interact with other medications and result in potential life-threatening toxic effects and reduced benefits from the drugs. Till date, very little work has been published in literature and little is known in the field of herb-drug interactions, but the practice of herbs and ayurveda is still on the rise throughout the world.

LongoVital (LV) being a herbal tablet is enhanced with the daily doses of vitamins and variety of herbs. LV has been considered to have an immuno-stimulatory effect and was developed to give more energy [3]. History of the LV tablet is as old as 40 years, when Professor Flemming Norgaard in 1974 in Denmark had a dish that made him feel reenergised and, as a result, he found that the various herbs used in the dish were various home remedies. He, later on, conducted numerous experiments on himself and friends that finally led to the discovery of the well known drug LongoVital. Till date, it is thought to be one of the premier-selling nutritional supplements in Denmark. Apart from its home market Denmark, it is sold in the other Nordic countries as well as Poland [4].

Available forms of LV are as follows-[5]

- LV anti-oxidant,
- LV beta-carotene,
- LV classic- Consists of various vitamins, well-known herbs, and a combination with strengthening effect,
- LV+Rosenrot- It includes arctic root along with herbs,
- LV + extra energy- Includes ginseng in addition to herbs, which has been used for numerous years due to its excellent

medicinal qualities. (Available only in Denmark),

- LV Ginseng.

Other ingredients also used in LV are as follows-[4]

- Cellulose,
- Calcium gluconate,
- Polyvinylpyrrolidon, Talcum,
- Silicon dioxide, Shellac,
- Magnesium salts from fatty acids,
- Coconut Oil,
- Palm Oil.

Mechanism of Action of LV: On reviewing literature, the precise mechanism of action of LV is not known. The probable mechanism of action based on various studies conducted so far, is the immuno-stimulatory effect, which is the marked increase in CD4+ lymphocytes (T helper /inducer) and minor increase in CD8+ lymphocytes (T cytotoxic) [6,7].

Ingredients of LV: LV is a herbal preparation based on dried and ground herbs including hawthorn (*Crataegus* spp.), milfoil (*Yarrow Achillae Millefolium*), paprika (*Capsicum annum*), peppermint (*Mentha Piperita*), pumpkin seeds (*Cucurbita pepo*) and rosemary leaves (*Rosmarinus officinalis*) supplemented with doses of vitamins. The recommended daily dose of vitamins is added to the preparation [3]. The combined mixture of these herbs, each with a unique medicinal quality, is the basis of LV success [4].

Hawthorn: It is used for treating diseases of the heart and blood vessels like-congestive heart failure (CHF), chest pain, and irregular heartbeat. It has also potential role in treating in both low blood pressure and high blood pressure, "hardening of the arteries" (atherosclerosis), and high cholesterol.

Rosemary (*Rosmarinus Officinalis*): is a woody evergreen shrub with fragrance, usually have needle-like leaves with variety of colors and has an effective role to play in cases of renal colic, headaches, digestive system disorders, respiratory disorders and stomach aches with an increase in the production of prostaglandins and inhibition of compliment system. It is also found to be beneficial in- [8].

- Improving digestion,
- Enhance memory and concentration,
- Neurological protection,
- Cancer.

Peppermint (*Mentha piperita*): Is used for its essential oil content to treat various ailments like gastric disorders, a toothache [9].

Paprika (*Capsicum annum*): It is an excellent source of a variety of vitamins like (vitamins B, C, E, provitamin A). It has varied uses like in toothache, diarrhea and muscular aches.

Yarrow Flower (*Achillea millefolium*): Is also known as Common Yarrow and Soldiers Woundwort because of its use in stanching (Restrict blood flow). During war times it was used to stop bleeding from various wounds. Apart from its use in stopping bleeding it also helps to prevent common cold, painful cramps and inflammation.

Pumpkin Seeds (*Cucurbita pepo*): It comprises of various active ingredients like iron, copper, selenium and beta-sitosterol, fatty acids, amino acids.

Vitamins in LV: It gives complete dietary coverage of vitamins for adults (niacin, pantothenic acid, vitamins A, B1, B2, B6, C, D). The preparation can be applied topically. It consists of no preservatives, artificial or flavorings. Although being a dietary supplement, it should not be used as a substitute for a variety of diet [9].

Dosage [10]: LV is available in tablet form.

Age group (2-7) years- 1 tablet daily.

Age group (8-14) years- 2 tablet daily.

Age group (15) years -3 tablet daily.

Applications in Dentistry

Its various uses in Orofacial diseases are as follows:

1. Treatment of Aphthous Stomatitis: Recurrent Aphthous Stomatitis (RAS) also known as canker sores manifested the small idiopathic oral painful ulceration with no extraoral manifestation and having an atypical clinical presentation in immunocompromised individuals. On reviewing literature, a relationship between immune-mediated reactions and development of RAS has been found. According to one theory, multiple immune reactions cause damage induced by deposition of immune complexes in the oral epithelium [11].

The exact aetiology of aphthous stomatitis is still not clear, and the currently available treatment is still insufficient [12]. Several studies have reported a relationship between RAS and various causes, but the results are conflicting [6]. It is suggested that immunologic factors and psychosocial stress with its assumed outcomes on the immune system constitutes a predominant causative factor of aphthous ulcers.

Numerous studies have been conducted so far for the evaluation of the effect of daily intake of LV vitamin tablets for 4-6 months in the prevention of RAS [3]. The recurrences were markedly reduced, and no adverse reactions were induced by LV and it proved to be harmless systemic treatment in the prevention of RAS [12]. A four month clinical study was conducted by Kolseth I to detect the inhibition of Recurrent Aphthous Ulceration (RAU) in 60 patients by daily intake of LV. The patients were randomly divided into three groups and administered LV, the herbs of LV-only, or placebo. The patients were advised to take three tablets everyday with breakfast for four months, and the hence were followed up for four months. Marked increases in ulcer free days during the first two months of treatment period were seen [13]. Pedersen A et al., concluded that a minimum six months period of intake of LV is required for apparent results and that there are no induced side effects associated with the use of LV [3].

As exact aetiology of aphthous stomatitis is unknown, treatment options are mainly palliative and aspire to reduce the symptoms of the patient. Diminution in symptoms like pain and healing time for RAS reinstates the patient's ability to eat and swallow. Integrating herb therapy and LV is a revolution in the treatment of oral stomatitis. LV is found to work effectively when taken correctly for the affected cutaneous or mucosal sites. On reviewing literature very few studies have been found showing therapeutic effects of LV in recurrent aphthous ulceration. The application of LV being a herb should be widely used with for a better results achieved in such type of oral diseases.

2. Treatment of Periodontal Disease: Now a day's numerous Ayurveda herbs, plants and its formulation in form of powder, paste, cream etc., are available for maintaining oral hygiene and cleaning of tongue. Periodontal disease is mostly caused by local factors like the accumulation of plaque, debris, calculus and gingivitis being the most common periodontal disease to occur in humans. Periodontal disease is primarily destruction of periodontium and is now a universal problem which is not only limited to oral disease but also in various systemic diseases. On reviewing literature, LV has shown marked results in the treatment of periodontal disease. The possible mechanism of action is the effect on CD4+ lymphocytes since CD4+ lymphocytes seem to play a role in the pathogenesis of the disease. An immunoregulatory disbalance is usually seen in the case of patients suffering from periodontal disease. Klausen B et al., conducted a study to see the outcome of LV in perio disease in 54 rat models and concluded that LV treated rats were free from periodontal disease [6].

3. Treatment of Sjogren's Syndrome: Sjogren syndrome also known as Sicca syndrome as well as Mikulic'z disease is an autoimmune disorder of central nervous system and is a diffuse connective tissue disease. This disease results in attack of immune cells that produce tears and saliva and also destruction of exocrine glands occurs. Various disturbances of the immune system (i.e. B-cell-activating factor/B-lymphocyte stimulator, B-cell hyper-reactivity) lead to autoimmune epithelitis. Whether this syndrome is an initial abnormality or the result of predisposing factors or infectious diseases, e.g. viral, agents remain uncertain. A clinical symptom shows dryness of mouth and eyes. Various studies have demonstrated that LV had effects on unstimulated and stimulated salivary flow rates. As pilocarpine has a high frequency of side effects, therefore, LV seems to be the first harmless systemic drug to show effects on both unstimulated and stimulated salivary secretion. LV is also beneficial in preventing the epithelial damage by improving the ocular surface condition.

LV being a herb may be recommended to suppress inflammation, and other immunosuppressive symptoms involved in Sjogren's syndrome. LV tablets may be applied to regulate the overactive immune system. Since, the complications of this disease differ from person to person; it is suitable to formulate a personalized treatment plan involving a specialist like eye-care specialist and a dentist. Pederson et al., conducted a study on 40 patients suffering from Sjogren's syndrome over a period of eight months. The patients were grouped into two groups (Group A-22 patients), administered LV for first four months and placebo for subsequent four months. (Group B-18 patients) administered LV for last four months and placebo for first four months. It was concluded that LV had beneficial and prolonged effects on some of the immunostimulatory markers [14]. It seems that LV improves the moisture and decrease inflammation in Sjogren's syndrome patients. Currently, there is no known curative treatment of Sjogren's syndrome and management is purely symptomatic.

4. Herpes Labialis Treatment: Herpes labialis, being a herpes simplex virus infection also known as Cold Sore is a self-limiting, infectious oral disease. Most common sites to get affected are oral mucosa, lips and adjacent skin. The cause of this disease is

transmission by direct contact with the lesions or body fluids of an infected individual. These modes of transmission pose a harmful risk to dental health care professionals. Although harmless but it is often an annoying ailment in immune competent patients and has a tendency to heal spontaneously within 10 days. Since, the risk of spread of infection is the greatest, treatment becomes problematic [3,15]. The viral counts are greatest in case of open lesions—and the risk to a dental surgeon is highest [16]. “United States Occupational Safety and Health Administration (USOSHA) publication” [17] and published literature has advised employees with HSV-1 to be restricted from working till the lesions heal.

Pedersen A, conducted a study to investigate possible mechanism of prevention of Recurrent Herpes Labialis (RHL) during four months daily intake of LV on 52 patients. The patients were given either LV or placebo for four months and subsequently followed-up for next four months. The number, duration and size of lesions were scrutinised. It was concluded that LV patients had less episodes after 2 months [18]. Recent advancement in the treatment options of herpes labialis is a LV, Helicase-primase inhibitors, needle-free mucosal vaccine and a new microbicide product named VivaGel.

DISCUSSION

Combination of balanced diet, plenty of nutrition and anti-oxidants helps to keep immune system strong. Herbal medications have always been popular since time immemorial because they carry least possible side effects. LV being a herbal medication has got various documented immunomodulatory effects and benefits in numerous oral conditions. Since, its discovery around 40 years back it is still one of the leading nutritional supplements used in Denmark and various Nordic countries. In spite of very less studies being conducted on its therapeutic effects, the ones conducted so far have documented it to be a powerful immunomodulatory medication. It mainly acts by markedly increasing the CD4+lymphocytes and CD8+lymphocytes.

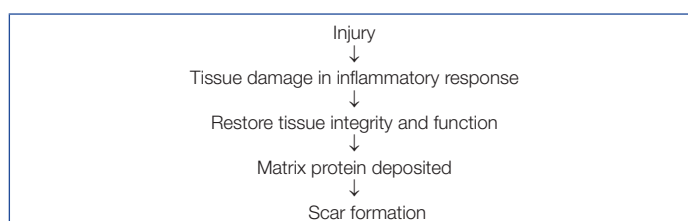
Kolseth et al., conducted various trials on patients with recurrent apthous stomatitis which showed significant reduction in ulcers with its use over a period of four months [13]. Klausen B et al., conducted a trial on 54 rat models which showed LV treated rats were preserved against periodontal diseases possibly by the correction of immunoregulatory mechanism by the use of LV and which is usually disrupted in case of periodontal diseases [6]. Pederson et al., in his study on 40 patients over a period of eight months suffering from Sjogren's syndrome, who were administered LV showed its beneficial and prolonged effects on immunostimulatory markers [14]. In other clinical trial conducted by Pederson et al., on 52 patients in 2001 suffering from Herpes labialis over a period of four months concluded that patients having LongoVital had reduced episodes after two months [18].

Burning mouth syndrome (Scalded Mouth Syndrome) is characterized by symptoms like continuous burning of the mucosa, tingling sensation in oral cavity which is also a feature seen in Sjogren syndrome. Various theories have been proposed for burning mouth but in all theories one theory states in which it is related to autoimmunity or neuropathic disturbances. Numerous studies have been done on burning mouth syndrome and it is still an enigma. It can also be seen in hypersensitivity related patients, stress induced, hormonal and in numerous systemic conditions. Burning mouth syndrome treatment can be only done by long treatment methods and changing of attitude and life style by the patients in which LongoVital can give a definite relief in such patients.

Immune system is a very important part in wound healing which modulates and perform their regular duties through innate and adaptive arms of immune system. The major function of immune system is not only to regulate wound healing but also enhance cellular events by secreting signaling molecules which includes

cytokines, chemokines and growth factors. Cytokines and chemokines are very important part of healing cascade and also a part of immune responses and immune stimulation. [Table/Fig-1] show various steps involved in the process of healing. LV herb can also be very effective in healing cascade by restoring tissue integrity, interfering in signaling cascade during protein kinase C activation and its function as it is immune stimulatory herb. We believe that by enhancing the immune system or immune stimulation by such herbs it will also enhance the cascade pathway of inflammation and in matrix remodeling. LV is a herb which is also useful in immune-inflammatory disease as few previous researches have proven its effects. Immune mediated inflammatory diseases are those diseases that don't have a definitive aetiology but gives characteristic features of inflammation or ailments which are triggered by dysregulation of normal immune responses i.e. inappropriate activation of inflammatory cytokines. Such types of diseases are as follows-

- Spondylitis.
- Psoriasis.
- Psoriatic Arthritis.
- Behcet's Disease.
- Inflammatory Bowel Disease.
- Any allergy.
- Neuromuscular, Cardiovascular and Infectious Disease.



[Table/Fig-1]: Steps of healing.

Numerous researches conducted till date on herbs and medicine for the treatment of cancer has demonstrated its significant therapeutic effects in the treatment of carcinoma. However, still major challenges lie in the treatment of cancer by immunotherapeutic agents, which involves poor immunogenicity of cancer vaccines. Herbs either used as a food or a medicine, can reinforce the body and increase its defiance to illnesses by acting on various components (like increase in immunoglobulin production) of the immune system. Healthy nutrition from a healthy and balanced diet with a plenty of nutrition and anti-oxidants helps to keep immunodefensive system strong. Cancer immunity consists of numerous key steps, including release of antigens from tumour beds, presentation of tumour antigens by Antigen-Presenting Cells (APCs), priming and activation of T cells by activated APCs, migration and infiltration of effector T cells back to the tumour, and in the end recognition and killing of these tumour cells by effector T cells [19]. In theory, each of these steps can be targeted with various therapeutic approaches. The current advancement in cancer immunotherapy is mainly driven by striking results obtained with inhibitors of harmful immune checkpoint molecules.

However, this approach is targeted at supplementing the potential of pre-existing tumour-specific T cells and benefits only a portion of patients as seen in recent clinical studies [20,21].

Immunity related to cancer consist of several steps-[19]

- Antigen release from tumour beds.
- Presentation of tumour antigens by antigen- presenting cells.
- Activation of T-cells by activated antigen- presenting cells.
- Recognition & killing of tumour cells by effector T Cells.

Bone morphogenic proteins which plays a key role in regulating T cells gives following effects-[22].

- It regulates function of CD4+, T cell population, activation and homeostasis.
- Also required for maintenance of cell survival.
- Activation of bone morphogenic protein regulates homeostatic proliferation for IL-T, a main factor for T cell Homeostasis.

LV can help by regulating all the aforementioned steps as it acts as an immunostimulatory herb. All the aforementioned diseases are related to generation of Reactive Oxygen Species (ROS). Further researches are required to prove the facts mentioned in this literature. We believe that the LV can give the rapid effects in the treatment of various malignant diseases. Further studies are required to know its efficient capacity to recognize and kill tumour cells, and if such studies are validated, LV will prove to represent a unique immune modulatory herb in an effort to improve the outcome of cancer by immunotherapeutic herbs.

CONCLUSION

Herbal medications are popular amongst people having chronic illness. Hence, we would like to conclude that LongoVital is a harmless herbal preparation with documented immunostimulatory effect in the treatment of various lesions. Therefore, LongoVital can be regarded as an upcoming therapeutic modality in orofacial diseases. Further studies are required to validate its effects.

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