ISSN: 2322 - 0902 (P)
ISSN: 2322 - 0910 (O)

International Journal of Ayurveda and Pharma Research

Review Article

A CONCEPTUAL REVIEW OF THE EFFECTIVENESS OF *LIMONIA ACIDISSIMA* DECOCTION IN VITILIGO MANAGEMENT

Hazari FS[1]*, Jayakody Jadpp[2], Daranagama Dada[3], Sunil-Chandra NP[4]*

*[1]PG Student, Faculty of Graduate Studies, University of Kelaniya, Sri Lanka.
[2]Lecturer, Department of Cikitsa, Faculty of Indigenous Medicine, Gampaha Wickramarachchi University of Indigenous Medicine, Sri Lanka.
[3]Professor, Department of Plant and Molecular Biology, University of Kelaniya, Sri Lanka.
[4]Professor Emeritus, Department of Medical Microbiology, Faculty of Medicine, University of Kelaniya, Sri Lanka.

Article info

Article History:
Received: 19-10-2024
Accepted: 29-11-2024
Published: 20-12-2024

KEYWORDS:
Limonia acidissima, Skin, *Shvitra*, Vitiligo, White patches.

ABSTRACT

Limonia acidissima also known as wood apple is a wild-growing medicinal plant distributed throughout India and Sri Lanka. Traditional practitioners in Sri Lanka, along with those using folk medicine and Ayurvedic toxicology principles, have reported that different extracts of *Limonia acidissima* are effective in managing vitiligo. Further research using advanced techniques is required to scientifically validate Ayurvedic and traditional medicines, yet there is limited emphasis on clinical studies and a deeper understanding of the specific properties of *Limonia acidissima*. This study aims to review and integrate current information on the pharmacological features of *Limonia acidissima* decoction component and assess its efficiency in treating vitiligo. Authentic Ayurvedic scriptures, modern writings, and previous research projects were used to gather information regarding *Limonia acidissima*. This study identified for various pharmacological properties, according to the Ayurveda, *Vishagna* (antitoxic), *Shotha* (anti-inflammatory), *Yakrut Uttejaka* (hepato-protective) along with its immune-modulatory, anti-oxidant, anti-inflammatory, regulation of cytokines and its potential utility in vitiligo treatment. Bioactive compounds present in wood apple contribute to its antioxidant functions. These are indirectly support vitiligo treatment and its application specifically to vitiligo is not well-established in direct clinical research. *Limonia acidissima* is used in traditional and folk medicine to treat vitiligo, a condition with white spots. However, there is a lack of scientific proof in clinical settings, mechanisms of action, including, autoimmune response regulation, melanogenesis enhancement, and interaction with other vitiligo-related signaling pathways. Therefore, clinical, immunological, and analytical research could provide valuable information for vitiligo treatment.

INTRODUCTION

In modern medical science, vitiligo is a long-term dermatological disorder, characterized by milky white macules or patches on the body, resulting from the loss of melanocytes [1]. Skin condition, *Śvitra*, is called vitiligo from the Allopathic medicine perspective [2]. *Śvitra* is a condition described in many classical Ayurvedic texts, characterized by the appearance of white patches on the skin across the entire body [2-9].

Access this article online

Quick Response Code

https://doi.org/10.47070/ijapr.v12i11.3451

Vitiligo poses significant challenges to individuals' quality of life and can incur substantial financial costs for treatment [10]. Ayurveda and traditional Sri Lankan medicine offer cost effective, patient-friendly treatment options. On the other hand, allopathic medicine can be expensive and may lead to complications if therapy is abruptly discontinued. Therefore, it's very important of personalized treatment strategies that enhance melanogenesis and promote skin re-pigmentation. Ayurveda and traditional medicine provide accessible solutions, while allopathic medicine requires careful management to avoid adverse effects.

Limonia acidissima commonly known as wood apple is a wild-growing medicinal plant is distributed throughout India and Sri Lanka. The various parts of the plant are practiced in different traditional systems of medicine around the world and popular among various ethnic groups for the treatment of a variety of ailments [11-15]. The practitioners of Sri Lankan traditional medicines, folk medicine and Ayurvedic principles of toxicology recommend the use of *Limonia acidissima* leaf, Loranthus (*Pilila*) for effective management of vitiligo [13-16]. Furthermore, in traditional Sri Lankan medicine, this is the existing decoction for the treatment of vitiligo that comprises the leaves, fruit, seeds, root, bark, and flower portions of *Limonia acidissima.*

Traditional medicine, including the use of *Limonia acidissima*, holds promise for vitiligo management, yet scientific research on their efficacy remains limited. To address this gap, a clinical, immunological and analytical research approach is needed to validate and optimize Ayurvedic therapies for vitiligo. By integrating traditional knowledge with modern scientific methodologies, safe and effective treatments can be developed to alleviate the suffering of vitiligo patients. Additionally, efforts should be made to make herbal medications more accessible and user-friendly, moving away from traditional decoctions towards more convenient and commercially viable formulations. This interdisciplinary approach aims to promote healthy lifestyles and well-being among vitiligo sufferers while advancing the understanding and treatment of this challenging condition. Due to few clinical studies the goal of this study was to establish the role of *Limonia acidissima* in the treatment of vitiligo based on pharmacological data.

RESEARCH METHODOLOGY

Authentic Ayurveda classics mainly such as *Charaka Samhitā, Susruta Samhitā, Ashtāngahrdya, Mādhava Nidāna*, *Sāranghadara Samhitā,* Ayurveda Pharmacopeia, *Talpate Piliyam* and other related books were referred. The review on vitiligo was conducted through recent scientific explanations and findings which published in official websites and indexed journals PubMed, Scopus, Web of Science, Google Scholar, and other Ayurvedic/pharmacological journals, articles, books, reports of WHO and encyclopedias year 1989 to 2023*. Keywords used "vitiligo", "Śvitra", "Limonia acidissima", Limonia acidissima* and vitiligo*", "Limonia acidissima* and skin disorders", *pharmacological activities, bioactive compounds.* The study selection process involves screening titles and abstracts for relevance, reviewing full-text articles, and selecting articles based on predefined criteria. The analysis of pharmacological properties, such as antioxidant, immunomodulatory actions, anti-inflammatory, antimicrobial, hepato-protective and wound-healing properties were screened. Bioactive compounds investigation involves discussing specific components in *Limonia acidissima*, such as flavonoids, tannins, coumarins, alkaloids, and phenolic compounds, and comparing them with known activities beneficial for skin health. Comparative analysis compares *Limonia acidissima* with other herbal remedies or pharmacological agents for skin conditions, highlighting unique contributions based on the presence of certain bioactive compounds on traditional usage. The traditional and ethnobotanical context is considered, including information from ethnobotanical literature describing the traditional use of *Limonia acidissima* for skin ailments. The study acknowledges limitations, such as the lack of direct clinical evidence, and highlights the need for further research and clinical trials. In cases where clinical evidence is lacking, pharmacological activities can be connected to their potential utility in managing skin conditions based on underlying pathophysiology.

Background on Vitiligo

Vitiligo is a long-term dermatological illness in which sections of skin lose their pigment, resulting in milky white macules or patches on the body. Ayurveda emphasizes nutrition as a significant factor in disease etiology. Conditions like *Kushtā* (skin disorders) and *Śvitra* are primarily attributed to an incompatible diet, which can lead to the formation of *Āma* (undigested food) an endogenous antigen source. *Charaka* also suggests that *Śvitra* may arise from sinful activities, transgressions from previous lifetimes, or unlawful conduct. Furthermore, the concept of *Dūshii Visha* (Cumulative toxicity) elucidates the various causes of *Śvitra* [1-12]. *Áchārya Bhõja* further explains that one type of *Śvitra* spreads through physical contact, such as touching, sleeping together, and other forms of close contamination [2].

Vitiligo is currently understood to result from a combination of genetic and non-genetic factors. While researchers have proposed auto-immunological, neurological, or auto-cytotoxic causes, none have been definitively confirmed. Despite various explanations, the primary cause of vitiligo remains elusive. However, a significant body of research indicates that environmental factors play a pivotal role in its development [1,10].

Vitiligo is classified into clinical variants based on the distribution of the disease. In Ayurveda, the classification is rooted in the types of bodily humors and body tissues. *Vāta Pradhān Śvitra*, where *Vata* is predominant, is considered difficult to cure, while *Pitta Pradhān Śvitra*, where *Pitta* is predominant, is even more challenging to treat. *Kapha Pradhān Śvitra*, where *Kapha* is predominant, is deemed incurable.

According to Ayurveda, *Śvitra* with black hairs, thin patches not joined together, of recent onset, and not caused by fire are considered curable. However, incurable, as well as those occurring on sensitive areas like the genitals, palms, soles, and lips, are also considered curable despite their location. Modern views of vitiligo associate the patches with their distribution across the body [1-6, 7-10].

The classical scriptures of Ayurveda, such as *Charaka Samhitā, Sushruta Samhitā*, and *Astãnga Hridaya*, clearly address the therapy of *Śvitra*, including classification and prognosis[3,4,5]. Vitiligo is an autoimmune illness that requires both systemic and local therapy. Most studies reveal *Śvitra* and its control by Ayurvedic treatment with external applications and internal medicines, particularly herbo-mineral pharmaceuticals. The management of the *Śvitra* is comparable to the *Kushtā*. *Shodhana* (purification) and *Shaman* (pacification) are mainstays for treating *Śvitra* [3]. *Shamana* therapy (pacifying) is performed using advanced UV therapy, local ointments, and Ayurvedic formulations. In allopathic treatment, vitiligo management primarily revolves around re-pigmentation therapies. This includes the topical administration of potent corticosteroids, Psoralen Photochemotherapy (PUVA), and surgical interventions such as skin grafting and medical tattooing. [8-11,13,14]. Ayurveda and traditional Sri Lankan medicine offer cost-effective, patient-friendly treatment options. On the other hand, allopathic medicine can be expensive and may lead to complications if therapy is abruptly discontinued. It is important of personalized treatment strategies that enhance melanogenesis and promote skin re-pigmentation. Ayurveda and traditional medicine provide accessible solutions, while allopathic medicine requires careful management to avoid adverse effects.

In Sri Lanka, studies investigating most of the state and private hospitals in Sri Lanka provides necessary inward care and outpatient care through general dermatology clinics but most of them tend to emphasize the clinical aspects only, such as treatment options, prevalence rates, psychiatric comorbidities and dietary restrictions with less focus on the psychosocial aspects of life.

Pharmacological Insights into Vitiligo [16-19]

Vitiligo is a skin disorder that causes the loss of melanocytes, cells that produce melanin which is the pigment responsible for determining color of skin hair and eyes. While the exact cause remains unclear, it is believed to involve an autoimmune attack on melanocytes by the immune system [15]. Effective vitiligo treatments generally focus on properties that can restore pigmentation, protect melanocytes, and modulate the immune system. Here are some key properties that aid in vitiligo treatment:

1. Immunomodulatory properties that modulate the immune response can protect melanocytes from immune attack i.e., corticosteroids, calcineurin inhibitors, JAK inhibitors
2. Melanogenesis- stimulating properties that enhance the melanin production in surviving melanocytes is crucial to regimenting affected areas. i.e., psoralens, phototherapy.
3. Antioxidant properties: oxidative stress can damage melanocytes, contributing to their destruction in vitiligo. Antioxidant can help by neutralizing harmful free radicals. i.e., vitamin C, Vitamin E.
4. Anti-inflammatory properties: this property accompanies melanocyte destruction in vitiligo. Anti-inflammatory agents can help reduce inflammation, making the environment more favorable for melanocyte survival.
5. Melanocyte-stimulating properties: these treatments encourage melanocyte migration and function to repopulate depigmented skin areas.

Effective vitiligo treatment typically involves a combination of these properties to protect melanocytes, restore melanin production, and balance immune activity. Furthermore Dopaquinone is the source of the pigment melanin, which shields human skin from ultraviolet light. Paracrine cytokines such as prostaglandins, melanocyte-stimulating hormone, and stem cell facto cause melanogenesis to occur in the melanosomes of melanocytes[17]. These chemicals activate pigment-related proteins such as tyrosine-related protein (TRP-2), microphthalmia-associated transcription factor, and tyrosinase. Vitiligo can result from TYR dysfunction, and it can be made worse by anomalies in melanogenic stimulators. Recent research on melanin re-pigmentation and natural treatments for vitiligo is helpful in the development of medicinal drugs, and new melanogenesis stimulating techniques are essential [18,19].

Some of the cytokines that are elevated in vitiligo they are: Interleukin (IL)-4, IL-6, and IL-17: These cytokines are involved in controlling melanocytic proliferation and differentiation and inhibiting melanogenesis. Interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α): These cytokines are produced by auto-reactive CD8+ T cells that destroy the melanocytes and promote their apoptosis. They also regulate the production of matrix metalloproteinase-9 (MMP-9), which degrades E-cadherin, a protein that maintains the adhesion between melanocytes and keratinocytes.IL-1: This cytokine is aberrantly produced by keratinocytes in vitiligo lesions and inhibits melanocyte function. [20-23].

According to the Ayurveda principle these properties contribute to its actions as *a Kushtagna* (relieving skin disorders), *Shõtah Hara* (anti-inflammatory), *Rakta Prasãdana* (blood purification),

Vishagna (anti-toxic) agent and *Yakrut Uttejaka* (hepato-protective) which may be beneficial in the management of vitiligo [2,4].

Ingredients of *Limonia acidissima* decoction: Fruit, leave, seed, bark, flower, root of *Limonia acidissima*

***Limonia acidicima:* Botanical and pharmacological profile**

Distribution

Limonia acidissima Linn is reported from India, Sri Lanka, Pakistan, Java and Malaysia. It is cultivated for its fruits throughout the plains, especially in the drier zones Sri Lanka [13,14]. Botanical description of *Limonia acidissima* is described in Table 1.

Table 1: Botanical description [14-17]

Kingdom	**Plantae**
Sub–Kingdom	Tracheobionta
Super-division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliospida
Sub-Class	Rosidae
Order	Sapindales
Family	Rutaceae
Genus	Limonia L
Species	L. acidissima
Synonyms	*Feroniaele phantum Correa, Feronia limonia* (L.) *Swingle, Schinus limonia* (L).
Different names of *Limonia acidissima*	English- Elephant apple, Wood apple Hindi- *Barnahi billan, Barnasi, Beli* Sinhala- *Divul* Sanskrit- *Kapitthah, Akshasasya, Atha,* Tamil- *Narivila, Nilavila, Vilaa, Vilanga*,

Morphological characteristics [22,23]

Limonia acidissima is a moderate-sized deciduous tree with a few upward-reaching branches that bend outward near the summit, where they divide into slender branchlets drooping at the tips. It typically grows up to 9 meters tall and is slow-growing. This tree is found throughout in dry and warm areas in Sri Lanka, generally up to 450 meters in elevation. It often features rough, spiny bark, with axillary spines that are short, straight, and measure 2-5cm long on some of the zigzag twigs. The leaves of *Limonia acidissima* are deciduous, alternate, dark-green, and leathery, typically measuring 3 to 5 inches long. They are often minutely toothed, blunt, or notched, and may appear dull-red or greenish. The leaves are borne in small, loose, terminal, or lateral panicles (Fig. 1, 2, 3).

Potential effects of *Limonia acidissima* on skin disorders [28-32]

Kumar & Mandal (2012) investigated the antioxidant and anti-inflammatory effects of *Limonia acidissima* extracts on animal models of skin inflammation. Results indicated that the plant's antioxidant compounds help reduce oxidative stress and inflammation in skin tissues, suggesting potential for treating inflammatory skin disorders like eczema or psoriasis. Rao et al. (2011) focused on the antimicrobial effects of *Limonia acidissima* extracts against common skin pathogens such as *Staphylococcus aureus* and *Candida albicans*. Singh et al. (2016) explored the effects of *Limonia acidissima* on UV-induced oxidative stress in skin cells. The extracts demonstrated protective effects against UV damage by reducing oxidative markers, suggesting that *Limonia acidissima* may help prevent photo aging and UV-induced skin damage. Joshi & Sharma (2018), this study examined the effect of *Limonia acidissima* on melanin synthesis, with a focus on pigmentation disorders. Results suggested that the plant extract influenced melanin production in vitro, indicating potential use in managing hyperpigmentation or conditions requiring controlled melanogenesis. Patel & Sahu (2015) explored the antimicrobial and antioxidant activities of *Limonia acidissima* and discussed its traditional uses in treating skin disorders. Though not specific to vitiligo, the study suggests that the plant may support skin health and potentially protect melanocytes from environmental damage, which could be beneficial for vitiligo.

Pharmacological properties of *Limonia acidissima* and its relevance to vitiligo treatment[21-27]

Pharmacological Properties of *Limonia acidissima*: (Ayurveda)

According to the Ayurveda pharmacopeia *Limonia acidissima* has pharmacological properties which are, *Rasa* (taste): *Kashãya* (Astringent), *Lavana* (sour), *Madura* (sweet). *Guna* (qualities): *Guru* (Heavy for digestion), *Ruksha* (Dry). *Vipãka*: *Katu* (undergoes pungent taste after digestion). *Veerya* (potency): *Sheeta* (cold), *Karma* (action): *Vãtapitta shãmaka* (reduces vitiated *Vãta* and *Pitta Dosha*). *Sangrãhi* (absorbent), *Vrnanãsha* (heals wound).[13,14]

Limonia acidissima has been studied for various pharmacological properties, but its application specifically to vitiligo is not well-established in direct clinical research.

Antioxidant Property

Several studies have investigated the antioxidant activity of different extracts from *Limonia acidissima* leaves. Srivastava et al. (2004) demonstrated that essential oils isolated from *Limonia acidissima* leaves exhibit antioxidant and cytotoxic activities[28]. Furthermore, in vitro antioxidant assays conducted by Srivastava et al. (2004) and Muthulakshmi et al. (2015) [28-30] revealed that petroleum ether, chloroform, and methanolic extracts of *Limonia acidissima* leaves possess significant antioxidant properties, as evidenced by their DPPH radical scavenging activity, nitric oxide radical scavenging activity, and hydrogen peroxide scavenging activity. Additionally, the methanolic extract was found to enhance the activity of antioxidant enzymes such as superoxide dismutase and catalase, as reported by Muthulakshmi et al. (2015) [30]. Moreover, Muthulakshmi et al. (2015) demonstrated that oral administration of the ethanolic extract of *Limonia acidissima* leaves for 30 days at 200 mg/kg body weight resulted in increased activity of enzymatic antioxidants such as glutathione, superoxide dismutase (SOD), catalase (CAT), and peroxidase. These findings suggest the potential therapeutic benefits of *Limonia acidissima* leaf extracts as natural antioxidants [30].

The antioxidant activity and anti-mutagenic effect of phenolic compounds in *Limonia acidissima* ripe fruit pulp were investigated by analyzing the total phenolic content using the Folin-Ciocalteu method and antioxidant activity using the DPPH assay [21]. The study revealed that the phenolic glycoside extract exhibited the highest total phenolic content (229.0 mg/g, GAE), followed by phenolic ester (37.5 mg/g) and free phenolics (11.0mg/g). Additionally, the antioxidant activity was found to be 88.7%, 11.8%, and 3.8% for the respective extracts. Notably, the antioxidant activity of the phenolic glycoside extract surpassed that of commercial antioxidants trolox (64.6%) and butylated hydroxytoluene (83.2%). These findings highlight the potential of *Limonia acidissima* ripe fruit pulp phenolic compounds as natural antioxidants with significant anti-mutagenic effects [21,23].

Other pharmacological actions related to anti-oxidant property

Phenolic compounds, in particular, exhibit antioxidant activity through their redox properties, acting as hydrogen donors, reducing agents, and singlet oxygen quenchers. These secondary plant metabolites are abundantly available in the plant kingdom and find wide applications in the cosmetic, food, and pharmaceutical industries. In addition to their antioxidant properties, phenolic compounds also possess various other activities such as anti-allergic, anti-inflammatory, antimicrobial, cardio-protective, anti-thrombotic, and vaso-dilatory effects [29-30] (Fig. 4).

It was found that that wood apple fruit pulp is effective against indomethacin-induced gastric ulcer in rats. At 500mg/kg it inhibits gastric ulceration by reducing gastric HCl concentration through increasing intra-gastric pH. The presence of fibres, phytosterols, saponins, polyphenols, flavonoids and ascorbic acid may be responsible for the anti-hyperlipidemic activity LH [31].

Hepato-protective Action [31-40]

Kamat et al. (2003) studied the hepato-protective potential of a methanolic extract and marmesin from *Limonia acidissima* root bark. The extract showed protective effects on the liver and kidney of phenyl hydrazine-induced wistar rats. The extract increased the activities of serum alanine transaminase, aspartate aminotransferase, and alkaline phosphatase in the non-treated groups, while also reducing urea, creatinine, potassium, and sodium levels. The aqueous leaf extract ameliorated these effects on the liver and kidney markers. The extract also showed hepato-protective effects against carbon tetrachloride-induced liver damage in rats. The methanol extract was found to be non-toxic and hepato-protective compared to the petroleum ether extract.

Anti-inflammatory Action [41,43]

Rao et al (2014) demonstrated that *Limonia acidissima* extracts have significant anti-inflammatory effects in animal models. Inflammation and immune response play a role in vitiligo progression, so these properties may provide a supportive environment for melanocyte survival. Patel et al. (2012) investigated the anti-inflammatory effects of methanolic extracts of *Limonia acidissima* in rats. It demonstrated significant reduction in paw edema and analgesic effects, suggesting anti-inflammatory potential comparable to standard drugs. Patil & Dhaneshwar (2015) highlights

the presence of bioactive compounds like flavonoids, phenolics, and triterpenoids in *Limonia acidissima*, which exhibit anti-inflammatory properties by reducing pro-inflammatory mediators. Swamy et al. (2013) compared the anti-inflammatory effect of *Limonia acidissima* with indomethacin, a standard NSAID, and found similar reductions in inflammation markers, such as TNF-alpha and IL-6, suggesting its effectiveness. Sharma et al. (2017) focused on the inhibition of pro-inflammatory cytokines by *Limonia acidissima* extracts. Furthermore the study found reductions in cytokines like TNF-alpha, IL-1, and IL-6 in treated animals, showing its immunomodulatory and anti-inflammatory potential.

Tyrosinase Activation Activity

Tyrosinase is a key enzyme involved in the biosynthesis of melanin and browning reactions in food. The activation of tyrosinase by *Limonoa acidissima* has been explored primarily through its phytochemical properties [61]. *Limonia acidissima* is rich in antioxidants, such as flavonoids and phenolic compounds, which contribute to its potential to influence enzymatic activities, including tyrosinase. But there is limited evidence suggesting significant tyrosinase activation by *Limonia acidissima*. Studies have shown that extracts of *Limonia acidissima* especially those from the fruit pulp, rind, and leaves demonstrate significant antioxidant and antimicrobial activities, which may relate to its ability to modulate enzyme actions, including tyrosinase activity [62].

Safety and Adverse Effects

There were not any records found harmful effect using the herbal formulation. *Limonia acidissima* toxicity with the different doses of chloroform and ethanolic extracts were screened for their acute oral toxicity of rats. No mortality was recorded till 2000mg/kg with chloroform and ethanolic extracts, hence the extracts were found to be safe up to the dose levels of 2000mg/kg. Thus the safe dose for experimental work is 1/10th of the limit dose i.e., is 200mg/kg body weight. The dose selected for pharmacological studies were 100mg/kg and 200mg/kg of body weight [64,65].

DISCUSSION

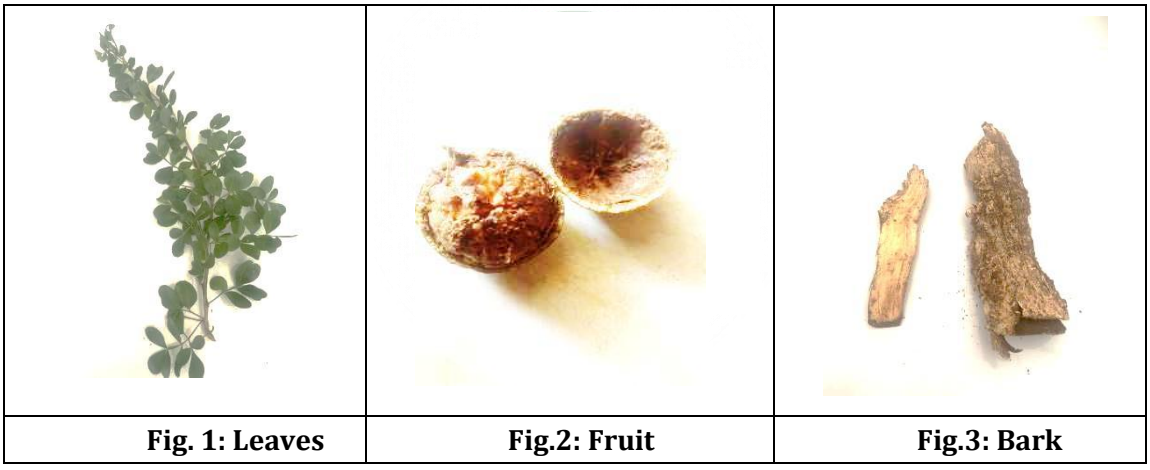

Fig. 1: Leaves | **Fig.2: Fruit** | **Fig.3: Bark**

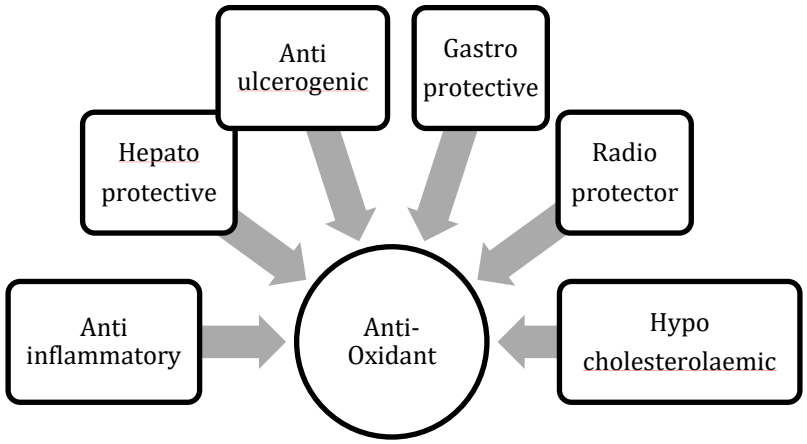

Fig.4: pharmacological actions related to anti-oxidant property

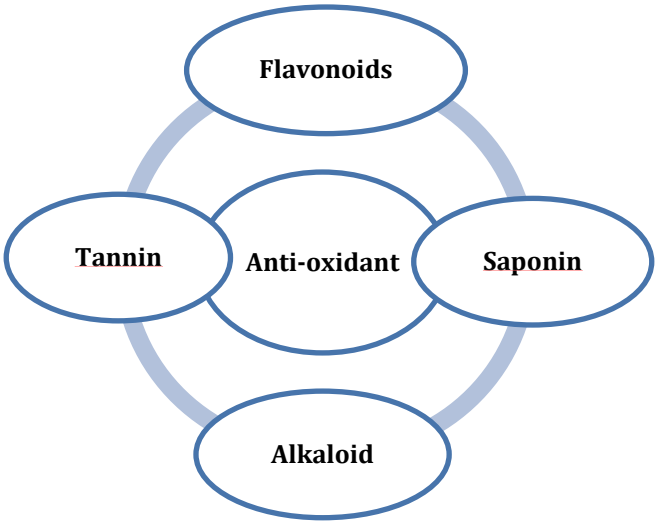

Fig.5: Bioactive compounds related to anti-oxidant property

Traditional and Ayurvedic approaches to vitiligo disorder include root elevation and a body-friendly, eco-friendly treatment plan based on herbal formulations. The primary medicinal substance used in herbal remedies is decoction. Numerous traditional Ayurvedic texts emphasize internal and exterior treatments that promote melanin synthesis and preserve the health of the skin in particular [13]. *Psoralea corylifolia, Curuma longa*, *Ginkgo biloba, Nigella sativa* and other plants are used to treat vitiligo[66]. For increased efficacy, several of these plants are combined in traditional systems such as Ayurveda and traditional medicine. For a variety of therapeutic uses, *Limonia acidissima* has also been used in traditional, folk, and Ayurvedic medicine. Although Ayurvedic literature may not specifically address the use of wood apples for vitiligo treatments, traditional medicine uses this medicinal plant to cure vitiligo.

According to the Ayurveda pharmacological actions of *Limonia acidissima* it reveals the tastes astringent, sour, and sweet which have specific properties and actions that make them beneficial in managing skin disorders. Astringent: reduce inflammation, soothes irritated skin and supporting healing wounds. Sour: improves digestion and metabolism which Ayurveda sees as essential for skin health, nourishes the skin by promoting healthy blood, mild detoxifier. Sweet: rejuvenates skin cells, enhance tissue repair, provide energy and supports immunity[13,14]. In Ayurvedic formulations, these tastes are often combined to achieve a synergistic effect. The qualities heavy and dry play specific roles in addressing skin disorders. Heavy: promote skin repair by nourishing deeper tissues, improve skin's elasticity, stabilizes the skin by supporting hydration. Dry: helps clear clogged pores, detoxify the skin, and reduce inflammation. *Katu vipaka* (pungent post-digestive effect) has specific roles in maintaining skin health i.e., clear toxins, drying and cleansing, promotes circulation, anti-inflammatory and antimicrobial. *Váta pitta shámaka* quality particularly beneficial for a variety of skin disorders i.e. moisturizing and hydration, anti-inflammatory action, balance temperature, in vitiligo it may help to stabilize imbalance in pigmentation caused by *Váta-pitta* imbalance. By calming *Váta Pitta*, these approaches promote a balanced internal environment, resulting in healthier, clearer, and more resilient skin [3-5].

Our body defense system is well established against reactive oxygen species (ROS) with the help of antioxidants. Reactive oxygen species are the harmful by-products generated during normal cell aerobic respiration. Antioxidants play an important role in building resistance against this reactive oxygen species (ROS) by scavenging free radicals, inhibiting lipid peroxidation, etc[28]. Free radical scavenging molecules, such as polyphenolic compounds, flavonoids, vitamins, nitrogen compounds, terpenoids, and other endogenous metabolites, are known for their potent antioxidant activity. These compounds have been found to be beneficial in the treatment and prevention of various diseases. *Limonia acidissima* is rich in antioxidants, which help neutralize free radicals and reduce oxidative stress. Since oxidative stress is known to contribute to melanocyte destruction in vitiligo, the plant's antioxidant properties may help protect melanocytes, supporting their survival and potentially aiding in repigmentation[21,23].

Limonia acidissima exhibits significant antioxidant activity due to its flavonoid and phenolic content. Methanolic extracts of its fruit and leaves have demonstrated free radical scavenging capabilities in DPPH and FRAP assays. This property is essential for conditions like vitiligo, where oxidative stress plays a central role[24]. Flavonoids, which are poly-phenolic compounds exhibit antioxidant properties by scavenging oxygen and nitrogen free radicals,

inhibiting oxyradical-producing enzymes, chelating iron, and reducing leukocyte adhesion during inflammation and reperfusion. Flavonoids such as kaempferol delay skin aging by inhibiting enzymes that break down the extracellular matrix, such as collagenase, elastases, and hyaluronidases[25]. Tannins act as astringents, antioxidants, and provide antibacterial activity, helping to prevent skin aging. Saponins, found in *Limonia acidissima* extract, are utilized in cosmetics for their antioxidant, regenerative, and anti-aging properties (fig. 5). Pyridine alkaloids exhibit strong anti-microbial properties and antioxidant activities by scavenging free radicals, donating hydrogen or electrons, or chelating metals. The antioxidant potential of this plant may indirectly benefit vitiligo patients by reducing oxidative damage[30].

According to Ayurveda, the concept of *Áma* elucidates the underlying causes of various illnesses. *Áma* refers to undigested or improperly metabolized toxins that accumulate in the body due to impaired digestion and metabolism. It is believed that by addressing and removing this pathological state of *Áma*, the liver can function optimally. *Áma* removal is considered essential for restoring overall health and well-being in Ayurvedic medicine. Furthermore, vitiligo is an autoimmune illness that produces harmful chemicals to be excreted, thus the liver must operate properly.[3,4].

Some studies suggest that *Limonia acidissima* has immunomodulatory effects, meaning it may help balance the immune system's activity. Since vitiligo involves an autoimmune component, where the immune system mistakenly targets melanocytes, the plant's immunomodulatory properties could help reduce immune-mediated damage to melanocytes, potentially slowing or stopping the progression of vitiligo [43-60]. Furthermore it has shown protective effects in inflammatory and oxidative damage contexts, which are beneficial in managing conditions that involve immune-mediates melanocyte damage [46].

Compared to *Psoralea cirylifolia*, a well-known herb in vitiligo management due to its furancocumarins and photochemo therapeutic effects, *Limonia acidicima* lacks direct clinical evidence for vitiligo but shown promise due to its broad pharmacological properties. *Curuma longa* and *Glycyrrhiza glabra* also target oxidative stress and inflammation in vitiligo[66]. *Limonia acidissima* might complement these by offering additional skin-healing and cyto-protective effects. The majority of research indicated that antioxidant and anti-inflammatory properties might potentially improve skin health and melanin synthesis. Furthermore Inflammation and immune response play a role in vitiligo progression, so these properties may provide a supportive environment for melanocyte survival[42,43].

Anti-oxidative capability could support tyrosinase modulation, as oxidative stress plays a role in tyrosinase activation and melanogenesis process. Additionally, the plant's bioactive components, such as alkaloids, tannins, and anthocyanins, contribute to its medicinal and enzymatic regulatory properties [63]. But most studies focus on its inhibitory effects due to the interest in anti-melanogenic and anti-browning applications.

Studies on animal models indicate that methanolic extracts of the fruit pulp enhance wound contraction and healing, which suggests potential for skin regeneration and repair. The plant is traditionally used for skin-related issues, including its application for cosmetic purpose like reducing pigmentation and skin lesions, which aligns indirectly with the goals of vitiligo treatment. While the pharmacological potential of *Limonia acidissima* is promising, there is a clear need for, clinical trials or specific in vitro studies to assess its melanocyte-protective effects or ability to stimulate melanogenesis. Furthermore, its extracts will be tested in topical formulations alongside UV therapy, which is a typical treatment for vitiligo, to investigate synergies.

CONCLUSION

Currently, there is limited direct research evidence specifically evaluating the effects of *Limonia acidissima* on vitiligo. However, several studies on the qualities of *Limonia acidissima* may support its potential usefulness in vitiligo treatment due to its effects on oxidative stress, immunological regulation, and inflammation-all of which are involved in vitiligo. Despite its traditional use for vitiligo, scientific evidence in clinical settings is lacking. Further research is warranted to elucidate the mechanisms of action of *Limonia acidissima*, including its potential autoimmune response regulatory effects, enhancement of melanogenesis, re-pigmentation, and interactions with other signaling pathways related to vitiligo. Clinical, immunological, and analytical research efforts are crucial to provide valuable insights into the therapeutic efficacy of *Limonia acidissima* in vitiligo management, thereby bridging traditional knowledge with evidence-based scientific research.

REFERENCES

1. Hasiett C, Chilvers ER., Boon, NA, Colledge NR., Hunter JAA. Davidson's Principles and Practice of Medicine. (18th ed). Churchill Livingstone, Edinburgh, London, New York, Sydney, Toronto, 2002. 1175-907.
2. Jayasinghe, DM. Charmaroga Nidana, Cikitsa Sangrahaya, Department of Ayurveda, Sri Lanka. 1990; 13-4, 35-6.

3. Dridhbala, C. (Ed).Charaka Samhitã, Kushtha chikitsitam. Chaukhambha Sanskrit Series, Varanasi, India. 2011; 2: 333.
4. Murthy KRS (ed. and. trans). Ashtanga Samgraha of Vagbhata, Nidana Sthana. Chaukhambha Orientalia, Varanasi, India. 1998; 14: 39-43.
5. Murthy KRS (ed. and. trans). Sushruta Samhitā, Nidana Sthana, Chaukhambha Orientalia, Varanasi, India. 2000; 5:97.
6. Buddhadasa R. Susrutha Samhitha (Sinhala translation). Government Press, Colombo, Sri Lanka. 1962; 66-8.
7. Murthy, K.R.S. (ed. and. trans.). Madhava Nidanam, Chaukhambha Orientalia, Varanasi, India. 1986; 49: 37- 39.
8. Charaka Kushtha chikitsitam. In: Buddadasa R. (ed). Charaka Samhitā, Department of educational publishing, Battaramulla, Sri Lanka. 2007; 531.
9. Tripathi B. (Ed). Charak Samhita, Chaukhambha Surbharti Publication. 2011; 333.
10. Hercogovā, J, Schwartz RA & Lotti TM. Classification of vitiligo: a challenging endeavor. Dermatol Ther. 2010.
11. Tewari PV. Kashyapa Samhita Cikitsa Stana, Kushta cikitsa Adhyaya, Chawkhamba Visvabharati oriental publishers & distributors, Varanasi 2008.
12. Sharma PV (eds. and. trans.). Charaka Samhitā, Chikitsa Sthana. Chaukhambha Orientalia, Varanasi, India. 1981; 173-176.
13. Talpathe Piliyam. Part 9, Department of Ayurveda, Sri Lanka. 1994.
14. Ayurveda pharmacopoeia. Vol I. Part I. Department of Ayurveda, Sri Lanka. 1996; 131, 278.
15. Thilaka S.Visha wedhakama. Sadeepa Publishers, Battaramulla, Sri Lanka. 2017;96
16. Bhadusha N & Ananthabaskaran T. Adsorptive Removal of Methylene Blue onto ZnCl2 Activated Carbon from Wood Apple Outer Shell: Kinetics and Equilibrium Studies, E-Journal of Chemistry. 2011; 1696-707.
17. Gianfaldoni S, Tchernev G, Wollina U, Lotti J, Satolli, F. et al. Vitiligo in Children: A Better Understanding of the Disease. J Med Sci. 2018 https://doi.org /10.3889/oamjms.2018.040
18. Jung E, Lee J, Huh S, Lee J, Kim YS, Kim G, Park D. Phloridzin-induced melanogenesis is mediated by the cAMP signaling pathway. Food Chem Toxicol. 2009; 47: 2436–2440. doi: 10.1016/j.fct.2009. 06.039.
19. Satomi H, Wang B, Fujisawa H, Otsuka F. Interferon-beta from melanoma cells suppresses the proliferations of melanoma cells in an autocrine manner. Cytokine,. 2002; 18: 108–115. doi: 10.1006/cyto.2002.1028.
20. Sangma LN, Nath J, & Bhagabati D. Quality of life and psychological morbidity in vitiligo patients: A study in a teaching hospital from North-East India. Indian Journal of Dermatology. 2015; 60(2): 142-16
21. Pratima V, & Rekha V. (2014). A Review on Limonia acidissima Multipotential Medicinal Plant, Int. J. Pharm. Sci. Rev. Res. 2014; 28(1): 191-5
22. Sachin S, & Arya, S. Antioxidant Activity of Jambhul, Wood Apple, Ambadi and Ambat Chukka: An Indigenous Lesser Known Fruits and Vegetables of India, Advance Journal of Food Science and Technology.2013; 5(3): 270-275,
23. Ilango K, & Chitra, V. (2010). Wound Healing and Anti-oxidant Activities of the Fruit Pulp of Limonia Acidissima Linn (Rutaceae) in Rats. Tropical Journal of Pharmaceutical Research.2010;9 (3): 223-230
24. Hagerman A, Muller I, & Makkar H. Quantification of tannins in tree foliage. A laboratory manual, Vienna. 2000; 4- 7.
25. Kumaran A, & Karunakaran R. Anti-oxidant and free radical scavenging activity of an aqueous extracts of Coleus aromaticus. Food chemistry. 2006; 97: 109-114.
26. Hertog MG, Hollman PC, Katan MB, & Kromhout D. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands. Nutr Cancer.1993
27. Sanad EM, El-Fallah AA, Al-Doori AR., & Salem RM. Serum Zinc and Inflammatory Cytokines in Vitiligo. J Clin Aesthet Dermatol. 2020; 13(12)
28. Kumar S, and Mandal S C. Evaluation of Anti-inflammatory and Antioxidant Activities of Limonia acidissima Linn. in Skin Disorders. Journal of Ethnopharmacology. 2012.
29. Rao MM. Antimicrobial Properties of Limonia acidissima Extracts Against Pathogens Causing Skin Infections. Asian Pacific Journal of Tropical Biomedicine, 2011.
30. Singh RK. Protective Effect of Limonia acidissima on UV Radiation-Induced Oxidative Stress in Skin Cells. Photochemistry and Photobiology. 2016.
31. Joshi SR. and Sharma N. Effect of Limonia acidissima Extract on Melanin Synthesis in Skin Cells. Journal of Cosmetic Dermatology. 2018.
32. Patel D, and Sahu A. Antioxidant and Antimicrobial Properties of Limonia acidissima: Relevance to Skin Health. Pharmacognosy Journal. 2015.
33. Srivastava R, & Kumar S. (2002). Fruits and vegetable preservation and principles and practices. International book. Distribution company, Lucknow 2002;192-197
34. Vidhya R, & Narain A. Development of preserved products using under exploited fruit wood apple

(Limonia acidissima). American Journal of Food Technology.2011; 6(4): 279-288

35. Muthulakshmi A, Jothibai MR, & Mohan VR. Analysis of bioactive components of Feronia elephantum Correa. Journal of Applied Pharmaceutical Science. 2012; 2(2): 69-74.
36. Singhania N, Kajla P, Bishnoi S, & Barmanray AR. Development and storage studies of wood apple (Limonia acidissima) chutney. Int. J. Chem. Stud. 2020; 8(1): 2473-6. doi: 10.22271/chemi.2020.v8 .i1al.8639.
37. Sonawane, S., Bhagwat, A., & Arya, S. Limonia acidissima and Citrullus lanatus fruit seeds: Antimicrobial, thermal, structural, functional and protein identification study. *Food Biosci*. 2018;26: 8-14. doi: 10.1016/ j.fbio.2018.09.001.
38. Thirugnanasampandan R & David D. In vitro antioxidant and cytotoxic activities of essential oil of Feronia elephantum Correa. Asian Pac. J. Trop. Biomed 2014; 4: 290-3
39. Banerjee S, Singha S, Laskar S, & Chandra G. Efficacy of Limonia acidissima L. (Rutaceae) leaf extract on larval immature of Culexquinque-fasciatus Say. Asian Pac. J. Trop. Med. 2004;711-716
40. Reegan, AD, Gandhi MR., Paulra MG & Ignacimuthu,\ S. Ovicidal and oviposition deterrent activities of medicinal plant extracts against Aedes aegypti L. and Culex quinquefasciatus Say Mosquitoes (Diptera: Culicidae). Osong Public Health Res. Perspect. 2014;6(1):64-69. doi: 10.1016/ j.phrp.2014.08.009.
41. Reegan AD, Gandhi, MR, Paulraj, MG, Balakrishna K, & Ignacimuthu, S. Effect of niloticin, a protolimonoid isolated from Limonia acidissima L. (Rutaceae) on the immature stages of dengue vector Aedesaegypti L. (Diptera: Culicidae). Acta. Trop.2014;39:6, 7-76.
42. Ishfaq A, Bukhari AD, & Rafeeq AK. Anti-nociceptive activity of methanolic extract of St. John's wort preparation. Pakistan Journals of Pharmaceutical Sciences. 2004; 17(2), 13-9.
43. ENVIS Centre on Medicinal Plants. (n.d). Plant Details for a Limonia acidissima, http://envis.frlht. org/plantdetails/4dae30264bb6a6605015c71c72 17e0c0/cd8e663947c36853c49538fba38af837
44. Macleod JK, Moeller PDR, Bandara BMR, Gunatilaka AAL & Wijeratne EMK. Acidissimin, a new limonoid from Limonia acidissima. J Nat Prod. 1990; 52: 882–5
45. Rakhunde PB, Saher S, Ali SA. Neuroprotective effect of Feronia limonia on ischemia reperfusion induced brain injury in rats. Indian Journal of Pharmacology. 2014; 46(6): 617-620.
46. Patel DK. Anti-inflammatory and Analgesic Activity of Methanolic Extract of Limonia Acidissima Linn. Research Journal of Pharmaceutical, Biological, and Chemical Sciences. 2012.
47. Patil VV, and Dhaneshwar SR. Phytochemical and Pharmacological Review of Limonia acidissima L. Pharmacognosy Journal. 2015.
48. Swamy HM. Anti-inflammatory Activity of Limonia Acidissima Linn. and Its Mechanism of Action." Journal of Ethnopharmacology. 2013.
49. Sharma P. Evaluation of Anti-inflammatory and Immunomodulatory Activity of Limonia Acidissima in Animal Models. Indian Journal of Pharmacology. 2017
50. Rao NS, Nagarjuna C, Raju B. Wood apple a suitable tree for farm lands and waste lands. Indian Farmers Digest, 1989; 22(12): 17-18.
51. Saima Y, Das AK, Sarkar KK, Sen AK, Sur P. An antitumor pectic polysaccharide from Feronia limonia. International Journal of Biological Macromolecules. 2000; 27(5): 333-335.
52. Shreya P, Kerkar Sonal Patil, Arya SS, Ashish Dabade, Sachin KS. Limonia acidissima: Versatile and nutritional fruit of India. International Journal of Fruit Science. 2020; 10: 108-110.
53. Shyamala DV, Kulkarni UN. Physico-chemical characteristics and nutrient composition of wood apple (Feronia limonia Swingle) fruit with and without seeds. J Farm Sci. 2018; 31(2):192-195.
54. Singh D, Chaudhary M, Chauhan PS, Prahalad VC, Kavita A. Value addition to forest produce for nutrition and livelihood. The Indian Forester. 2009; 1271-1287.
55. Sonawane S, Arya SS. Antioxidant activity of jambhul, wood apple, ambadi and ambat chukka: An indigenous lesser known fruits and vegetables of India. Adv. J FoodSci. Technol. 2013; 5(3): 270-275.
56. Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM., Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. Journal of American College of Nutrition, 2003; 22(4): 316-321.
57. Okwu DE, Emenike IN. Evaluation of the phytonutrients and vitamins contents of citrus fruits. International Journal of Molecular Medicine and Advance Sciences. 2006;2(1):1-6.
58. Vaya J, Belinky PA, Aviram M. Antioxidant constituents from licorice roots: Isolation, structure elucidation and antioxidative capacity towards LDL Oxidation. Free Radical Biology Medicine, 1997; 23: 302-313.
59. Cook NC, Samman S. Flavonoids-chemistry, metabolism, cardioprotective effects, and dietary

sources. Journal of Nutritional Biochemistry. 1996; 7: 66-76.

60. Havsteen BH. The biochemistry and medical significance of the flavonoids. Pharmacology and Therapeutics. 2002; 96: 67-202
61. Mapoung S, Semmarath W, Arjsri P, Umsumarng S, Srisawad K et al. (2021). Determination of Phenolic Content, Antioxidant Activity, and Tyrosinase Inhibitory Effects of Functional Cosmetic Creams Available on the Thailand Market. Plants, 2021; 10(7): 1383. https://doi.org/10.3390/plants 10071383
62. Kruk J, Duchnik E. Oxidative stress and skin diseases: Possible role of physical activity. Asian Pac. J. Cancer Prev. 2014; 15, 561–568
63. Bickers D.R., Athar M. (2006). Oxidative stress in the pathogenesis of skin disease. J. Investig. Dermatol. 2006; 126, 2565–2575.
64. Rupal A, Amaravadi VR, Narasimhacharya. Limonia fruit as a food supplement to regulate fluoride-induced hyperglycaemia and hyperlipidaemia. J. Sci. Food Agric. 2013; 93(2): 422-426. doi: 10.1002/ jsfa.5762.
65. Yusnaini Rika, Nasution R, Saidi N, Arabia T, Idroes R. et el. Ethanolic Extract from Limonia acidissima L. Fruit Attenuates Serum Uric Acid Level via URAT1 in Potassium Oxonate-Induced Hyperuricemic Rats" Pharmaceuticals. 2013;419. https://doi.org/10.3390/ph16030419
66. Gianfaldoni S, Wollina U, Tirant M, et al. Herbal Compounds for the Treatment of Vitiligo: A Review. Open Access Maced J Med Sci. 2018; 6(1): 203-207. Published 2018 Jan 21. doi:10.3889/ oamjms.2018.048

Cite this article as:
Hazari FS, Jayakody Jadpp, Daranagama Dada, Sunil-Chandra NP. A Conceptual Review of the Effectiveness of Limonia Acidissima Decoction in Vitiligo Management. International Journal of Ayurveda and Pharma Research. 2024;12(11):82-92.
https://doi.org/10.47070/ijapr.v12i11.3451
Source of support: Nil, Conflict of interest: None Declared

***Address for correspondence**
Dr. Hazari FS
PG Student,
Faculty of Graduate Studies,
University of Kelaniya.
Sri Lanka.
Email: fathimashein@gmail.com