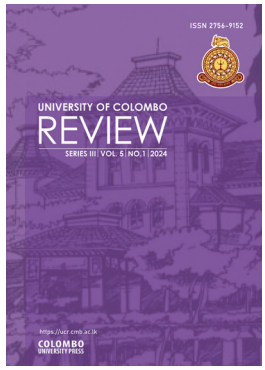

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Impact of herbal treatments for Vitiligo disease

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ABSTRACT

Vitiligo is a common skin disorder resulting from the breakdown of functional epidermal melanocytes. The global prevalence of vitiligo ranges from 0.5% to 2%, with higher rates reported in certain populations. Melanocytes, responsible for skin color, are destroyed in vitiligo condition leading to the appearance of smooth, white patches on the skin. The progression of vitiligo is influenced by various factors, including genetics, autoimmunity, psychosis, melanocyte self-destruction, trace element deficiency, oxidative stress, and other biochemical and environmental variables. Recent research has identified herbal plant extractions as potential agents for re-pigmentation and regeneration of normal skin color. Specific components of these herbal plants, such as furocoumarin, thymoquinone, flavonoids, curcuminoids, and glycyrrhizin, play crucial roles in promoting re-pigmentation. Combination therapies involving these herbal compounds have shown promise in increasing tyrosinase activity and reducing oxidative stress, which are two important aspects of vitiligo treatment. The review aims to comprehensively evaluate the efficacy of herbal plant therapies for melanocyte re-pigmentation in vitiligo patients. By analyzing the effectiveness of various herbal extracts and their active components, this study seeks to advance the understanding and potential application of herbal treatments for vitiligo. The findings from this review may contribute to the current knowledge on therapeutic options available for vitiligo patients.

KEYWORDS:
Vitiligo, Melanogenesis, Tyrosinase, Herbal plants, Melanocytes, Oxidative stress

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Introduction

A common skin condition called vitiligo is characterized as an acquired loss of inherent pigmentation that appears as white macules and is caused by the destruction of functioning epidermal melanocytes (Moreira et al., 2015). The first descriptions of vitiligo date back more than 3000 years to the earliest Vedic and Egyptian manuscripts, and it has been described in the religious texts of every major religion (Millington & Levell, 2007). The prevalence of vitiligo varies between 0.5% and 2% worldwide (Bergqvist & Ezzedine, 2020; Gao et al., 2022). However, some South Asian, Mexican, and American groups have reported prevalence rates as high as 4% (Parsad et al., 2003).

Vitiligo leads to the destruction of melanocytes, the cells responsible for producing melanin, the pigment that gives skin its color. As a result, typically colored skin becomes scattered with smooth white areas (Abu Tahir et al., 2010). These sharply defined, irregularly shaped depigmented macules or patches commonly appear on the face, hands, axillae, umbilicus, sacrum, inguinal region, and anogenital area (Ezzedine et al., 2015). The development of general vitiligo is complicated by the interaction of inheritance, autoimmunity, psychosis, melanocyte self-destruction, trace element insufficiency, oxidative stress, and other biochemical and environmental factors (Zhou et al., 2022).

Vitiligo is primarily diagnosed based on clinical observations (Halder & Chappell, 2009). It shows a link between vitiligo and other autoimmune diseases with 32% of patients having a family history of an autoimmune disease (Halder & Chappell, 2009). Thus, a number of screening laboratory tests, such as thyroid–stimulating hormone, antinuclear antibody, and total blood count, are beneficial (Halder & Chappell, 2009). Wood's lamp is used to measure vitiligo activity to assess the stability of the condition, the timing of surgical grafting, and the early detection of re-pigmentation after grafting (Wang et al., 2017).

Patients suffering from vitiligo have different treatment options, such as topical corticosteroids, immunomodulators, calcipotriol, pseudo catalase, systemic treatments, vitamin D analogs, phototherapy, excimer laser, depigmentation, and surgical techniques (Halder & Chappell, 2009). However, many patients do not respond to the therapy or exhibit side effects, making it difficult for them to adhere to the prescribed course of action. Research projects are focusing on gaining a better understanding of the illness and looking for novel therapeutic targets (Moreira et al., 2015). In addition, alternate herbal therapeutic options, such as *Ginkgo biloba*, khellin, and capsaicin, are available with pharmacological benefits for vitiligo treatment (Pekmezci, 2019).

The novel field of herbal treatments has recently attracted the attention of researchers. In the last decade, several treatment methods studies have identified herbal plant extraction variants responsible for re-pigmentation (Gianfaldoni

et al., 2018b). These herbal plants complex components play a major role in re-pigmentation and regeneration of normal skin color. Plants such as *Atractylodes*, *Arisaema amurense*, *Sophora flavescens*, *Xanthium strumarium*, *Carthamus tinctorius*, *Eclipta prostrata*, *Pleuropterus multifloris*, *Salvia miltiorrhiza*, *Sesamum indicum*, *Spatholobus suberectus*, and *Rehmannia glutinosa* have already been studied in several research, which could lead to a better understanding of the re-pigmentation activity (Gianfaldoni et al., 2018b). The potential herbal plants and their active components for vitiligo treatment, as well as the combined active ingredients for treatment success, will be discussed in this review. This review will further contribute to the current knowledge by exploring the efficacy of herbal plant treatments for melanocyte re-pigmentation in vitiligo patients.

Vitiligo Disease

A complicated etiology characterizes the multifactorial polygenic illness known as vitiligo (Dizon et al., 2016). Vitiligo affects a considerable percentage (0.5% - 2%) of the world's population (Bergqvist & Ezzedine, 2020; Gao et al., 2022). The condition typically manifests in childhood or early adulthood, peaking between the ages of 10 and 30 (Halder & Chappell, 2009). All ethnicities and sexes are affected by vitiligo, but it has been found to be more common in women than in men (Halder & Chappell, 2009).

Although the exact pathogenesis is still unknown, several suggestions have been made to explain why this condition results in the loss of epidermal melanocytes (Halder & Chappell, 2009). Melanocytes in the epidermis work together with keratinocytes to form a functional and structural unit. In fact, direct cell-to-cell contact enhances melanocyte proliferation, and growth factors generated by nearby keratinocytes influence melanocyte proliferation and differentiation. According to the majority of research, apoptotic keratinocytes reduce the production of keratinocyte-derived proteins, including stem cell factor, in the depigmented epidermis, resulting in passive melanocyte death resulting in vitiligo disease (Dizon et al., 2016) as shown in figure 1. The categories of the proposed mechanisms include autoimmune, biochemical, oxidant-antioxidant, neurological, and viral factors. Studies have also shown that a genetic predisposition to vitiligo plays a crucial influence in the condition (Halder & Chappell, 2009).

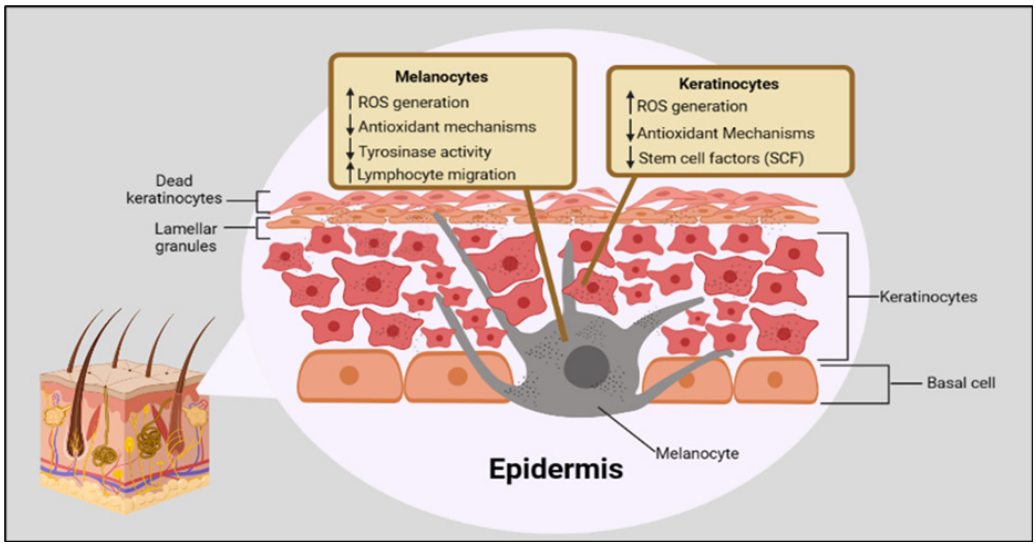

Figure 1: An overview of the cellular alterations in vitiligo affected skin.

The non-Mendelian inheritance pattern of vitiligo is characterized by genetic heterogeneity, numerous susceptibility regions, and incomplete penetrance (Alzolibani et al., 2011). Genes involved in melanin biosynthesis, oxidative stress response, and autoimmune control may be passed down through inheritance (Alzolibani et al., 2011). Investigations into potential human leukocyte antigen correlations in vitiligo have been conducted as a result of the common correlation between vitiligo and autoimmune disorders. Various studies have linked different haplotypes to vitiligo (Alzolibani et al., 2011). In Sri Lanka, research on vitiligo has been conducted using rat models, with a focus on understanding the underlying mechanisms of the pathogenesis for vitiligo disease (Palitharathne et al., 1998).

Vitiligo is exceedingly challenging to differentially diagnose. One must be able to distinguish between various skin abnormalities, such as total depigmentation, hypopigmentation, and normal skin tone, in order to accurately diagnose vitiligo (Kakourou, 2009). Patients with light skin tones have an extremely difficult time getting a vitiligo diagnosis. For patients with skin type I (white / pale / freckled-extremely fair skin, always burns, never tans) and type II (white /pale /with beige tint–fair skin, usually burns, sometimes tans), Wood's light is quite helpful in making a vitiligo diagnosis (Lakhani & Deshpande, 2014).

The two basic kinds of vitiligo

Non-segmental and segmental vitiligo are the two main types of the condition. The differences in prognosis and response to therapy between these two main types form the basis for this classification (Ezzedine et al., 2012; Taieb et al., 2007). The

non-segmental vitiligo shown in figure 2, includes localized, mucosal (when affecting more than one mucosal location), acrofacial, generalized, universal, mixed, and others (Abdel-Malek et al., 2020). Segmental vitiligo shown in figure 3, manifests as a block-like or linear patch that usually does not cross the midline on one, or very rarely, numerous, body segments (Hann & Lee, 1996). One or more macules or patches without a segmental distribution that are present in one location and are persistent for at least two years are referred to as focal vitiligo (Hann & Lee, 1996), which may be a prelude to generalized vitiligo (Ezzedine et al., 2012). Multiple depigmented patches involving the oral and/or vaginal mucosa are referred to as mucosal vitiligo (Ezzedine et al., 2012). Patches that are largely confined to the face and distal extremities are the hallmarks of acrofacial vitiligo. Vitiligo that is distributed widely in sporadic patches is referred to as generalized vitiligo, while depigment of more than 80% of the body surface area is referred to as "universal vitiligo" (Ezzedine et al., 2012). Segmental vitiligo is less frequent than other varieties. It advances more quickly over a six-month to two-year period and tends to stop on its own. Also, it is frequently linked to leukotrichia, and responds less to treatment than other forms (He et al., 2017).

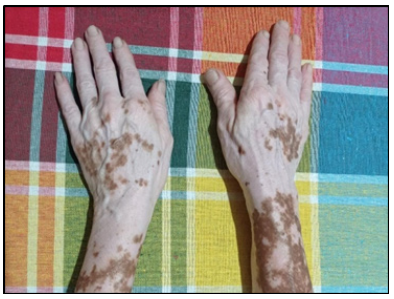

Figure 2: Clinical presentation of non-segmental vitiligo

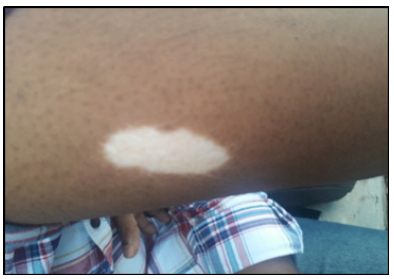

Figure 3: Clinical presentation of segmental vitiligo

Minor cases of vitiligo can usually be treated with oral or topical medication formulations alone. But in severe cases, light treatment is frequently used to intensify the effects of medication on skin pigmentation. In order to achieve an even distribution of the typical quantity of cutaneous coloring, the therapy for leukoderma or vitiligo necessitates not only the deposition of pigment in the areas of depigmentation, but also the redistribution of pigment from borders that are hyperpigmented (Falabella, 2009).

The role of melanogenesis in vitiligo treatment

The most significant physiological role of melanin, which is generated from dopaquinone, is to protect human skin from ultraviolet (UV) radiation. Melanogenesis occurs in specific organelles called melanosomes in melanocytes and can be sparked by a number of paracrine cytokines, such as melanocyte-stimulating hormone (MSH) (Hachiya et al., 2004), stem cell factor (SCF) (Suzuki et al.,1996), endothelin-1 (ET-1) (Imokawa et al., 1995), nitric oxide (NO) (Schauer et al., 1994),

adrenocorticotropic hormone (ACTH) (Thody & Graham,1998) , prostaglandins (Nordlund et al., 1986), and thymidine dinucleot (Eller et al.,1994). These substances all stimulate the expression and activation of pigment-related proteins such as microphthalmia-associated transcription factor (MITF), tyrosinase (TYR), tyrosine-related protein-1 (TRP-1), and tyrosine-related protein-2 (TRP-2), which all operate as signaling pathways that drive melanogenesis (Sánchez-Ferrer et al., 1995).

The melanosome membrane contains TYR, a multifunctional copper containing metalloenzyme with most of the membrane-bound functions. Tyrosinase (TYR) is generated in melanocytes (Lerner & Fitzpatrick, 1950). Dysfunction or reduced activity of TYR can have a significant impact on melanogenesis and contribute to the development of vitiligo (Passeron et al., 2005). Abnormalities in melanogenic stimulators such as melanogenic enzymes and regulatory factors within the pathway can further exacerbate the condition (Niu & Aisa, 2017). Thus, novel melanogenesis activating methods are crucial. Here, the focus will be on the recent findings of melanin re-pigmentation, including plant extracts and natural remedies for vitiligo. This will also be useful in the development of therapeutic medications that can promote re-pigmentation in vitiligo-affected skin.

Active ingredients in herbal plants

An active ingredient in an herbal plant refers to a specific chemical compound present in the plant that is responsible for its medicinal properties or therapeutic effects (Patel & Patel, 2016). *Arisaema amurense*, *Sophora flavescens*, and *Xanthium strumanum* are some of the Chinese herbal remedies used to cure vitiligo. There are several other herbs as well, including *Carthamus tinctorius*, *Eclipta prostrata*, *Pleuropterees multiflorus*, *Salvia miltiorrhiza*, *Sesamum indicum*, *Spatholobus suberectus*, and *Rehmania glutinosa*, that can be applied topically to the skin to treat vitiligo (Lakhani & Deshpande, 2014). *Psoralea corylifolia*, *Semecarpus anacardium*, and *Ficus hispida* are examples of photosensitizing agents which are chemical entities that modulate the chemical changes inside the cells by absorbing light, such as UVA or UVB radiations, while *Curcuma longa, Eclipta alba, Tinospora cardifolia*, *Hemiclascus indicus, Acasia catechu*, and *Acaranthus aspara* are examples of blood purifiers in Indian herbs (Yoon et al., 2011). Alkaloids, phenols, terpenes, flavonoids, lectins, saponins, glycosides, triterpenoids, furocoumarin, and stigmasterols are some of the main components of these plants, which are used to treat vitiligo (Abu Tahir et al., 2010).

Furocoumarin / Bergapten (BP)

Bergapten or 5-methoxypsoralen (5-MOP) is a psoralen compound, also known as furocoumarin. This furanocoumarin derivative may also be found in a broad range of therapeutic plants, most notably belonging to the *Rutaceae* and

Umbelliferae families, such as figs, parsley, celery, and anise. Several biological properties of furanocoumarins produced from herbal and citrus extracts have been described, including antibacterial, antioxidant, immunomodulator, apoptotic, and anticancer activities (Mirzaei et al., 2017). Numerous preclinical and in vitro investigations have demonstrated the therapeutic activity of BP and has been shown to enhance melanocyte migration and pigmentation (Quintão et al., 2019). BP clinical studies are mostly for people with skin problems such as psoriasis or vitiligo (Mahira et al.,2019). The treatment of BP in conjunction with ultraviolet A radiation (UVA) causes meaningful lesion clearance rates in these experiments (Anbar et al., 2012).

In Mengeaud and Ortonne's investigation, the combination of BP and UVA was reported to stimulate melanogenesis in S91 murine melanoma cells and normal human melanocytes, due to the increase in tyrosinase expression (Mengeaud & Ortonne, 1996). Melanogenesis and dopachrome tautomerase (DCT) activity were negatively associated in normal melanocytes, but not in murine melanoma cells, indicating that the therapy initiates the metabolic pathway of dark eumelanin with a strong UV-protective potential (Mengeaud & Ortonne, 1996).

A clinical study conducted in 1998 examined how bergapten is used to treat depigmentation disorders in animals (McNeely & Goa, 1998). The authors used Hydroquinone (HQ) induced vitiligo mice (HQ-used to lighten the dark patches of skin or hair) that exhibited evident whitening of their dorsal skin on days 9 and 12 following depilation and therapy, and they concluded that bergapten has a beneficial effect on hair pigmentation. They also measured early pharmacological activity of bergapten in animals and cells, which is useful in understanding the mechanisms of furocoumarins in the treatment of depigmentation disorders (Zhao et al., 2020).

Heracleum is also a well-known source of furanocoumarins (e.g., bergapten, byakangelicol, phellopterin, xanthotoxin, isopimpinellin, and imperatorin) with broad-spectrum biological effects (Trott et al., 2008). Application of furocoumarins extracted from *Heracleum laciniatum* on a vitiligo patient, by 1 minimal erythema dosage at 300-310 nm UV radiation, increased light tolerance (Kavli et al., 1983). Another study tested seven extracts from *Umbelliferae* plants with murine B16 melanoma cells, in which *Heracleum lanatum* showed stimulatory effect on melanogenesis with significant enhancement of cell proliferation. Furthermore, sixteen extracted coumarins were tested and linear furocoumarins were found to be more effective in melanogenesis (Matsuda et al., 2005).

Many studies have been conducted to evaluate the efficacy of *Ammi majus* seeds, which contain furanocoumarins up to 1.88% (Al-Snafi, 2013) for the treatment of vitiligo, psoriasis, and hypopigmentation tinea versicolor (Al-Snafi, 2013; Monem el Mofty, 1948). In a study with six vitiligo patients, oral and topical treatment on affected area with *Ammi majus* followed by exposure to the sun and/or UV lamps was found to be effective (El-Mofty, 1952; Monem el Mofty, 1948). In another

study conducted by Sidi & Bourgeois – Gavardin (1952), it was observed that in all individuals, the re-pigmentation manifested as pigmented minute macules with hair follicles in the middle. These macules were spread across the leucodermic plaques and grew in size until they combined to create bigger islands, noticeably in the lesions on the trunk and limbs. In the face, re-pigmentation progressed quickly from the perimeter to the center (Sidi & Bourgeois - Gavardin, 1952). Many clinical trials have been conducted to investigate the efficacy of *Ammi majus* in vitiligo. Patients with leucodermis who took oral *Ammi majus* powdered fruits while exposing the affected patches to direct sunlight for 1 hour developed symptoms of itching, redness, oedema, vesiculation, and oozing in the leucodermic patches. Al-Snafi reported that following a few days, the damaged skin began to develop deep dark pigmentation (Al-Snafi, 2013).

Thymoquinone (TQ)

Thymoquinone (TQ) is a bioactive component of the volatile oil of *Nigella sativa*, *Thymus valgaris*, *Monarda didyma*, and *Thymus pulegioide* (Gali-muhtasib et al., 2006). It accounts for 30% of the fixed oil and 18.4 % to 24% of the volatile oil in *Nigella sativa* (Norsharina et al., 2011). Thymoquinone has been proven in vitro and in vivo to have anti-inflammatory, antioxidant, and anti-neoplastic properties (Liu et al., 2022; Pagola et al., 2004; Ragheb et al., 2009).

The melanin dispersion effects of *N. sativa* and its active component thymoquinone appear to require muscarinic cholinergic receptors in Ali and Meitei's investigation, as evidenced by results utilizing blockers and a potentiator. Furthermore, thymoquinone was investigated as a new melanogen for therapeutic use in skin disorders such as hypopigmentation and vitiligo (Ali & Meitei, 2011). Sarac et al. (2019) discovered considerable re-pigmentation in the hands, face, and vaginal area of 33 vitiligo patients after using topical *N. sativa* cream twice daily for 6 months. Ghorbanibirgani et al. (2014) also discovered substantial improvements in 26 patients treated twice daily with *N. sativa* for 6 months, as measured by a significant drop in the Vitiligo Area Scoring Index from 4.98 to 3.75.

Flavonoids

Flavonoids are phenolic phytochemicals with potential to have strong pharmacological effects as modulators of numerous signal transduction pathways (Castellano et al., 2012; Yu et al., 2021). Thousands of phytochemicals have been extracted and identified from plants, making phytochemicals a huge and varied category of compounds (Cao et al., 2017; Singh & Chaudhuri, 2018). Phenolic compounds are reducing agents, and they all operate as potent antioxidants, playing essential roles through many mechanisms such as the control of antioxidant enzyme activity, chelation of metal ions (Fe, Cu, and others), and anti-inflammatory effects

(Giordano et al., 2014; Nicod et al., 2014). Flavonoids are the most common secondary plant metabolites found in fruits and vegetables (Mutha et al., 2021). They are powerful antioxidants that also have antiviral, antibacterial, anti-inflammatory, and antiallergenic activities (Karak, 2019; Mutha et al., 2021).

There is compelling evidence that oxidative stress plays an important role in the onset and development of vitiligo, because it causes melanocyte molecular malfunction, melanocyte-specific antigen exposure, and melanocyte cell death (Pang et al., 2021). Oxidative stress is commonly recognized as an imbalance between the formation of free radicals/oxidants and the antioxidant system in the human body. Oxidative stress causes DNA damage, lipid peroxidation, protein oxidation, and a cascade of signaling pathway activation/inactivation, which contribute to the formation and progression of many skin disorders (Xian et al., 2021). Flavonoids are combinations of aglycones and lipophilic glycosides. This chemical structure enhances their antioxidant activities and allows them to scavenge all forms of free radicals. Quercetin, which is a flavonoid, can reduce the oxidative reaction processes mediated by H2O2, ultimately decreasing the vitiligo condition (Guan et al., 2015). Furthermore, flavonoids reduce skin aging by inhibiting multiple reactive oxygen species (ROS) production mechanisms (Hoang et al., 2021).

Quercetin

Quercetin, a flavonoid, has been shown to be effective in treating pigmentary diseases both in-vivo and in-vitro (Gianfaldoni et al., 2018a). It is abundant in apples, onions, and green tea, as well as *Asparagus racemosus*, *Ficusingens*, *Coriandrum sativum*, and *Capparis spinosa* (Alvarez-Arellano et al., 2020). Quercetin may protect melanocytes and keratinocytes from oxidative damage (Gianfaldoni et al., 2018a). Quercetin treatment of cultivated melanoma cells or normal human epidermal melanocytes (NHEM) increases melanin production and tyrosinase activity. Nagata et al. (2004) showed that quercetin might be a powerful natural melanogenic inducer in cell culture. Their findings indicate that quercetin promotes melanogenesis in human melanoma cells and human melanocytes through increasing tyrosinase activity.

Baicalein

Baicalein is another flavonoid derived from the roots of *Scutellaria baicalensis* that has been widely used in Asian traditional medicine (Kim et al., 2014). It has been found to have anti-cytotoxic, anti-inflammatory, and anti-tumor properties (Huang et al., 2005; Hwang et al., 2005; Yarla et al., 2016). Furthermore, the antioxidant activities of baicalein have attracted considerable attention in recent decades, including the reduction of ROS created by chemical agents (Chiu et al., 2010; Choi et al., 2016; Zhao et al., 2018). According to Liu et al., Baicalein at a concentration of 40 μM showed the greatest protective impact on melanocytes

(Liu et al., 2012). Baicalein stimulates the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and protects human vitiligo melanocytes from oxidative stress by alleviating H2O2-induced mitochondrial breakdown and cellular damage (Ma et al., 2018).

Kaempferol

Kaempferol is a flavonoid present in the rhizome of Kaempferia galanga (Liu et al., 2021). Kaempferol extracted from *Baccharoides anthelmintica* reduced oxidative stress and promoted melanogenesis (Maimaiti et al., 2017; Tuerxuntayi et al., 2014).

Puerarin

Puerarin is an isoflavonoid derivative extracted from the root of *Pueraria lobata*, a traditional Chinese medicine (Zhang et al., 2019). Puerarin shows clear pharmacological activity against vitiligo both in vitro and in vivo. Park et al. (2014) discovered that puerarin could increase the melanin content of melanocytes in vitro, and topical application could improve the melanin content of mouse skin tissue. This mechanism is via activation of the cAMP pathway. It is followed by elevation of MITF, tyrosinase, Trp-2, and Bcl-2 to increase melanocyte survival and melanin content (Park et al., 2014).

Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is mostly found in green tea and black tea produced from *Camellia sinensis* plant. Although EGCG possesses anti-cancer, antioxidant, and anti-inflammatory properties, its limited bioactivity after oral administration limits its application and inhibits lymphocyte migration to epidermal melanocytes by inhibiting Janus Kinase 2 gene (JAK2) (Zink & Traidl-Hoffmann, 2015).

Curcuminoids

Curcumin / Curcuminoids is a polyphenolic molecule derived from turmeric (*Curcuma longa*) that has anti-inflammatory, antibacterial, antioxidant, and anti-neoplastic activities (Vaughn et al., 2016). Curcumin appears to be a therapeutic alternative for the treatment of vitiligo due to its antioxidant properties. One study looked into whether combining narrowband ultraviolet B (NB-UVB radiation, which is used to treat photosensitive skin condition) with topical tetrahydro curcuminoid may result in synergistic anti-vitiligo benefits (Asawanonda et al., 2010). The study involved ten participants with localized or generalized vitiligo. Two identical lesions were treated with either NB-UVB with topical tetrahydrocurcuminoid or UVB alone. UVB treatments were given twice a week for 12 weeks. The results showed statistically significant re-pigmentation in both treatment groups as compared

to baseline at the end of the research. Furthermore, at 8 and 12 weeks, the total degree of re-pigmentation was somewhat higher in the combination group, and the tetrahydrocurcuminoid was well-tolerated (Asawanonda et al., 2010).

According to the study by Becatti et al. (2010), curcumin may constitute as viable strategy for limiting keratinocyte damage in perilesional vitiligo skin and might be employed as a therapeutic intervention to prevent vitiligo development.

Glycyrrhizin and Glycyrrhetinic Acid

Glycyrrhizin is a saponin glycoside derived from licorice (*Glycyrrhiza glabra*) that contains one glycyrrhetinic acid (GA) and two glucuronic acids with anti-inflammatory, antioxidant, and antiviral properties (Yang et al., 2006). Anti-inflammatory properties of Glycyrrhizin are connected to its capacity to block the high-mobility group box-1 gene (HMGB1), which promotes the production of pro-inflammatory cytokines such as TNFα (Liu et al., 2019). Furthermore, glycyrrhizin was discovered to protect melanocytes from oxidative stress by activating the nuclear translocation of Nrf2 in human melanocytes, therefore promoting the production of heme oxygenase-1 (HO-1), an antioxidant enzyme involved in heme breakdown (Mou et al., 2019). Actions of Glycyrrhizin on melanocytes include melanogenesis stimulation: glycyrrhizin may raise tyrosinase mRNA levels, TRP-2 expression, and melanin content in a dose-dependent manner (Yang et al., 2006).

Lee et al. (2005) found that glycyrrhizin can induce melanogenesis through a mechanism involving cAMP signaling activation. Oral glycyrrhizin treatment in conjunction with UVB irradiation resulted in re-pigmentation of lesions in 87.5% of patients, with no new lesions appearing in previously active vitiligo patients (Mou et al., 2016). Glycyrrhizin was also found to have anti-depressant characteristics in patients, which were linked to its anti-inflammatory properties. Patients with high levels of inflammatory markers at baseline saw greater clinical relief (Yan et al., 2020).

Combination effect of herbal plant for vitiligo treatment

Nigella sativa (Black seeds)

Nigella sativa (black seed or black cumin), a member of the Ranunculaceae family, is an annual plant with several medicinal benefits (Ziaee et al., 2012). Many active components of *N. sativa*, such as thymoquinone (TQ) (30% - 40%), alkaloids (nigellicines and nigelledine), saponins (alpha-hederin), flavonoids, proteins (26.7%), fatty acids, and others, have been shown to improve the treatment of vitiligo patients with combined effect (Butt & Sultan, 2010; Shafiq et al., 2014). For many years, diverse cultures have used the herb as a source of medicine (Saad et al., 2005; Solmaz Mohammed et al., 2017).

Ginkgo biloba

Ginkgo biloba is one of the world's oldest trees, and its leaves and seeds have long been utilized in medicine. Ginkgo extracts have been demonstrated to be useful in the treatment of a variety of disorders including allergies, varicose veins, premenstrual syndrome, headache, and vertigo (Brendler et al., 2004). *Ginkgo biloba* extract possesses antioxidant and anti-inflammatory properties. When administered to individuals with vitiligo, considerable re-pigmentation, cessation of depigmentation, and significant improvements were noted (Parsad et al., 2003; Szczurko et al., 2011).

Green Tea

Green Tea polyphenols are extracts of *Camellia sinensis* tea leaves that have been utilized in medicine since antiquity. They have anti-inflammatory, antioxidant, and immunomodulatory properties owing to their high content (50% - 80%) of Epigallocatechin-3-gallate (EGCG) (Zhu et al., 2014). The medication can be given both internally and topically (Eken, 2016). Recent research suggests that green tea polyphenols may be effective in the treatment of vitiligo by reducing oxidative stress in the melanocytes (Jeong et al., 2005). Quercetin is the other compound contained in green tea. It is also an active ingredient of vitiligo treatment (Alvarez-Arellano et al., 2020). Therefore, it may give combined effect for vitiligo patients to treat their condition.

Ammi majus

Ammi species, which are members of the *Umbelliferae* family, contain bioactive chemicals with important biological activity. All the flavonoids found in Ammi species may be divided into flavonols (quercetin, kaempferol, isorhamnetine) and flavones (apigenin, luteolin, chrysoeriol). These flavonoids have been shown to be effective antioxidants and free radical scavengers (Harborne & King, 1976). The main components of *Ammi majus* are furocoumarins, which include xanthotoxin (up to 1.15%), imperatorin (up to 0.75%), and bergapten (up to 1.88%). Also, Ammi majus contain tannin (0.45%), glucoside 1% as well (A. E. Al-Snafi, 2013; Prajapati et al., 2010). *Ammi majus* also give combine effect because of the flavonoid derivatives such as quercetin and kaempferol (Al-Snafi, 2013; Prajapati et al., 2010).

Eclipta alba

The medicinal plant *Eclipta alba* is a member of the *Asteraceae* family. This plant is also known as bhringaraj and fake daisy (Mukhopadhyay et al., 2018). It has a long history of usage as traditional medicine in many countries, notably in the tropics (Pandey et al., 2011). This plant has many properties that can help to treat a variety of diseases, including diabetes, coronary heart disease, gastrointestinal disease, skin disease, vitiligo, skin sores, respiratory diseases, and high blood pressure (Khan &

Khan, 2008; Rahmatullah et al., 2009). *Eclipta alba* has yielded a diverse set of primary and secondary metabolites, while flavonoids, triterpenes, coumestans, and steroids are considered as major constituents (Chung et al., 2017).

Product development by natural plant materials

The active components mentioned for each herbal plant are not exhaustive lists, and there may be additional compounds that contribute to their overall therapeutic effects. The combination effect of these herbal plants lies in the synergistic interaction between their various active compounds, working together to provide more comprehensive approaches to vitiligo treatment. There are many products developed from natural plant materials for vitiligo disease. Vitilinex® cream, Ruxolitinib cream, "Bakuchi Oil" and "Kakodumbaradi thaila" are some of them which are proven by research works (Nguyen Van et al., 2019; Rosmarin et al., 2022; Ediriweera et al., 2009).

According to Nguyen Van et al. (2019), Vitilinex® herbal bioactive molecule in conjunction with narrow band UV B (NB-UVB) radiation is an effective treatment for vitiligo. Vitilinex® is made up of two parts: skin prep lotion (including centipeda cunninghamii, aloe vera, terpinol-4-ol, and dihydro avenanthramide-D) and Emmolient (containing *Nigella sativa* seed oil, black pepper coleus forskohlii, Psoralea coryfolia, thyme oil, myrrh, and neroli extracts). Vitilinex® in combination with NB-UVB radiation was administered for 15 seconds to the afflicted region, weekly for 12 weeks and 87% of the patients had 50% higher re-pigmentation rates than the control group (Nguyen Van et al., 2019).

Recent research demonstrated that Ruxolitinib cream was linked to a clinically significant improvement in facial and whole-body re-pigmentation (Ramírez-Marín & Tosti, 2022). It is made up of cetylalcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, propylparaben, stearyl alcohol, and xanthan gum (Rosmarin et al., 2022). Application of Ruxolitinib cream for 52 weeks led to a better re-pigmentation of vitiligo lesions than the vehicle-controlled trials, but it was also accompanied by acne and itching at the application site. The effectiveness and safety of Ruxolitinib cream in vitiligo patients must be studied further (Rosmarin et al., 2022).

A 120-day study on "Kakodumbaradi Thaila," a traditional Sri Lankan Ayurvedic oil containing four herbs (*Atylosia trinervia* (DC.) *Gamble*, *Eclipta prostrata L.*, *Ficus hispida Linn*, and *Sesamum indicum L.*), found effective in treating Vitiligo (Ediriweera et al., 2009). The treatment showed re-pigmentation in affected white patches and reduced symptoms, suggesting it could be a promising treatment approach (Ediriweera et al., 2009). It has also been reported that an Ayurvedic medicinal oil called "Bakuchi Oil" prepared from the dried fruits of *Psoralea corylifolia L.* (Fabaceae) which contains furanocoumarin and psoralen is used for the treatment of vitiligo in Sri Lanka (Abeysekera et al., 2012).

Conclusion

Vitiligo is a common skin disorder characterized by an acquired loss of constitutional pigmentation manifested as white macules and caused by the elimination of functional epidermal melanocytes. The interaction of genetics, autoimmunity, stress, melanocyte self-destruction, trace element deficiency, oxidative stress, and other biochemical and environmental variables complicates the progression of general vitiligo. Most of the herbal medicine plants function as activators of tyrosinase, one of the key players in melanin production, while some herbal plants focus on addressing oxidative stress. All the herbal plants have a combination of active ingredients which are used for vitiligo treatment. By critically reviewing the main components of the herbal plants and the research work, it becomes evident that the combinational effect of these herbs, with optimum ratios, can provide significant benefits for the treatment of vitiligo.

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