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A review of herbal therapeutics for the treatment of vitiligo

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Abstract
Vitiligo is a depigmenting disease caused by the destruction of healthy melanocytes. Due to side effects and inconsistent outcomes associated with traditional therapies, there is growing interest in herbal therapies for vitiligo. *Ixora coccinea* and *Acalypha indica* may be useful treatments for vitiligo. *Acalypha indica* contains flavonoids, tannins, and alkaloids with anti-inflammatory and antioxidant properties that may protect melanocytes and stimulate melanogenesis. *Ixora coccinea* contains phenolic compounds, flavonoids, and anthocyanins that may have immunomodulatory and melanin-inducing properties. Based upon their potential to regulate immune response and reduce melanocyte death, both plants may contribute to restoring skin homeostasis. Efficacy and safety studies (clinical and formulation studies) are needed to ensure their effectiveness for treating vitiligo.

Keywords: Vitiligo, *Acalypha indica*, *Ixora coccinea*, repigmentation

1. Introduction
Melanocytes, the cells that produce melanin in the basal layer of the epidermis, are specifically destroyed in vitiligo, a chronic, acquired pigmentation disorder. The clinical presentation of vitiligo is defined by the appearance of well-defined, milky-white macules and patches on the skin and mucosal surfaces. Despite not causing any direct morbidity or mortality, the high visibility of vitiligo makes it a psychologically distraught disorder that has a great effect on a patient's quality of life, social interactions, and self-esteem. While cultural/ social judgments of the condition differ by region, it is estimated that the prevalence of vitiligo is between 1-2% of the population and occurs without preference for sex or ethnicity.[1]

Although the etiology of vitiligo is still unclear, multi-factorial evidence suggests complex etiology with environmental factors, oxidative stress, autoimmune, and genetic predisposition. In recent decades, the evidence has indicated that multiple cellular stress combined with immune response contributes to melanocyte death in vitiligo, as opposed to a single, independent mechanism.[2]

In vitiligo, a chronic skin disease characterized by non-scaly macules or patches that are chalky-white and have clear borders, melanocytes—the cells that generate melanin—are particularly destroyed. Worldwide, vitiligo affects a population of 0.5% to 2% and can present at any age irrespective of sex or ethnicity. [1, 3] Vitiligo is now more commonly thought of as an autoimmune disease in which the immune system mistakenly targets and destroys melanocytes. Other contributory factors include oxidative stress, metabolic disturbances, environmental stressors, and genetic susceptibility. The disease usually presents as white areas in areas prone to stress or friction such as the mouth, eyes, knuckles, and fingertips. Such autoimmune classification permits distinction of the two major types of vitiligo: nonsegmental vitiligo, which is more common, is usually bilateral, and is progressive, and segmental vitiligo socially, which is more localized and may have neurological determinants. [1, 4] Though mainly considered a cosmetic disorder, vitiligo impacts psychological well-being and quality of life for those affected due to the visibility of the cosmetic appearance and social stigma. The clinical evaluation technique consists of a thorough history and skin assessment and includes assessment of disease severity and progression, familial history and potential triggers (e.g., stress or skin trauma). [1] There is a variety of personalized treatment options, which can include topical corticosteroids, immunosuppressants, phototherapy, and occasionally, surgical intervention. Repigmentation

is a possibility with these therapies, but no treatment can offer the promise of a complete cure and further research is still needed for improvements. [1]

2. Disease Mechanism of Vitiligo:
Several theories have been suggested for the pathophysiology of vitiligo, many of which address overlapping pathways:

2.1 Autoimmune hypothesis
Vitiligo is considered an autoimmune disease wherein the target cells are melanocytes, including autoantibodies and cytotoxic (CD8+) T cells. Antibodies to melanocyte-specific antigens, particularly tyrosinase, gp100, and MART-1, have been demonstrated in circulation in studies and there is evidence that activated CD8+ T lymphocytes penetrate depigmented lesions and secrete cytokines (such as TNF-α and IFN-γ) which inhibit melanogenesis and promote apoptosis. [1, 2, 5]

2.2 Oxidative Stress hypothesis
The oxidative stress hypothesis explains that melanocytes are particularly sensitive to oxidative stress because of their high metabolic activity in melanin synthesis. Overproduction of reactive oxygen species (ROS) and hydrogen peroxide ($H2O_2$) induce lipid peroxidation, protein oxidation, and mitochondrial dysfunction. In vitiligo, depletion of antioxidant defenses (including decreased glutathione peroxidase and catalase activity) further enhances cellular damage, leading to melanocyte death. [6]

2.3 Neurogenic hypothesis
Melanocytes may be affected in a toxic manner by neurochemical mediators produced from peripheral nerve terminals. This mechanism has potential relevance in segmental vitiligo when the depigmented skin appears in a dermatomal distribution. [1, 7]

2.4 Genetic hypothesis
Multiple susceptibility loci, related to: melanocyte biology (e.g. TYR, NLRP1), and to a lesser extent, immunological modulation (e.g. HLA, PTPN22) have been associated with vitiligo. The genetic basis is further supported by familial clustering. Irrespective of the mechanisms, they all have the same net effect of reducing melanin production and reducing functioning melanocytes, leading to the characteristic lesion with loss of pigmentation.[8, 9]

3. Types of Vitiligo
Vitiligo has a variety of clinical presentations:

- Non-segmental vitiligo (NSV): the most common type, with symmetrical bilateral depigmented patches
- Segmental vitiligo (SV): typically the starting and quickly stabilizing type with unilateral lesions in a dermatomal pattern.[1, 4]
- Mixed vitiligo: co-occurrence of SV and NSV.
- Focal vitiligo: persist long-term local patches of depigmentation that persists.
- Universal vitiligo: depigmentation affecting more than 80-90% of body surface area. [4, 10, 11, 12]

Understanding these clinical subtypes is important for choosing treatment, as they often differ in response to treatment.

4. Limitations of Current Therapies
Given the frequent discrepancies in treatment responses due to varying diagnosis, it is important to understand these clinical subgroups as it pertains to treatment options.

- Topical calcineurin inhibitors and topical corticosteroids - commonly used first line treatments, although prolonged therapy can lead to recurrence, telangiectasia, and atrophy. [13]
- Phototherapy (PUVA and narrowband UVB) - helpful in many instances, but carries risk of phototoxicity or skin cancer, and treatment should encompass longer courses of treatment and patient compliance. [14]
- Surgical therapies (e.g., melanocyte or skin grafting) - useful treatment for stable vitiligo, but labor intensive and expensive. [15]

The need for alternative and adjunctive methods of therapy is underscored by the recurrence rate, side effects, and limited efficacy.

5. Herbal Therapeutics in Vitiligo
Herbal therapies have been utilized for pigmentary disorders for numerous years, including use in Ayurvedic, Siddha, and Unani systems of medicine. Medicinal plants contain bioactive compounds such as flavonoids, alkaloids, tannins, and phenolic acids that either modulate immunity, have antioxidant effects, or promote melanogenesis. Herbal therapies likewise may have advantages over synthetic pharmacologic agents in terms of a larger margin of safety, cost, and acceptance in the culture. [16, 17]

6. Role of Acalypha indica
Acalypha indica, commonly referred to as *"Kuppaimeni"* or Indian nettle, is a plant in the Euphorbiaceae family and has historically been popular in treating respiratory disorders, eczema, scabies, and skin diseases. It comprises phytoconstituents that include flavonoids, alkaloids, tannins, and saponins.

- **Antioxidant activity:** *Acalypha indica* can neutralize reactive oxygen species (ROS); it protects melanocytes from oxidative stress, which is an important aspect of its pathophysiological features in vitiligo. [18]
- **Immunomodulatory effect:** The plant mitigates autoimmune damage to melanocytes by dampening inappropriate immune responses to the tissue. [19]
- **Melanogenesis stimulation:** Experimental studies showed that it can enhance the activity of tyrosinase, increasing melanin production. [18, 20]

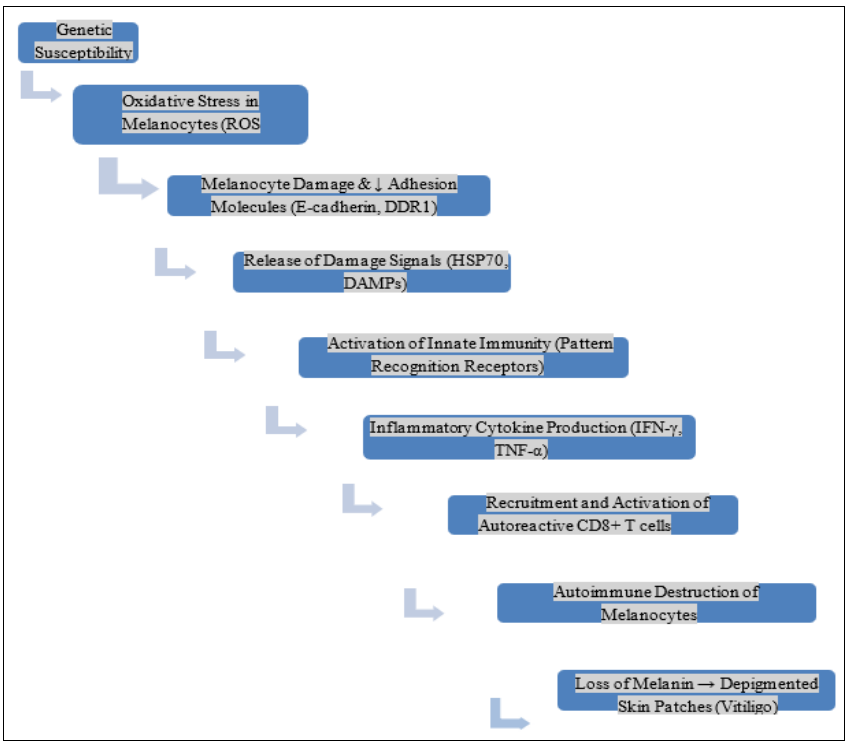
Considering these synergistic properties, *Acalypha indica* demonstrates promise as a healing agent for stopping melanocyte loss and stimulating repigmentation.

7. Role of Ixora coccinea
Ixora coccinea, a flowering shrub of the Rubiaceae family, is also called *"Rugmini"* or Jungle Geranium, and is used in treating inflammation, ulcers, skin diseases, and diarrhea in Ayurveda. The fruit contains anthocyanins, flavonoids, phenolics, and glycosides as indicated by phytochemical analyses. [16]

- **Free radical scavenging:** *Ixora coccinea* has a significant phenolic and flavonoid content; strong antioxidant protection against melanocyte damage is provided.
- **Tyrosinase activation:** The extracts of *Ixora coccinea* increase the activity of tyrosinase involved in melanogenesis, helping to promote pigmentation. [21]

Its potential use as a herbal remedy for vitiligo care, either as an extract alone or in conjunction with other melanogenic herbs, is supported by these pharmacological properties.
Vitiligo is a multifactorial condition resulting in the loss of skin pigmentation that has autoimmune, oxidative, neurogenic, and hereditary elements. Given the significant limitations and partial effects of available treatments, there is a need for safer and more sustainable alternatives. One approach is herbal therapy, and in particular, *Acalypha indica* and *Ixora coccinea* show promise because of their immunomodulatory, antioxidant and melanogenesis properties. While there are some preliminary positive results, further detailed *in vivo* and clinical proposed research is necessary to support therapeutic efficacy and safety. The use of these herbs in standardized formulations could lead to new and inexpensive socially acceptable options for treating vitiligo. [1, 16, 20]

8. Mechanism of Action



9. Introducton of Plants

9.1 *Acalypha indica*

The medicinal herb *Acalypha indica* has a long history of use in traditional medicine throughout Asia and other tropical areas. Numerous review papers suggest that the herb's complex biochemical make-up, which includes phenolics, flavonoids, alkaloids, tannins, saponins, and other volatile compounds, provides it with various medicinal properties. [18, 20] Anti-inflammatory, antibacterial, anti-cancer, anti-diabetic, antioxidant, wound-healing, anti-venom, hepatoprotective, and anthelmintic properties, have been used traditionally for the treatment of infections, respiratory diseases, gastrointestinal diseases, arthritis, wounds, and skin diseases. While it still requires clinical trials to fully support its efficacy, some of its medicinal uses have been supported through research trials. [23]

9.2 *Ixora coccinea*

Ixora coccinea is a dense, multi-stemmed evergreen shrub native to Bangladesh, Sri Lanka, and southern India often called jungle geranium, flame of the woods, or jungle flame. It forms a rounded shape and has glossy leathery, oblong leaves that are roughly four inches long. It usually grows 4-6 feet tall but may reach twelve feet in height. The plant produces clusters of tiny tubular scarlet flowers that are dense and rounded almost year-round. [16] This species, a member of the Rubiaceae family, is a common ornamental shrub in tropical and subtropical regions, especially in South Florida. It can tolerate a small amount of shade, but prefers full sun and moist, well-drained acidic soil. *Ixora coccinea* is a major favorite used for hedges, borders, screens, and plants for display in landscapes and gardens because of its colorful flowers that bloom in red, orange, yellow, pink or white continuously. The genus Ixora has over 500 species, with the majority occurring in fresh and damp forests. *Ixora coccinea* is recognized for its beautiful flowers and ornamental value. The Latin coccinea meaning "scarlet" or "bright red", indicates the color of the flower. Another source of the name "Ixora" stems from the Sanskrit word "Iswari" which may be associated with the Hindu goddess Parvati. [21, 24]

10. Plant Profile of Acalypha Indica

- **Synonyms:** *Acalypha chinensis benth, Ricinarpus indicus forssk*
- **Biological Source:** *Acalypha indica L.*
- **Family:** Euphorbiaceae

10.1 Taxonomical Classification

- **Kingdom:** Plantae
- **Phylum:** Tracheophyta
- **Class:** Magnoliopsida
- **Order:** Malpighiales
- **Family:** Euphorbiaceae
- **Genus:** Acalypha
- **Species:** *Acalypha indica*

10.2 Vernacular Names

- **English:** Indian acalypha, Indian copperleaf, Indian mercury
- **Hindi:** Kuppaimeni, Dadaro
- **Tamil:** Kuppaimeni
- **Marathi:** Khajati
- **Gujarati:** Vaichikato
- **Telugu:** Haritamanjari
- **Malayalam:** Kuppaimeni

10.3 Geographical Features

Acalypha indica acclimatizes well in tropical/subtropical climates across numerous continents, found naturally throughout the Old world tropics. Its distribution occurs in African countries (Nigeria, Sudan, DRC, Kenya, Mozambique, Tanzania, South Africa, and West Africa), Asian countries (India and Southeast Asia in particular), the Arabian Peninsula, in Oceania, and throughout the New World tropics. Frequently observed in disturbed habitats, Acalypha indica is located in wastelands, along roadsides or rocky hillsides, near woodland edges, and along riverbanks. It does well in moist, moderate to tropical temperatures and in wet/warm, shady sites, growing from sea level to about 1350 m elevation.

10.4 Botanical Description

Table: 01 [18, 20, 23, 25]

S. No	Parts	Description	Chemical Constitiuents
1	Stem	Young stems are hairy, angular and longitudinally ribbed; as they age, they change to more terete and less hairy.	Saponins, Flavonoids, Alkaloids, Phenols, Tannins, Resins, Steroids
2	Leaves	Dark green above with pale green below, that are ovate to rhomboid-ovate shaped with long hairy petioles and serration on the edges on the top half	Rich with phenolic compounds, Flavonoids and have anti-oxidant properties and contain Acalyphamide, Aurantiamide, Succinimide
3	Inflorescence	The spikes are androgynous with male and female flowers clustered together with the male clustered at to top of a stalk and the female clustered above the leafy bracts.	Flavonoids, Tannins, Cyanogenic glucoside, Alkaloids
4	Flowers	Female flowers have a three-celled ovary with 3 styles and male flowers have a calyx with 4 lobes and 8 stamens but lack petals.	Flavonoids, especially Kaempferol glycosides (mauritianin, clitorin and viorotan), pyranoquinolione alkaloids, tannins, saponins
5	Fruits and Seeds	Small, hispid capsules that opens up to 3 cocci; smooth, ovoid, pale brown seeds	Flavonoids, Alkaloids, stored oils, proteins, and phenolics analogous

10.5 Ethnomedicinal Uses

- Respiratory Conditions: It serves as an expectorant for cough, pulmonary TB, pneumonia, bronchitis, and asthma. The leaves and roots are commonly consumed in decoction form for a variety of ailments. [18]
- Skin Conditions: Leaves, applied externally as a paste or juice, are used to treat ringworm, eczema, ulcers, scabies, insect bites, wounds, and wounds that have maggots in them. [20]
- Digestive ailments: Roots are strong purgatives, while fresh juice or decoction is used as both an emetic and purgative. It is used for stomach aches, diarrhea, dysentery, and constipation.
- Pain and Inflammation: Root paste and extracts can treat (or relieve) symptoms from rheumatism, toothaches, migraines, and pain related to arthritis. Leaf extract is used for headaches and earaches. [23]
- Anthelmintic (anti-parasitic): Leaf sap can be used to treat infections in the eye, while the whole plant or leaf extracts are eaten for intestinal worms.
- Neurological Uses: Used in folk medicine for neuralgia and epilepsy (leaf extract is placed on the eyelids).
- Diverse Traditional Applications: Leaf juice is used for liver purification and treating jaundice. Castor oil is either used as oil extract or as a decoction to assist with urticaria. The stems act as a natural toothbrush for dental hygiene. Utilized for lowering blood glucose levels and as a natural contraceptive. A root infusion is utilized for paralysis. Used for snake bites, hemorrhoids, fever, and bleeding issues. [23, 25]

11. Plant Profile of *Ixora coccinea*

- **Synonym:** *Ixora bandhuca Roxb, Ixora eekhautii Gentil, Ixora fraseri Gentil, Ixora grandiflora Ker Gawl.*
- **Biological Source:** *Ixora Coccinea L.*
- **Family:** Rubiaceae

11.1 Taxonomical Classification

- **Kingdom:** Plantae
- **Phylum:** Tracheophyta
- **Class:** Magnoliopsida
- **Order:** Gentianales
- **Family:** Rubiaceae
- **Genus:** Ixora
- **Species:** *Ixora coccinea*

11.2 Vernacular Names

- **English:** Jungle Geranium, Flame of the Woods, Scarlet Jungle Flame
- **Hindi:** Rugmini
- **Tamil:** Vedchi
- **Bengali:** Rangan
- Malayalam: Chethi
- **Marathi:** Bakali
- **Telugu:** Koranam
- **Sanskrit:** Bandhuka

11.3 Geographical Features

Ixora coccinea, a compact, multibranched, evergreen shrub, is native to Bangladesh, Sri Lanka, and southern India on the Indian subcontinent. It is widely cultivated and naturalized in tropical and subtropical regions, including Southeast Asia (Indonesia, Malaysia, Philippines, Vietnam, Cambodia, Laos, and Thailand) as well as South Florida, Puerto Rico and the Caribbean.

11.4 Botanical Description

Table: 02 [16, 21, 22, 24, 27]

S.No	Parts	Description	Chemical Constituents
1	Leaves	Sessile or short petioled, oblong/elliptic 8-12 cm long, glossy, leathery, simple, opposite or whorled complete margins	Alkaloids (camptothecin), sterols (sitosterol), proanthocyanidins, coumarins, diterpenoids, quinones, peptides (Ixora peptides), triterpenoids (lupeol, ursolic acid, oleanolic acid, cycloartenol esters), flavonoids (kaempferol, quercetin, rutin) and proanthocyanidins
2	Flowers	Corolla tube, persistent small triangular calyx lobes and tiny tubular scarlet/red/orange flowers densely clustered (corymbose cymes) 4- petals, 4- stamens, bicarpellary syncarpous ovary, 3-3.5 cm long	Ursolic acid, anthocyanins and other phytochemicals
3	Stem	Woody, green, branching cylindrical aerial portions (with internodes having nodes)	Anthocyanins, ursolic acid and other phytochemicals Fatty acids (linoleic, oleic, stearic and palmitic), flavone glycosides, betulin, erythrodiol, lupeol and stigmasterol
4	Root	Tap root, branched	Di-n-octyl phthalate and fatty acids (9,12-octadecadienoic acid)

11.5 Ethnomedicinal Uses

- **Diarrhea and Dysentery:** Leaves, roots, and flowers have been utilized historically to treat these conditions due to their anti-bacterial, antidiarrheal effects. [16]
- **Skin Conditions:** Leaves and roots are utilized externally to help heal wounds, eczema, sores, ulcers, and skin conditions. [21]
- **Respiratory disorders:** Used to manage hemoptysis, asthma, cough, bronchitis, catarrhal disorders. [22]
- **Digestive Issues:** Management of colic hiccups, nausea, loss of appetite, and general gastrointestinal upset. [23]
- **Female Reproductive Health:** Traditionally flowers have been used to manage leucorrhea, dysmenorrhea, infections of the female reproductive organs, and control of irregularities during menstruation.[24]
- **Other:** To aid in resolving anti-influenzal diseases, fever, hypertension, urinary tract health.
- **Pharmacological significance:** Anti-inflammatory, anti-bacterial, anti-oxidant, hepatoprotective, gastroprotective, antinociceptive, antimutagenic, antineoplastic, and chemopreventive. [27, 28]

Roots, leaves, flowers, barks and, to a lesser extent, fruits are commonly used.The phytochemical constituents (i.e., flavonoids, triterpenoids, anthocyanins and essential oils) in different parts of the plant, suport touring therapeutic use, suggesting a diverse potential for therapeutic application in traditional medicine.

12. Promising Role of Medicinal Plants in Vitiligo Therapy

The wide range of phytochemical profiles and biologically active compounds in medicinal plants such as *Ixora coccinea* and *Acalypha indica* make them attractive candidates for treating vitiligo in particular. These plants in general promote melanogenesis (melanin production required for skin pigmentation), modulate the immune response, reduce oxidative stress, and address the variances of causes of vitiligo. *Acalypha indica* in particular is well-known for its high antioxidant capacity due to the presence of flavonoids and alkaloids, which can scavenge reactive oxygen species (ROS), reduce cellular stress and the loss of melanocytes and damage associated with the formation of the white patches found with vitiligo. Aside from antioxidant functions, the immunomodulatory properties of the plant support recovery of melanin-producing cells (melanocytes) by preventing the improper autoimmune processes associated with this disease. [16, 29] The ability of *Acalypha indica* to stimulate tyrosinase activity supports the repigmentation of skin and creation of new melanin. *Ixora coccinea* enhances skin health by providing phenolic compounds and anthocyanins that have high free radical scavenging potential, reinforcing antioxidant defenses, and supporting the maintenance of melanocyte viability. Furthermore, the extracts deplete immunomodulatory benefits to restore tyrosinase activity and mitigate immune-mediated melanocyte damage. When combined, all these mechanisms make both herbs highly relevant for natural or supplemental vitiligo therapies. Current pharmacotherapy data endorses the study of these herbs in conjunction with traditional vitiligo treatments, even given that clinical data is still nascent and further research is warranted to standardize and verify their use. The proven safety profile, affordability, and appropriateness of these herbs make them an accessible alternative for individuals seeking improved clinical outcomes and quality of life with respect to management of this skin condition. [29, 30]

13. Conclusion

Acalypha indica and *Ixora coccinea* exhibit a considerable potential as botanical treatments of vitiligo based on their multifunctional medicinal profiles and documented traditional use for an array of skin conditions. Vitiligo is a complex autoimmune depigmenting disorder characterized by the progressive loss of melanocytes and the formation of hypopigmented macules. Conventional medicine is often characterized by restriction of safety, efficacy, and recidivism, which has led to the interest in affordable and less intolerable herbal alternatives. *Acalypha indica* and *Ixora coccinea* are rich in numerous phytochemicals comprising anti-inflammatory, antioxidant, and immunomodulatory actions (i.e. flavonoids, tannins, alkaloids, anthocyanins, and phenolic acids). *Acalypha indica*, according to preclinical and experimental studies, may assist in targeting key pathogenesis mechanisms: Reactive oxygen species (ROS) can be scavenged by *Acalypha indica* and protect melanocytes from oxidative stress which are integral to melanocyte apoptosis and vitiligo. It can stimulate melanin production and promote repigmentation by enhancing tyrosinase activity and other melanogenic pathways. *Ixora coccinea* has also exhibited strong immunomodulatory and antioxidant properties. The extracts can restore skin pigmentation and homeostasis by decreasing autoimmune-mediated melanocyte death and stimulating tyrosinase activity to facilitate depigmentation reversal. The extensive application in traditional medicine, along with ethnopharmacological applications particularly for dermatological conditions, has emphasized the potential of *Acalypha indica* and *Ixora coccinea*. The acceptance and apparent safety of these agents among a wide cultural spectrum adds to their attractiveness as natural treatments or options for traditional medical management of vitiligo. It is worth noting, however, that although the pharmacological and biochemical rationale seems persuasive, robust clinical confirmation is still a way off. Thorough *in vivo* studies and clinical studies are still required to confirm efficacy, standardize formulations, and rate safety in long-term vitiligo patients. Due to their synergistic antioxidant, immunomodulatory, and promotion of melanogenesis properties, *Acalypha indica* and *Ixora coccinea* may promote safe and value-added herbs in the treatment of vitiligo. In order to translate these hopeful results into clinical practice we need to conduct more studies on clinical outcomes, product standardization, and dosage optimization. If there is a basis for using herbs in the care of vitiligo, these herbs are certainly complementary therapy for improving and expanding treatment options that are creative, approachable, and culturally acceptable, particularly if we have a mind of improving patients' quality of life and the psychological significance of managing this condition.

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