ORIGINAL ARTICLE

VERNONIA ANTHELMINTICA (L.) WILLD IN THE TREATMENT OF VITILIGO: INSIGHTS FROM TRADITIONAL UYGHUR MEDICINE PERSPECTIVE

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ABSTRACT

While a wide variety of treatment approaches and multiple hypotheses towards disease pathophysiology, vitiligo remains an enigma in medical science. Vernonia anthelmintica (L.) Willd. (Kaliziri), a medicinal plant rooted in Traditional Uyghur Medicine (TUM), has been used to treat patients with vitiligo historically. Here, the review comprehensively discusses existing literature studies associated with Kaliziri, aiming to bridge ethnopharmacological knowledge with contemporary scientific insights into vitiligo and provide clues about priorities for its future application in vitiligo research and clinical studies. Achieved literature sources highlight a diverse phytochemical composition of Kaliziri, including flavonoids, terpenoids, saponins, and alkaloids, which are associated with mechanisms of melanocyte protection and functions, such as stimulation of melanogenesis, immunomodulation, antioxidant activity, and anti-inflammatory effects. Preliminary clinical data suggest potential repigmentation effects, although the quality and consistency of available studies remain limited. Major bottlenecks in clinical translation include the lack of standardized extracts, challenges in quality control, and regulatory barriers. Overall, Kaliziri shows promise as a complementary therapeutic approach for vitiligo, warranting further exploration through well-designed clinical trials and standardized preparation protocols to ensure efficacy, safety, and broader acceptance in modern dermatological practice.

***Keywords**: Vitiligo, Vernonia anthelmintica, Kaliziri, Traditional Uyghur Medicine.*

INTRODUCTION

Vitiligo is a chronic, immune-mediated disorder resulting in the loss of functional melanocytes and subsequent depigmentation of the skin. Approximately 1-4% of the global population across different races or skin types are diagnosed with vitiligo, and approximately 50% of cases occur in patients under the age of 20.[1,2] Although the pathogenesis of vitiligo remains unclear, genetic predisposition, autoimmune responses, melanocyte defects, oxidative stress, and neurochemical factors are implicated in disease development.[3,4] Clinically, vitiligo presents as well-demarcated, achromic macules and patches on various body parts. Beyond the cosmetic impact, the disfigurement often leads to significant psychiatric morbidity. Studies report that 16-35% of patients with vitiligo experience psychiatric discomfort such as depression (10%), dysthymia (7-9%), sleep disturbances (20%), suicidal ideation (10%), and anxiety (3.3%).[5] The psychosocial impact extends to difficulties in forming relationships, social avoidance, diminished self-esteem, social stigma, and emotional distress.

Despite its prevalence and profound impact, current therapeutic options for vitiligo remain suboptimal.[6] In the literature, several reviews have provided modern treatments including topical corticosteroids, narrowband ultraviolet B (NB-UVB) phototherapy, psoralen plus ultraviolet A (PUVA), topical calcineurin inhibitors (tacrolimus, pimecrolimus), calcipotriol, excimer laser, and surgical grafting.[7-11] Despite advances in vitiligo treatment, it remains challenging and incurable. Topical immunomodulators show promise but require further evaluation, while phototherapy offers efficacy but raises concerns about long-term phototoxicity and skin cancer risks.[12,13]

This therapeutic gap has intensified the need for novel techniques and multidisciplinary approaches for effective treatment involving different complementary approaches derived from traditional medical systems as well. The World Health Organization (WHO) acknowledges that herbal products are safer, more natural alternatives to synthetic drugs [14]. Traditional Uyghur Medicine (TUM) views vitiligo (Beres) as a manifestation of systemic imbalances in the body's fluids [15,16] and individual constitution. Diagnosis relies on pulse examination, symptom assessment, and evaluation of constitution, while treatment seeks to restore balance through lifestyle, dietary, sleep, physical activity, and elimination measures.[17] TUM employs a multimodal therapeutic approach that includes herbal medicine, oral and injectable traditional formulations, heliotherapy, intralesional therapies, and adjunctive techniques such as cupping, needling, thermotherapy, and psammotherapy. Among these interventions, *Vernonia anthelmintica* (Kaliziri) is regarded as the principal herbal remedy for vitiligo due to its longstanding use in TUM and extensive traditional research (Figure 1).[18] Although Kaliziri has shown therapeutic potential, its clinical value requires further scientific validation. Accordingly, this review examines its ethnomedicinal role, phytochemical composition, proposed mechanisms of action, and preclinical and clinical evidence for efficacy and safety. It identifies current knowledge gaps and future research directions to support its integration into evidence-based dermatology.

Figure 1. Specific treatment approaches for vitiligo in TUM. The treatment methods involve prevention, nutrition, medication, topical medication, sunlight, and psychotherapy.

METHODOLOGY

A comprehensive literature review was conducted to identify relevant research on the role of Kaliziri (*Vernonia anthelmintica*) in the treatment of vitiligo, with particular emphasis on its application in TUM. Major academic databases, including PubMed, Google Scholar, EBSCO, Web of Science, and Baidu Xueshu, were queried for publications. The search strategy utilized a combination of keywords and their variants/synonyms in English, Chinese, and Uyghur languages: "Kaliziri" (كالیزىرە), "*V. anthelmintica*" (卡力孜然, 驱虫斑鸠菊), "Uyghur Medicine," "Vitiligo," and "Vitiligo Treatment." In addition to database searches, relevant information was extracted from authoritative Uyghur medical texts, pharmacopoeias, books, and relevant Uyghur and Chinese scientific journals to incorporate traditional knowledge and regional research findings. Reports from the Ministry of Health or the WHO about traditional medicine use were also considered.

Inclusion criteria for studies were: 1)Focused on the therapeutic role, pharmacology, phytochemistry, or ethnomedicinal use of Kaliziri/ *V. anthelmintica*, specifically treatment for vitiligo; 2)Discussed pharmacological properties, mechanisms of action, or clinical/preclinical efficacy/safety

related to Kaliziri; 3) Addressed the role of TUM in treatment of vitiligo using herbal drug-Kaliziri; 4) Studies conducted in the Uyghur region including national and international collaborative studies or used samples collected from the region; 5) Published in peer-reviewed scientific journals, recognized books or official reports in English, Uyghur or Chinese languages.

Exclusion criteria were: 1) Studies that are not relevant to Kaliziri or vitiligo; 2) Studies lacking sufficient data or advanced methodologies; 3) Non-peer-reviewed articles (except classical texts and official reports); 4) Duplicated publications (most comprehensive or methodologically robust studies were included).

RESULTS

TUM is a dialectical theoretical system that is based on "body fluidic theory". Namely, the human body consists of four types of body fluids, including Kan (blood), Belghem (phlegm), Sapra (yellow bile), and Savda (black bile). The balance of these four types of body fluids in the human body is the basis of health. If there is an imbalance in temperament due to various internal and external causes, the life activities of the organism will be hindered, and these abnormalities will trigger different types of pathogenic conditions such as vitiligo. From TUM's perspective, vitiligo can be defined as one type of non-contagious skin disease in which part or most of the skin area, even the entire body, changes its original color and turns white. In the classic TUM, it is called "Beres" or "Pise" or "Ak kisel". According to TUM, vitiligo is attributed to three main pathogenic mechanisms: internal, external, and specific causes. Internal causes include humoral imbalance, impaired organ function, immune dysfunction, dietary disturbances, food poisoning, infection, psychological instability, and impaired metabolism. External causes include poor personal hygiene, clothing-related factors, physical injury, poisoning, and pathogen exposure. Specific causes include genetic- and occupation-related factors.

According to TUM, treatment methods for vitiligo involve prevention, nutrition, medication, topical medication, sunlight, and psychotherapy (Figure 1). Kaliziri is the most widely used herbal drug for vitiligo in TUM as it can restore the balance of black pigment, remove carp worms, and have an anti-inflammatory effect. Until now, Kaliziri's different forms, such as tablets, injections, and tincture, are being used widely for vitiligo treatment (Figure 2).

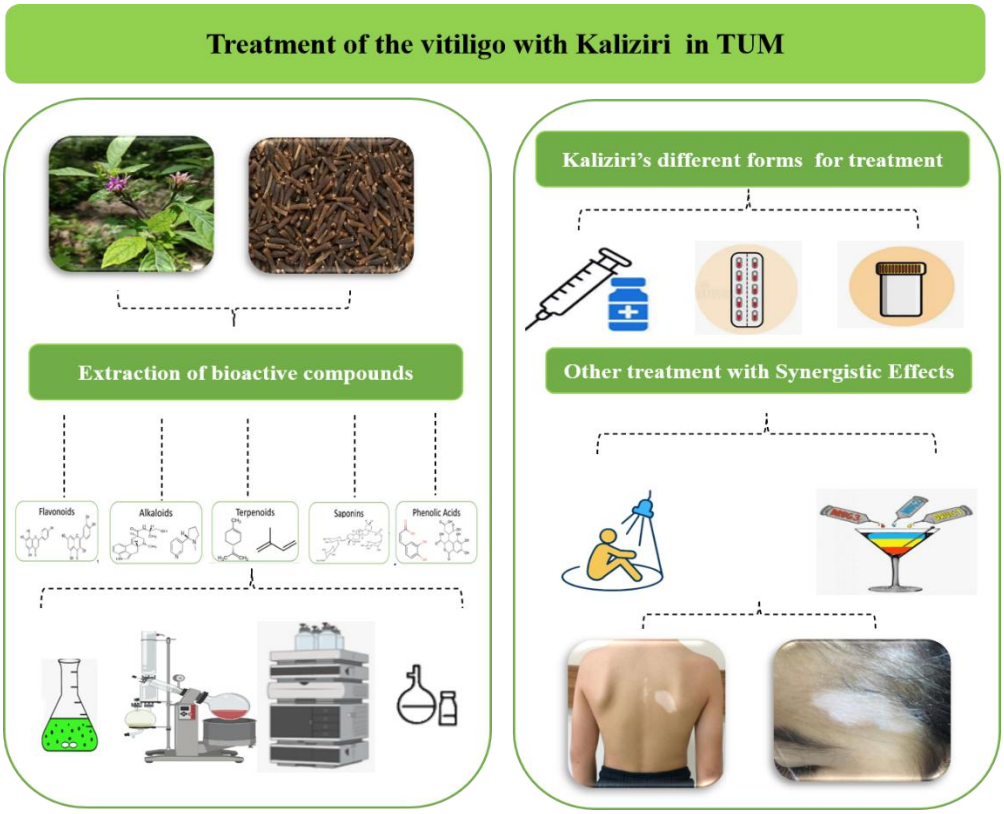

Figure 2. Treatment of vitiligo with different forms of Kaliziri in the TUM. The photos of vitiligo with typical lesions were taken with the patients' permission.

Kaliziri is abundant in bioactive compounds, including flavonoids, terpenoids, and alkaloids, which are recognized for their roles in melanogenesis and skin health.[19,20] Until now, more than 190 chemical compounds have been identified in this plant.[20,21] Yet many of these compounds are still awaiting further investigation for preclinical or clinical studies.[20]

Flavonoids: Flavonoids are primary compounds identified in Kaliziri, consisting of two aromatic rings connected by a three-carbon bridge.[22,23] Researchers identified 36 different flavonoids from Kaliziri.[19] Among these compounds, isorhamnetin, butin, luteolin, and kaempferol are closely associated with repigmentation.[19,24,25] Isorhamnetin has been demonstrated to induce melanogenesis through the upregulation of genes involved in melanin production.[19,25] Butin has shown protective properties against cellular damage induced by oxidative stress.[26] Huo et al. (2017) demonstrated that butin increased melanin-containing hair follicles in a vitiligo mouse model, and Zang et al. [27] showed pigmentation restoration in both mice and guinea pigs. Recently, Ma et al. [28] have identified three key bioactive compounds responsible for melanogenesis-promoting activity, including vernodalin, 3,5-O-dicaffeoylquinic acid, and butin. Luteolin, another significant flavonoid, has been associated with anti-inflammatory effects. It has been reported to mitigate oxidative stress *in in vitro* cell models, providing clues about significant potential properties for the maintenance of skin health.[29,30] Additionally, Kaliziri-derived flavonoids have been reported to impede glucose absorption and augment insulin sensitivity, associated with the management of diabetes.[31,32] They also exhibit anticancer activity through apoptosis induction and cell cycle arrest in malignancies.[19,24,25]

Terpenoids: Terpenoids, organic compounds derived from five-carbon isoprene units, are also abundant in Kaliziri.[33,34] Aobuli et al. Have identified 64 distinctive compounds in the volatile oil of Kaliziri, with terpenoids comprising 73.53% of the total content.[33] In particular, caryophyllene, sabinene, α-thujene, thymol, limonene, and 4-epi-α-acoradiene are the most prevalent terpenoids in the composition. These bioactive compounds exhibit anti-inflammatory, antibacterial, antioxidant, and anticancer effects.[35,36] For instance, the sesquiterpenoid compound vernodalin has demonstrated notable antibacterial properties against multiple pathogens.[37,38] Moreover, terpenoids can scavenge free radicals and reduce oxidative stress in cells.[39,40] This property is particularly important in vitiligo treatment, where oxidative stress plays a pivotal role in its development.[30]

Saponins: Saponins are another prominent category of phytochemicals found in kaliziri, characterized by their amphipathic structure consisting of a hydrophobic aglycone linked to hydrophilic sugar chains.[41,42] These compounds exhibit antimicrobial, antifungal, and antiviral properties.[43-45] Extracts with high saponin content have been shown to impede the growth of various bacteria.[46,47] Furthermore, saponins in Kaliziri contributes to its overall antioxidant activity by scavenging free radicals and reducing oxidative stress.[48,49] The presence of saponins has been associated with the treatment of various ailments, including skin diseases.[30,50] Ethnobotanical surveys also support the link between traditional use and phytochemical composition.[51]

Alkaloids: Alkaloids are organic compounds containing nitrogen atoms, typically within a heterocyclic ring structure.[52] Alkaloids have been shown to possess various health benefits, including antimicrobial and anti-inflammatory properties.[53,54] For instance, the antibacterial properties of alkaloids have been substantiated through experiments demonstrating their efficacy against strains such as Staphylococcus aureus and Pseudomonas aeruginosa.[53] Studies have demonstrated the efficacy of alkaloids in expelling helminths in infected animals, underscoring their practical utility in ethnomedicine.[54] Furthermore, alkaloids are also considered a key factor in the treatment of infections and digestive disorders.[55]

Phenolic and fatty acids: Phenolic acids are aromatic plant metabolites characterized by a phenolic ring and a carboxylic acid group, with chlorogenic and caffeic acids being notable examples found in Kaliziri.[56] Chlorogenic acid is recognized for its capacity to mitigate oxidative stress by neutralizing free radicals and fortifying the body's immune system against various diseases.[30] Caffeic acid has been known for its role in promoting skin health and its potential in managing vitiligo by enhancing melanogenesis.[25] Additionally, studies have reported that fatty acids such as vernolic acid, oleic acid, linoleic acid, palmitic acid, and stearic acid have been extracted from the seeds of Kaliziri.[57,58]

Notably, oleic and linoleic acid exhibit antioxidant properties by neutralizing free radicals.[59] These acids also nourish the skin barrier, enhance hydration, and promote overall skin integrity. These properties render Kaliziri a valuable component in traditional remedies for vitiligo.[59]

Understanding the structure-activity relationships of these bioactive compounds is crucial for identifying key contributors to therapeutic efficacy. Analytical techniques like HPLC and MS are essential for ensuring the quality control and consistency of Kaliziri-based preparations. Recent phytochemical research focusing on isolating and characterizing active compounds provides a crucial scientific foundation for validating traditional uses (Table 1). However, most studies investigating *V. anthelmintica* conducted in the Uyghur region have been limited to *in vitro* cell-based experiments and *in vivo* animal models. Clinical studies evaluating *V. anthelmintica* are scarce. These methodological limitations have restricted a comprehensive understanding of the therapeutic potential of Kaliziri and have hindered its translation into clinical practice.

Table 1. Research Studies on *Vernonia anthelmintica* in the Uyghur *Region*

No	Year	Study Location	Sample	Sample Location	Study Design	Key Findings	Ref.
1	2020	XTIPC*, Uyghur Region	*Seeds of Kaliziri*	Uyghur Region, Pakistan	Analytical chemistry-based study using HPLC-DAD, HPTLC, and chemometric methods	Developed an accurate method for quantitative analysis; revealed variations based on geographical origin and storage time; confirmed antioxidant activity	60
2	2014	XTIPC*, Uyghur Region	Seeds of Kaliziri	High-altitude areas in the Uyghur Region	Experimental research using extraction, LC-MS/MS, evaluation of tyrosinase activity, and melanin content	Flavonoids identified as primary compounds; KZE increased tyrosinase activity and melanin content in B16 cells; enhanced expression of tyrosinase, TRP-1, TRP-2, and MITF; minimal cytotoxicity	22
3	2018	XTIPC*, Uyghur Region	Seeds of Kaliziri	Xinjiang Meditsina Uyghur Pharmaceutical Co., Ltd., Xinjiang, Uyghur Region	Experimental study analyzing volatile oil using GC-QTOF-MS and testing bioactivities	AVO increased melanin synthesis in B16 cells; identified 64 compounds; showed potential protective effects against oxidative stress	33
4	2017	Shihezi University ,Uyghur Region and East China University of Science and Technology, China	Kaliziri extract	High-altitude areas in the Uyghur region	Combined in silico methods with in vitro experiments	Isorhamnetin and Kaempferide increased melanogenesis by upregulating melanin-biosynthetic genes; targeted pathways such as MC1R-MITF signaling and MAPK signaling	25

5	2017	XTIPC*, Uyghur Region	Isoxazole chalcone derivative	Laboratory	experimental study on murine B16 melanoma cells	PMPP identified as a potent tyrosinase activator; enhanced melanogenesis via Akt/GSK3β/β-catenin signaling pathways, and increased tyrosinase activity and melanin content	13
6	2017	Key Laboratory of Plant Resources and Chemistry of Arid Zone, Chinese Academy of Sciences, Urumqi, Uyghur Region	Kaliziri extract	Review article - not applicable	Summarizing advances in melanogenesis stimulators	Highlighted the importance of melanogenesis stimulators for treating vitiligo; discussed signaling pathways and protein expression related to melanogenesis	61
7	2018	XTIPC*, Uyghur Region	Murine B16 melanoma cells	Laboratory	Experimental study on 1,5-dicaffeoylquinic acid effects	1,5-dicQA stimulated melanogenesis by increasing melanin levels and tyrosinase activity; upregulated melanogenic enzymes via MAPK and cAMP/PKA signaling pathways	62
8	2021	XTIPC*, Uyghur Region	Melanocytes, C57BL/6 mice, guinea pigs	Laboratory	Experimental study on Kaliziri standard extracts (CAM-Y7)	CAM-Y7 promotes melanogenesis via p38 MAPK signaling pathway; restored pigmentation in vitiligo models; shows potential as a therapeutic agent	27
9	2022	Second Hospital of Hebei Medical University, Shijiazhuang, China	Seeds of Kaliziri	Local farm market in Uyghur Region	Comparative analysis of extraction methods	ASE showed the highest extraction efficiency and antioxidant activity; extracts demonstrated potent antioxidant abilities	63
10	2022	XTIPC*, Uyghur Region	Kaliziri injection (KZI)	Beagle plasma samples	Analytical study using UHPLC-Q-Orbitrap-MS and HPLC-MS/MS	Identified 60 caffeoyl quinic acid derivatives in KZI; quantified six major derivatives in beagle plasma; analytes showed rapid absorption and clearance	64
11	2016	Uyghur Medicine Hospital, Urumqi,	G-361 human skin	Health Science Research Resources	Experimental study on Bairesi complex	Hot water extracts are more effective in increasing melanin production; the	65

		Uyghur Region and School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan	melanoma cells	Bank, Japan	prescription	prescription showed greater efficacy than individual components; increased TRP-1 and TYR protein levels	
12	2024	Xinjiang Normal University, Urumqi, Uyghur Region	Human immortalized epidermal cells (HaCaT)	Shanghai Cell Bank, Chinese Academy of Sciences	Experimental research on flavonoids against H2O2-induced damage	Flavonoids demonstrated protective effects against oxidative stress damage; increased SOD activity; reduced MDA content; regulated Nrf2, HO-1, and NQO1 genes	[66]
13	2017	Xinjiang Institute of Traditional Uyghur Medicine, Urumqi, Uyghur Region	Male C57BL/6 mice	Shaved dorsal skin areas of mice	Experimental study using hydroquinone-induced vitiligo model	Butin increased melanin-containing hair follicles and melanocytes; enhanced TYR and TRP-1 protein expression; decreased MDA content and CHE activity	[67]
14	2023	People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Uyghur Region	Human keratinocytes	Laboratory	Experimental study on isorhamnetin against H2O2 damage	ISO pre-treatment increased cell viability; reduced MDA content; enhanced SOD activity; reduced mitochondrial membrane potential loss; inhibited apoptosis	[30]
15	2024	State Key Laboratory Basis of Xinjiang Indigenous Medicinal Plants Resource Utilization, Urumqi, Uyghur Region	Effective part of *Kaliziri* (VAEP)	15 production areas in the Uyghur Region, Pakistan, and India	Spectrum-effect relationship analysis	Vernodalin, 3,5-O-dicaffeoylquinic acid, and butin were identified as key components for melanogenesis-promoting activity	[28]

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DISCUSSION

The therapeutic effect of Kaliziri in vitiligo involves multiple molecular and cellular pathways, reflecting its complex phytochemistry:

Melanogenesis Stimulation and Melanocyte Proliferation: Bioactive compounds in Kaliziri, potentially including flavonoids[19,25], are reported to stimulate melanocyte proliferation and enhance melanin synthesis. These properties address the core pathology of pigment loss in vitiligo. The regulation often involves key transcription factors like

Microphthalmia-associated transcription factor (MITF), which governs the expression of melanogenic enzymes such as tyrosinase (TYR), tyrosinase-related protein 1 (TRP-1), and TRP-2 (DCT). [61,68]

Figure 3 depicts the most frequently involved signaling pathways, including the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA), Wingless-related integration site (Wnt)/ß-catenin, and mitogen-activated protein kinase (MAPK) pathways, associated with melanin formation. Mamat et al. [62] demonstrated that 1,5-dicaffeoylquinic acid enhances melanogenesis through both MAPK and cAMP/PKA signaling pathways, while Zang et al. [27] showed that standardized extracts specifically utilize the p38 MAPK signaling pathway. Also, Wang et al. [25] identified isorhamnetin and kaempferide as compounds that upregulate melanin-biosynthetic genes via MC1R-MITF signaling, and Yin et al. [13] found that a synthetic derivative of Kaliziri compounds enhances melanogenesis through Akt/GSK3ß/ß-catenin pathways.

Although three enzymes (TYR, TRP-1, and TRP-2) are involved in the melanogenesis pathway, only TYR is exclusively necessary for melanogenesis. In addition, MITF plays a central role in melanocyte biology by governing differentiation, pigmentation, proliferation, and cell survival [49]. Tuerxuntayi et al. extracted components from Kaliziri seeds (KZE) using an ethanol-water solution and identified their composition by using liquid chromatography–tandem mass spectrometry (LC–MS/MS). In addition, B16 melanoma cells treated with KZE were examined for the melanin synthesis signaling pathway by western blotting. The experimental results have revealed that KZE upregulates the expression of TYR, TRP-1, TRP-2, and MITF in B16 cells [22].

Immunomodulation and Anti-inflammatory Effects: Given the autoimmune component of vitiligo, Kaliziri's immunomodulatory and anti-inflammatory properties are highly relevant. Zhao *et al.*[69] investigated the efficacy of Compound Kaliziri tincture in the vitiligo treatment. A total of 150 patients were equally divided into experimental and control groups. In the experimental group, Compound Kaliziri tincture was applied externally to the vitiligo lesion area, and NB-UVB therapy was simultaneously applied. In the control group, only local NB-UVB light therapy was applied to the vitiligo lesion area. They found that the therapy was 86.7% effective in the experimental group and 65.3% effective in the control group. This difference of 21.3 percentage points was statistically significant (95% CI, 8.1–34.6; p = 0.002), with an estimated NNT of approximately 5. However, the evidence should be interpreted cautiously because the study provides limited information on allocation concealment, blinding, and outcome assessment. Thus, its methodological quality would be considered low-to-moderate by Jadad/RoB-2 criteria, with potential concerns regarding selection and performance bias. The authors suggest that Th17 cells and their cytokine IL-17 contribute to vitiligo pathogenesis by promoting inflammation and impairing melanogenesis. Overall, these clinical studies demonstrate that the external use of Kaliziri tincture in combination with local NB-UVB therapy is highly effective in the treatment of vitiligo.

Antioxidant Activity: Oxidative stress has been considered as an important factor in the pathogenesis of vitiligo. [70, 71] Melanocytes can be defined as the result of reactive oxygen species (ROS) accumulation and, in turn, triggering destruction of the structural and functional integrity of their DNA, lipids, and proteins. Kaliziri's rich content of antioxidants can neutralize reactive oxygen species, thereby protecting melanocytes from oxidative damage and creating a more favorable environment for their survival and function[39,40]

Synergistic Effects: As is well known, the synergistic effects of herbal medicine refer to the use of two or more herbal plants to enhance therapeutic efficacy and reduce toxicity compared with single-herbal treatments [72]. In TUM, more than 450 herbal drugs are used in clinical practice, among which 12 prescriptions, including Kaliziri, are associated with melanogenesis-related effects in the treatment of vitiligo[73]. Recent studies suggest that combining Kaliziri with other TUM ingredients can enhance overall therapeutic efficacy by targeting multiple pathogenic pathways simultaneously. For instance, Huang et al. [65] showed that the Bairesi complex formulation was more effective and less toxic than the single crude herbal extracts included in the prescription.

Collectively, the reported pharmacological activities of Kaliziri provide a plausible basis for its traditional use in vitiligo and other hypopigmentation disorders. However, the evidence should be interpreted cautiously because the current literature is dominated by *in vitro* findings, with only limited animal

studies and limited human clinical trials. Consequently, the therapeutic efficacy and safety of *Kaliziri* cannot yet be considered clinically established. Nevertheless, the consistency between traditional applications and several reported biological activities supports continued scientific investigation of Kaliziri and provides a basis for further evaluation of its therapeutic potential.

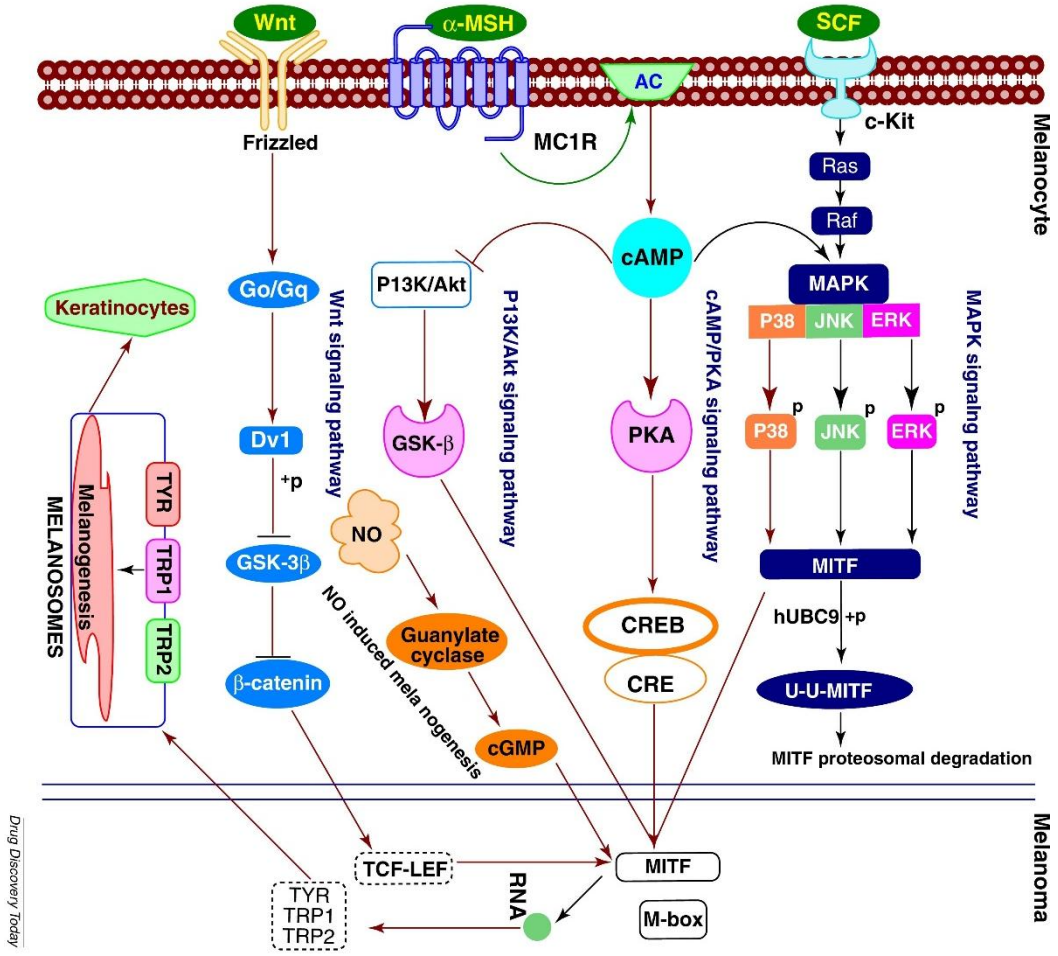

Figure 3: Regulation of melanogenesis pathways. Schematic representation of the major signaling pathways involved in melanin synthesis, including the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA), Wingless-related integration site (Wnt)/ß-catenin, and mitogen-activated protein kinase (MAPK) pathways. Extracted from [12, 49] with permission under CC-BY-4.0.

CONCLUSION AND FUTURE PERSPECTIVES

Overall, researchers have made significant contributions in elucidating the phytochemical composition, biological activities, and molecular mechanisms of this important ethnomedicinal resource over the past decade. This review demonstrates that Kaliziri exerts its melanogenesis-stimulating effects through multiple signaling pathways, including MAPK, cAMP/PKA, and Akt/GSK3ß/ß-catenin pathways. In addition to melanogenesis stimulation, Kaliziri demonstrates significant antioxidant properties that may facilitate its repigmentation effects. Despite its promising therapeutic potential, several significant challenges hinder the broader clinical adoption and scientific validation of Kaliziri. One of the foremost issues is that variations in genetics, geographical origin, harvesting, processing, and extraction can alter its phytochemical profile and therapeutic consistency. Therefore, standardized cultivation, processing, formulation, and validated analytical methods are essential for reproducible outcomes. Another critical bottleneck is that most of the existing evidence is limited by small sample sizes, inadequate controls, non-standardized

interventions, and subjective outcome measures. Future clinical research must adhere to CONSORT guidelines for randomized controlled trials to produce robust and generalizable findings. Regulatory hurdles also present a challenge, as approval pathways for traditional herbal medicines vary globally. Additionally, knowledge gaps and limited research funding for traditional medicinal plants like Kaliziri impede progress towards their reliable clinical application.

From a future perspective, several emerging research directions offer promising opportunities to advance the therapeutic use of Kaliziri in the treatment of vitiligo. The development of novel drug delivery systems and optimized transdermal patches could significantly improve the bioavailability, skin penetration, and targeted delivery of Kaliziri's bioactive compounds. Investigating combination therapies could yield additive or synergistic effects, potentially reduce required doses and side effects while improving repigmentation outcomes. Furthermore, comprehensive PK/PD studies are essential to characterize the absorption, distribution, metabolism, and excretion of Kaliziri compounds and their relationship with therapeutic effects. Ultimately, bridging traditional knowledge with modern scientific rigor through interdisciplinary collaboration is essential to fully utilize Kaliziri in the treatment of vitiligo and integrate it into evidence-based dermatological practice.

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REFERENCES

1. Halder RM, Nootheti PK. Ethnic Skin Disorders Overview. In: Journal of the American Academy of Dermatology 2003; doi: 10.1067/mjd.2003.274.

2. Parsad D, Pandhi R, Juneja A. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. Clin Exp Dermatol 2003;28(3); doi: 10.1046/j.1365-2230.2003.01207.x.

3. Xie H, Zhou F, Liu L, et al. Vitiligo: How Do Oxidative Stress-Induced Autoantigens Trigger Autoimmunity? J Dermatol Sci 2016;81(1); doi: 10.1016/j.jdermsci.2015.09.003.

4. Patel S, Rauf A, Khan H, et al. A Holistic Review on the Autoimmune Disease Vitiligo with Emphasis on the Causal Factors. Biomedicine and Pharmacotherapy 2017;92; doi: 10.1016/j.biopha.2017.05.095.

5. Garg S, Sarkar R. Impact of vitiligo in afflicted patients. Pigment International 2014;1(2); doi: 10.4103/2349-5847.147045.

6. Sawant NS, Vanjari NA, Khopkar U. Gender Differences in Depression, Coping, Stigma, and Quality of Life in Patients of Vitiligo. Dermatol Res Pract 2019;2019; doi: 10.1155/2019/6879412.

7. Krishnan A, Kar S. Smashed skin grafting or smash grafting - a novel method of vitiligo surgery. Int J Dermatol 2012;51(10); doi: 10.1111/j.1365-4632.2012.05513.x.

8. Post NF, Ezekwe N, Narayan VS, et al. The Use of Lasers in Vitiligo, an Overview. Journal of the European Academy of Dermatology and Venereology 2022;36(6); doi: 10.1111/jdv.18005.

9. Juntongjin P, Sangganjanavanich P. Efficacy of the combined excimer light and topical calcipotriol for acral vitiligo: A randomized double-blind comparative study. Dermatol Ther 2021;34(2); doi: 10.1111/dth.14886.

10. Bouceiro Mendes R, Alpalhão M, Filipe P. UVB Phototherapy in the Treatment of Vitiligo: State of the Art and Clinical Perspectives. Photodermatol Photoimmunol Photomed 2022;38(3); doi: 10.1111/phpp.12740.

11. Bishnoi A, Parsad D. Phototherapy for vitiligo: a narrative review on the clinical and molecular aspects, and recent literature. Photodermatol Photoimmunol

Photomed 2024;40(3):e12968.doi: 10.1111/phpp.12968.

12. Szczurko O, Boon HS. A Systematic Review of Natural Health Product Treatment for Vitiligo. BMC Dermatol 2008;8; doi: 10.1186/1471-5945-8-2.

13. Yin L, Niu C, Liao L xin, et al. An isoxazole chalcone derivative enhances melanogenesis in b16 melanoma cells via the Akt/GSK3β/β-catenin signaling pathways. Molecules 2017;22(12); doi: 10.3390/molecules22122077.

14. Kothawade KA, Siddiqui AR. A comprehensive review on pharmacological activity of *Vernonia anthelmintica* and *Corallocarpus epigaeus*. Asian Journal of Pharmaceutical Education and Research 2018;7(2):28-35.

15. Abdukadir A, Dubrovin D, Amat N, et al. The origins of Uyghur medicine: Debates and perspectives. Journal of Traditional Chinese Medical Sciences 2015;2(4); doi: 10.1016/j.jtcms.2016.03.003.

16. Ma ZQ, Hu H, He TT, et al. An Assessment of Traditional Uygur Medicine in Current Xinjinag Region (China). African Journal of Traditional, Complementary and Alternative Medicines 2014;11(2); doi: 10.4314/ajtcam.v11i2.13.

17. Obulkasim AHMET. Treatment Of Skin Diseases İn Uyghur Medicine. 2004.

18. Siddik H. . Practical Experiences of Vitiligo Treatment İn Uyghur Medicine. 2004.

19. Hu W, Wang H, Li K, et al. Identification of active compounds in *Vernonia anthelmintica* (L.) willd by targeted metabolome MRM and kaempferol promotes HaCaT cell proliferation and reduces oxidative stress. Front Pharmacol 2024;15:1343306.doi: 10.3389/fphar.2024.1343306.

20. Dogra NK, Kumar S, Kumar D. *Vernonia Anthelmintica* (L.) Willd.: An Ethnomedicinal, Phytochemical, Pharmacological and Toxicological Review. J Ethnopharmacol 2020;256; doi: 10.1016/j.jep.2020.112777.

21. Fatima I, Waheed S, Zaidi JH. Elemental analysis of *Anethum gravedlens*, *Sismbrium Irio* Linn and *Veronia Anthelmintica* seeds by instrumental neutron activation analysis. Applied Radiation and Isotopes 2013;71(1); doi: 10.1016/j.apradiso.2012.09.022.

22. Tuerxuntayi A, Liu Y qiang, Tulake A, et al. Kaliziri extract upregulates tyrosinase, TRP-1, TRP-2 and MITF expression in murine B16 melanoma cells. BMC Complement Altern Med 2014;14; doi: 10.1186/1472-6882-14-166.

23. Butnariu M. Plant Genome Engineering for Improved Flavonoids Production. In: Plants as Bioreactors: An Overview 2023; doi: 10.1002/9781119875116.ch8.

24. Lai Y, Feng Q, Zhang R, et al. The great capacity on promoting melanogenesis of three compatible components in *vernonia anthelmintica* (L.) willd. Int J Mol Sci 2021;22(8); doi: 10.3390/ijms22084073.

25. Wang JY, Chen H, Wang YY, et al. Network pharmacological mechanisms of *Vernonia anthelmintica* (L.) in the treatment of vitiligo: Isorhamnetin induction of melanogenesis via up-regulation of melanin-biosynthetic genes. BMC Syst Biol 2017;11(1); doi: 10.1186/s12918-017-0486-1.

26. Fernando PDSM, Piao MJ, Kang KA, et al. Butin Protects Keratinocytes From Particulate Matter 2.5 and Ultraviolet B-Mediated Damages. Photodermatol Photoimmunol Photomed 2024;40(6):e13001.doi: 10.1111/phpp.13001.

27. Zang D, Maimaiti Z, Mamat N, et al. Pigmentation Effects of Kaliziri Standard Extracts on Melanocytes,

C57BL/6 mice of Hydroquinone-Induced and Guinea Pigs of Hydrogen Peroxide-Induced Hyperpigmentation Model. 2021.doi: 10.21203/rs.3.rs-870219/v1

28. Ma X, Turak A, Abdulla R, et al. Spectrum–effect relationship between ultra-performance liquid chromatography fingerprints and melanogenic effect of *Vernonia anthelmintica* effective part. Biomedical Chromatography 2024;38(6); doi: 10.1002/bmc.5863.

29. Rajan M, Soororbhavan S, Chandran V, et al. Callus induction, indirect organogenesis and plantlet regeneration from different explants of *vernonia anthelmintica* (L.) willd. J Appl Biol Biotechnol 2020;8(3); doi: 10.7324/JABB.2020.80304.

30. Hu W, Zhang J, Wang H, et al. Protective effects of isorhamnetin against H2O2-induced oxidative damage in HaCaT cells and comprehensive analysis of key genes. Sci Rep 2023;13(1); doi: 10.1038/s41598-023-27575-7.

31. Ding Z, Yuan C, Peng X, et al. Direct 4D printing via active composite materials. Sci Adv 2017;3(4):e1602890.doi:10.1126/sciadv.1602890

32. Som S, Antony J, Palanisamy Dhanabal S, et al. A preliminary investigation of anticholinesterase and antioxidant properties of various extracts of *vernonia anthelmintica* in relation to the treatment of alzheimer's disease. International Journal of Research in Pharmaceutical Sciences 2020;11(3); doi: 10.26452/ijrps.v11i3.2679.

33. Aobuli A, Maitusong J, Bakri M, et al. The Effect of Volatile Oil from *Vernonia anthelmintica* Seeds on Melanin Synthesis in B16 Cells and Its Chemical Analysis by GC-QTOF-MS. Evidence-based Complementary and Alternative Medicine 2018;2018; doi: 10.1155/2018/6291281.

34. Davies FK, Jinkerson RE, Posewitz MC. Toward a Photosynthetic Microbial Platform for Terpenoid Engineering. Photosynth Res 2015;123(3); doi: 10.1007/s11120-014-9979-6.

35. Niu L, Rustamova N, Ning H, et al. Diversity and Biological Activities of Endophytic Fungi from the Flowers of the Medicinal Plant *Vernonia anthelmintica*. Int J Mol Sci 2022;23(19); doi: 10.3390/ijms231911935.

36. Oladele JO, Oyeleke OM, Oladele OT, et al. Covid-19 treatment: Investigation on the phytochemical constituents of *Vernonia amygdalina* as potential Coronavirus-2 inhibitors. Computational Toxicology 2021;18; doi: 10.1016/j.comtox.2021.100161.

37. Dumas NGE, Anderson NTY, Godswill NN, et al. Secondary metabolite contents and antimicrobial activity of leaf extracts reveal genetic variability of *Vernonia amygdalina* and *Vernonia calvoana* morphotypes. Biotechnol Appl Biochem 2021;68(4); doi: 10.1002/bab.2017.

38. Gbadeyan A. F, Orole O. O, Ajala O. O, et al. The Effect of Bitter Leaves (*Vernonia amygdalina*) Extract on *Salmonella typhi* and *Salmonella paratyphi*. International Journal of Research and Innovation in Applied Science 2021;06(06); doi: 10.51584/ijrias.2021.6607.

39. Valente M dos A, Ferreira P, Lima K, et al. *Vernonia britteniana* Root Phytochemical Studies, In Vitro Cercaricidal Activity on the Larval Stage of *Schistosoma mansoni* and Antioxidant Activities. Plants 2023;12(9); doi: 10.3390/plants12091788.

40. Egbung GE, Atangwho IJ, Kiasira ZB, et al. Antioxidant activity of

the inflorescents of *Vernonia calvoana* growing in Yakurr Local Government Area of Cross River State, Nigeria. Global Journal of Pure and Applied Sciences 2016;22(2); doi: 10.4314/gjpas.v22i2.3.

41. Lorent JH, Quetin-Leclercq J, Mingeot-Leclercq MP. The Amphiphilic Nature of Saponins and Their Effects on Artificial and Biological Membranes and Potential Consequences for Red Blood and Cancer Cells. Org Biomol Chem 2014;12(44); doi: 10.1039/c4ob01652a.42.

42. Khan JS, Saleem A, Akram M, et al. Pharmacological evaluation & phytochemical screening of seed extracts of kaliziri (*Centratherum anthelminticum*). World Journal of Biology and Biotechnology 2024;9(2):53–58. doi:10.33865/wjb.009.02.1286.

43. Man J, Shi Y, Huang Y, et al. PnMYB4 negatively modulates saponin biosynthesis in Panax notoginseng through interplay with PnMYB1. Hortic Res 2023;10(8); doi: 10.1093/hr/uhad134.

44. Van Le TH, Lee GJ, Vu HKL, et al. Ginseng saponins in different parts of *Panax vietnamensis*. Chem Pharm Bull (Tokyo) 2015;63(11); doi: 10.1248/cpb.c15-00369.

45. O.R. A, O.O. E, B.M. A, et al. Nutritional, Phytochemical and Fourier Transform Infra-Red Spectroscopy Profiling of *Vernonia amygdalina* Seeds. Scientific Research Journal 2019;VII(VII); doi: 10.31364/scirj/v7.i7.2019.p0719669.

46. El Khodary YA, Ayoub IM, Pério P, et al. A comparative untargeted metabolomic analysis and assessment of antiplasmodial potential of nine Albizia species. Arch Pharm (Weinheim) 2024;357(6); doi: 10.1002/ardp.202300543.

47. Owoyale ADM, Galadimma M, Daniyan SY, et al. Antifungal Activities of *Vernonia amygdalina* Crude Extracts and Fractions against Strain1161, P37005 and RM1000. Microbiol Res J Int 2020; doi: 10.9734/mrji/2020/v30i930267.

48. Alam MF, Chopra AK, Safhi MM, et al. Toxicity of *Vernonia anthelmintica* Linn. (Asteracea) seeds against mosquitoes vectors. Journal of Applied and Natural Science 2010;2(2); doi: 10.31018/jans.v2i2.118.

49. Adiukwu PC, Bonsu M, Okon-Ben I, et al. Ultraviolet spectroscopic evaluation of bioactive saponin fraction from the aqueous extract of *Vernonia amygdalina* [Esteraeceae] leaf. Int J Biol Chem Sci 2017;11(4); doi: 10.4314/ijbcs.v11i4.38.

50. Ekam VS, Ebong PE, Umoh IB. Phytochemical Screening Of Activity Directed Extracts A Of *Vernonia Amygdalina* Leaves. Global Journal of Pure and Applied Sciences 2010;16(1); doi: 10.4314/gjpas.v16i1.62824.

51. Teraishi M, Tojo Y, Yamada N, et al. Identification of environmentally stable QTLS controlling saponin content in Glycine max. Breed Sci 2017;67(2); doi: 10.1270/jsbbs.16086.

52. Gutiérrez-Grijalva EP, López-Martínez LX, Contreras-Angulo LA, et al. Plant Alkaloids: Structures and Bioactive Properties. In: Plant-Derived Bioactives: Chemistry and Mode of Action 2020; doi: 10.1007/978-981-15-2361-8_5.

53. Mabhiza D, Chitemerere T, Mukanganyama S. Antibacterial Properties of Alkaloid Extracts from *Callistemon citrinus* and *Vernonia adoensis* against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Int J Med Chem 2016;2016; doi: 10.1155/2016/6304163.

54. Iqbal Z, Lateef M, Jabbar A, et al. Anthelmintic activity of *Vernonia anthelmintica* seeds against trichostrongylid nematodes of sheep. Pharm Biol 2006;44(8); doi: 10.1080/13880200600896512.

55. Matthew EO, Ozigi IA, Uthman AI, et al. Phytochemical Screening of Coconut Water and Bitter Leaf Extract and Antibiogram of the Mixture (Coconut Water+ Bitter Leaf) on *Salmonella Typhi* and *Streptococcus Spp*. 2024. doi:10.21203/rs.3.rs-4458581/v1

56. H. Al Mamari H. Phenolic Compounds: Classification, Chemistry, and Updated Techniques of Analysis and Synthesis. 2022; doi: 10.5772/intechopen.98958.

57. Li R, Yu K, Hatanaka T, et al. Vernonia DGATs increase accumulation of epoxy fatty acids in oil. Plant Biotechnol J 2010;8(2); doi: 10.1111/j.1467-7652.2009.00476.x.

58. Kumar G, Bhardwaj M. Gamma Rays Induced Oil and Fatty Acid Alteration in Cumin (*Cuminum cyminum* L.) Seeds. European J Med Plants 2020; doi: 10.9734/ejmp/2020/v31i1630326.

59. Orsavova J, Misurcova L, Vavra Ambrozova J, et al. Fatty acids composition of vegetable oils and its contribution to dietary energy intake and dependence of cardiovascular mortality on dietary intake of fatty acids. Int J Mol Sci 2015;16(6); doi: 10.3390/ijms160612871.

60. Maimaiti Z, Turak A, Ma QL, et al. Quantitative Determination of Marker Compounds and Fingerprint Analysis of the Seeds of *Vernonia anthelmintica*. Int J Anal Chem 2020;2020; doi: 10.1155/2020/8859425.

61. Niu C, Aisa HA. Upregulation of Melanogenesis and Tyrosinase Activity: Potential Agents for Vitiligo. Molecules 2017;22(8); doi: 10.3390/molecules22081303.

62. Mamat N, Lu XY, Kabas M, et al. Potential anti-vitiligo properties of cynarine extracted from *Vernonia anthelmintica* (L.) Willd. Int J Mol Med 2018;42(5); doi: 10.3892/ijmm.2018.3861.

63. Bian G li, Hu Y lin, Yan K, et al. Characterization of constituents by UPLC-MS and the influence of extraction methods of the seeds of *Vernonia anthelmintica* willd.: extraction, characterization, antioxidant and enzyme modulatory activities. Heliyon 2022;8(8); doi: 10.1016/j.heliyon.2022.e10332.

64. Liu C, Wahefu A, Lu X, et al. Chemical Profiling of Kaliziri Injection and Quantification of Six Caffeoyl Quinic Acids in Beagle Plasma by LC-MS/MS. Pharmaceuticals 2022;15(6); doi: 10.3390/ph15060663.

65. Huang X, Ishikawa M, Mansur A, et al. The Effects of Bairesi Complex Prescription (a Uyghur Medicine Prescription) and Its Five Crude Herbal Extracts on Melanogenesis in G-361 Cells. Evidence-based Complementary and Alternative Medicine 2016;2016; doi: 10.1155/2016/8415359.

66. Eibulayin G, Rahman N, Fu JH, et al. Study on the Protective Effect of Flavonoids in *Vernonia anthelmintica* (L.) Willd on Oxidative Stress Damage of HaCaT Cells. Nat Prod Commun 2024;19(4):1-15. Doi: 10.1177/1934578X241245866.

67. Huo SX, Wang Q, Liu XM, et al. The Effect of Butin on the Vitiligo Mouse Model Induced by Hydroquinone. Phytotherapy Research 2017;31(5); doi: 10.1002/ptr.5794.

68. Zang D, Niu C, Lu X, et al. A Novel Furocoumarin Derivative, 5-((diethylamino)me-13 thyl)-3-phenyl-7H-furo [3,2-g] chromen-7-one Upregulates Melanin Synthesis via the Activation of cAMP/PKA and MAPKs Signal Pathway: In Vitro and In Vivo Study. Int J Mol Sci

2022;23(22); doi: 10.3390/ijms232214190.

69. ZHAO Lei. Effects and Prognosis of Narrow-band Ultraviolet Wave Combined with Compound Kaliziran Tincture in the Treatment of 150 Cases of Vitiligo. Journal of rare and uncommon diseases70. Laddha NC, Dwivedi M, Mansuri MS, et al. Vitiligo: Interplay between oxidative stress and immune system. Exp Dermatol 2013;22(4):245–250; doi: 10.1111/exd.12103.

71. KU. S. Successful treatment of oxidative stress in vitiligo. Skin Pharmacol Appl Skin Physiol 1999;12(3):132–8; doi: DOI: 10.1159/000029867.

72. Wang X, Shi X, Xi Z, et al. The scientific basis of synergy in traditional Chinese medicine: physicochemical, pharmacokinetic, and pharmacodynamic perspectives. Chinese Medicine (United Kingdom) 2026;21(1):1–21; doi: 10.1186/s13020-025-01291-y.

73. Mikami M, Sonoki T, Ito M, et al. Glycosylation of tyrosinase is a determinant of melanin production in cultured melanoma cells. Mol Med Rep 2013;8(3):818–822; doi: 10.3892/mmr.2013.1602.