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## EDITED BY

Tingting Cui,  
Fourth Military Medical University, China

## REVIEWED BY

Ankit Tanwar,  
Albert Einstein College of Medicine,  
United States  
Mithun Rudrapal,  
Vignan's Foundation for Science, Technology  
and Research, India

## \*CORRESPONDENCE

Bingnan Cui  
✉ cbn1998@163.com

†These authors have contributed  
equally to this work and share  
first authorship

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# Polyphenols targeting multiple molecular targets and pathways for the treatment of vitiligo

Yixuan Yang<sup>†</sup>, Yanyuan Du<sup>†</sup> and Bingnan Cui\*

Department of Dermatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China

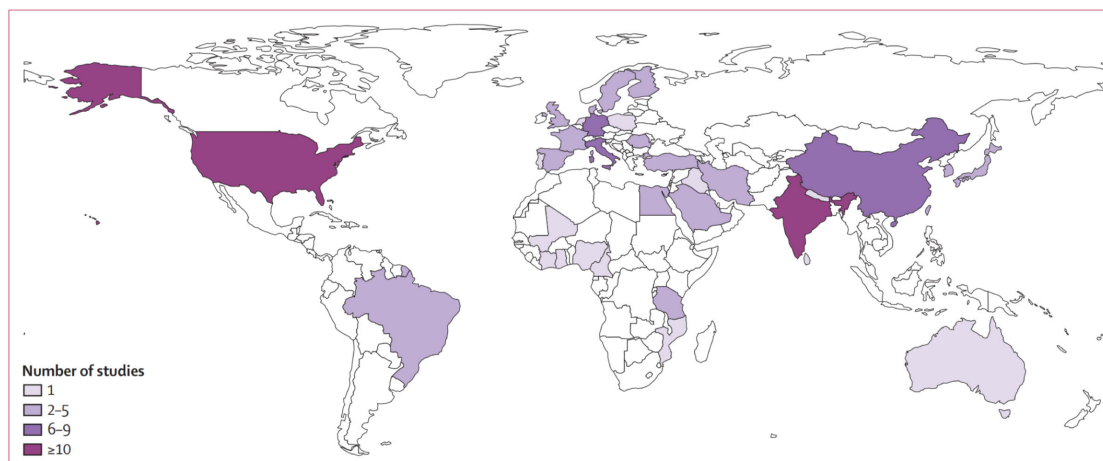
Vitiligo, a pigmentary autoimmune disorder, is marked by the selective loss of melanocytes in the skin, leading to the appearance of depigmented patches. The principal pathological mechanism is the melanocyte destruction mediated by CD8<sup>+</sup> T cells, modulated by oxidative stress and immune dysregulation. Vitiligo affects both physical health and psychological well-being, diminishing the quality of life. Polyphenols, naturally occurring compounds with diverse pharmacological properties, including antioxidant and anti-inflammatory activities, have demonstrated efficacy in managing various dermatological conditions through multiple pathways. This review provides a comprehensive analysis of vitiligo and the therapeutic potential of natural polyphenolic compounds. We examine the roles of various polyphenols in vitiligo management through antioxidant and immunomodulatory effects, melanogenesis promotion, and apoptosis reduction. The review underscores the need for further investigation into the precise molecular mechanisms of these compounds in vitiligo treatment and the exploration of their combination with current therapies to augment therapeutic outcomes.

## KEYWORDS

vitiligo, polyphenols, mechanisms, oxidative stress, immunity

## 1 Introduction

Vitiligo, an autoimmune disorder, is characterized by the selective loss of melanocytes, leading to depigmentation of skin, which appears as white patches (1). Globally, approximately 0.5–2% of the population is affected by vitiligo, with its prevalence exhibiting no significant variation across genders, races, or geographic regions (2–6). The results of distribution of studies included in the analysis of vitiligo prevalence are depicted in Figure 1 (7). This condition not only impacts the physical health of patients but also significantly affects their mental well-being, resulting in a diminished quality of life (8). Hence, vitiligo should not be perceived solely as a cosmetic or trivial concern, but rather as a condition capable of causing considerable psychological distress, imposing a substantial burden on the patient (9). Enhanced understanding of the pathogenesis of vitiligo which



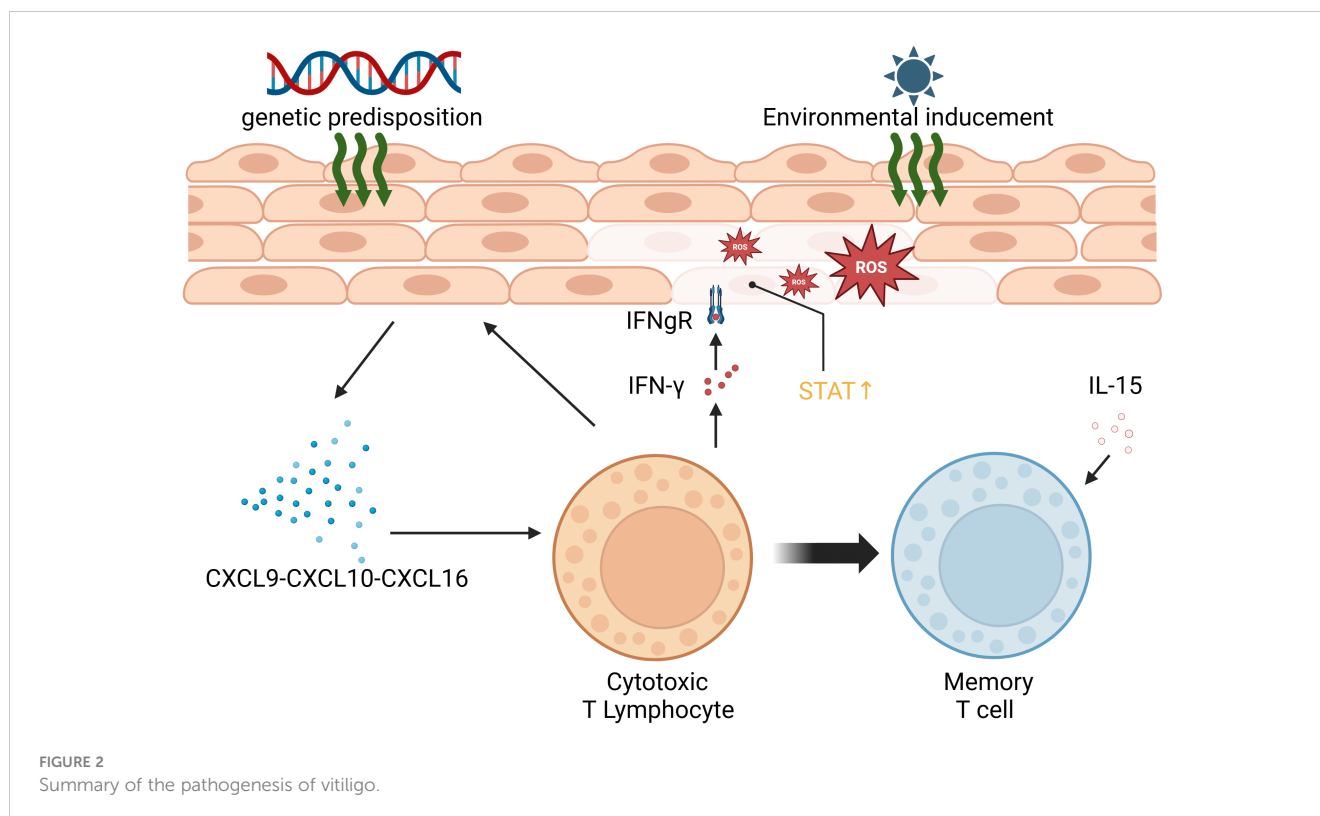
**FIGURE 1**  
Distribution of studies included in the analysis of vitiligo prevalence. Reprinted with permission from ref (7). Copyright © 2024 The Author(s).  
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may facilitate the development of more effective therapeutic strategies, could bring positive benefits to individuals suffering from vitiligo.

Vitiligo primarily affects melanocytes, the pigment-producing cells located in the epidermis between hair follicles. Autoimmunity is a key factor in its development. Vitiligo results from the progressive autoimmune destruction of cutaneous melanocytes by  $CD8^+$  T cells (10). The presence of numerous melanocyte-reactive cytotoxic T cells in the peripheral blood of vitiligo patients, along with perifocal T-cell infiltration causing melanocyte loss, is closely associated with vitiligo development. This process is further enhanced by the secretion of  $IFN-\gamma$  by T cells, stimulating the production of CXCL9 and CXCL10 by keratinocytes and the recruitment of more T cells (11).  $IFN-\gamma$  signaling can activate downstream  $IFN-\gamma$ -inducible genes by binding to the cell surface receptor, forming a complex of two different proteins that recruits JAK1 and JAK2 kinases, resulting in STAT phosphorylation and nuclear translocation (12, 13). Vitiligo often recurs, possibly due to the activity of CD8 tissue-resident memory T cells (TRM), which are responsible for its reactivation. TRM can detect self-antigens in the skin during the stable phase of the disease, leading to the production of  $IFN-\gamma$ , CXCL9, CXCL10, and  $TNF-\alpha$  (14). Additionally, interleukin-15 plays a role in maintaining TRM (15). Oxidative stress is also a significant factor in vitiligo. When melanocytes experience stress, they release reactive oxygen species (ROS), leading to an imbalance of pro-oxidants (superoxide dismutase, malondialdehyde, xanthine oxidase) and enzymatic and non-enzymatic antioxidants (catalase, glutathione reductase, glutathione peroxidase, thioredoxin reductase, thioredoxin, superoxide dismutase, as well as the restorative enzymes methionine sulfoxide reductase A and B). This process accelerates the cellular pre-senescent state (16, 17). Furthermore, the production and accumulation of ROS induce DNA damage, protein oxidation and fragmentation, as well as lipid

peroxidation, all of which impair cellular function (18). The mechanisms underlying vitiligo are depicted in Figure 2.

Current management of vitiligo mainly includes drug therapy, phototherapy, surgical treatment, and self-management of patients (19, 20). These treatments aim to halt the progression of pigment loss, restore skin color, and improve the psychological well-being of patients. However, the existing treatment options have some limitations. 1) Drug therapy: Commonly used drugs include corticosteroids and immunomodulators. Although these drugs can control the condition to some extent, long-term use may lead to a series of side effects, such as skin atrophy, immunosuppression, and the risk of rebound depigmentation if treatment is suddenly stopped. In addition, the effect of drug therapy varies from person to person, and some patients may not achieve the desired treatment outcomes. 2) Phototherapy: Phototherapy such as NB-UVB can promote repigmentation. However, it requires regular treatments over a long period of time and carries risks of sunburn and skin cancer. Excimer laser may be effective for localized areas but could be costly and impractical for larger areas. 3) Surgical treatment: Although skin grafting may be effective for certain patients with localized and stable vitiligo, its application scope is limited by issues such as surgical risks, the survival of transplanted skin, and high costs. 4) Depigmentation therapy: When vitiligo covers a large area, it may be considered to depigment the remaining normal skin to create a uniform skin tone. However, this is a radical measure that is irreversible. 5) Self-management: Although self-management of patients is important, it is often challenging to sustain long term. For example, maintaining good lifestyle habits, avoiding excessive exposure to the sun, and fostering a positive mindset all influence the condition of vitiligo. However, in practice, patients may struggle to adhere to these practices due to various reasons. Therefore, while progress has been made in the management of vitiligo, there are still numerous limitations, including limited efficacy, side effects and risks, economic burden, and a lack of personalized treatment options.



Polyphenols, widely distributed in nature, are increasingly recognized for their pivotal role in safeguarding human health. They derive their name from the multiple phenolic hydroxyl groups present in their structures. Polyphenols can be broadly categorized into phenolic acids, flavonoids, tannins, stilbenes, and lignans based on their chemical composition. These compounds display a broad spectrum of pharmacological effects, encompassing antioxidant, anti-inflammatory, anti-tumor, anti-proliferative, and anti-angiogenic properties (21–25). Various polyphenols have also shown effectiveness in treating diverse types of skin diseases through multiple mechanisms (25, 26).

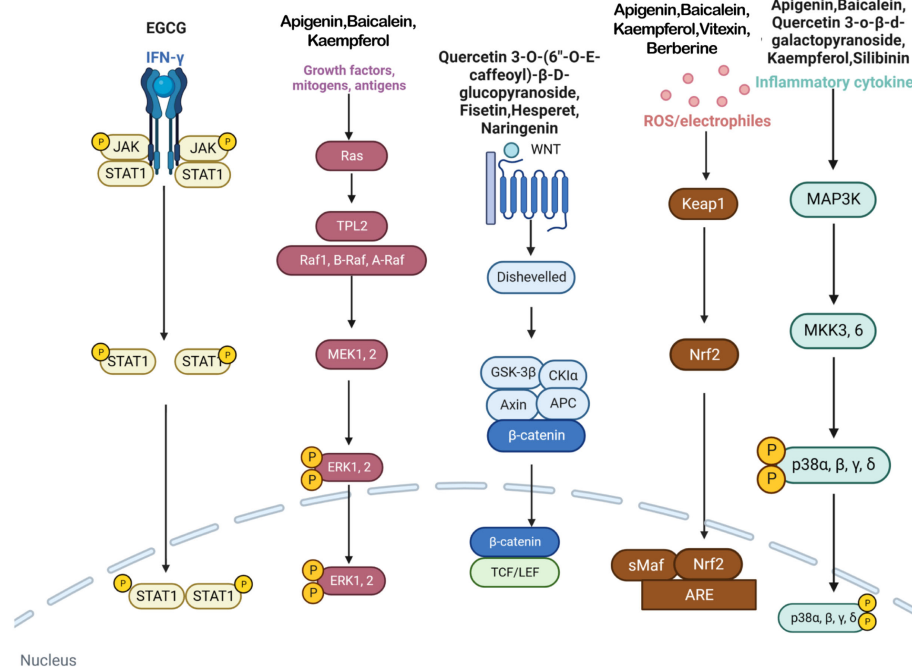
Compared with other natural compounds, polyphenols offer unique advantages in the treatment of vitiligo. 1) Polyphenols possess potent antioxidant and anti-inflammatory properties. Vitiligo involves the damage and death of skin pigment cells, with oxidative stress being a key pathological factor. Polyphenols reduce oxidative stress and inhibit inflammatory responses by effectively scavenging free radicals and suppressing lipid peroxidation (27), which may help protect skin pigment cells. 2) Polyphenolic compounds exhibit more significant and broad activity in immune modulation. They achieve this by mechanisms including antioxidant action, regulation of cellular signaling pathways, and influencing the expression of cytokines (28, 29). For example, polyphenols can regulate the function of T cells, which play a crucial role in adaptive immune responses. While terpenoids and other natural compounds like alkaloids and glycosides also possess immunomodulatory properties, their mechanisms of action may be more specific or limited compared to polyphenols. 3) Polyphenols are abundant in sources. As crucial secondary metabolites in plants,

their widespread distribution is closely tied to their roles in plant physiology, encompassing defense mechanisms (such as anti-microbial and anti-feedant properties), antioxidants, and influencing plant coloration (30). Currently, approximately 8000 types of polyphenol structures have been identified in plants (31), and their diverse biosynthetic pathways (32) make them more readily available. 4) Some polyphenols are generally considered to have lower toxicity and side effects compared to certain alkaloids and terpenoids (33). The presence of polyphenols in the natural environment and long history of human consumption indicate their safety at normal dietary intake levels.

This study investigates the potential role of polyphenolic compounds in treating vitiligo, a dermatological condition characterized by the loss of skin pigmentation, for which effective treatment is currently lacking. Renowned for their antioxidative and anti-inflammatory properties, polyphenolic compounds are believed to positively impact the pathogenesis of vitiligo by modulating multiple molecular targets and signaling pathways (Figure 3). This study systematically reviews the potential mechanisms by which polyphenolic compounds may affect the treatment of vitiligo, thereby providing a scientific basis for the development of novel therapeutic strategies and medications.

## 2 Polyphenols targeting multiple molecular targets and pathways

Polyphenols have been demonstrated to target multiple molecular pathways and modulate various cellular processes. For



**FIGURE 3**  
In vitiligo cells, various polyphenols target IFN- $\gamma$ /JAK/STAT/CXCL10 pathway, MAPK/ERK pathway, WNT pathway, Nrf2/ARE pathway, p38 MAPK pathway and many other pathways.

the treatment of vitiligo, polyphenols may aid in reducing oxidative stress, promoting melanocyte survival and regeneration, and modulating immune responses, all of which are relevant to the pathogenesis of vitiligo. Polyphenolic compounds curtail oxidative stress via diverse mechanisms. Their structure incorporates multiple phenolic hydroxyl groups (-OH) that donate hydrogen atoms or electrons, neutralizing free radicals and reducing cellular oxidative damage. Catechins in tea polyphenols, exemplified by epigallocatechin-3-gallate (EGCG), efficiently neutralize superoxide anion radicals ( $O_2^{\bullet-}$ ), hydroxyl radicals ( $\bullet OH$ ), and hydrogen peroxide ( $H_2O_2$ ) (34). Furthermore, these compounds can chelate transition metals such as  $Fe^{2+}$  and  $Cu^{2+}$ , thereby inhibiting their catalytic role in ROS-generating reactions. Flavonoid polyphenols chelate iron ions, preventing free radical generation catalyzed by iron (35). They also interact with cell membrane lipids to enhance stability and thwart lipid peroxidation, safeguarding cellular integrity. Quercetin, for example, integrates into lipid bilayers to increase fluidity and stability, reducing membrane vulnerability to free radicals (34). Polyphenols promote melanocyte survival and proliferation by enhancing melanocyte stem cell proliferation and differentiation, supporting pigmentation maintenance in skin and hair (36). They also regulate melanocyte function by modulating the expression of genes like the Microphthalmia-associated transcription factor (MITF), which is pivotal for melanocyte differentiation and survival, thereby promoting melanin production (37). In addition to these direct effects, polyphenols influence vitiligo pathophysiology by modulating key signaling pathways. Table 1 summarizes the different classes of polyphenols targeting multiple molecular targets and pathways, along with their chemical structures.

## 2.1 Flavonoids

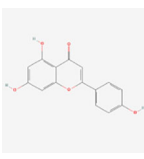
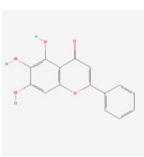
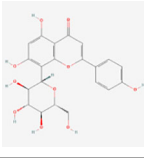
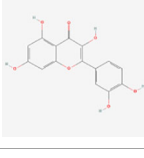
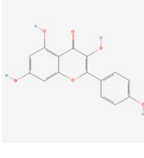
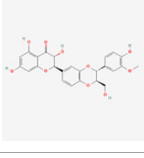
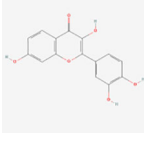
### 2.1.1 Flavones

#### 2.1.1.1 Apigenin

Apigenin (4',5,7-trihydroxyflavone) is a natural flavonoid found in a wide variety of vegetables, fruits, leaves, peas, and flowers, and is the predominant type of flavonoid in celery, parsley, and chamomile (71). Apigenin glycoside, as the glycosylated form of apigenin, have been proven to possess anticancer (72–74) and antiviral (75) properties, as well as antioxidant (76), anti-inflammatory (77), and neuroprotective (78) effects. Apigenin also contributes to the alleviation of various skin injuries, including vitiligo, UV-induced skin damage, dermatitis, wounds, skin aging, and certain types of skin cancer (79). The therapeutic effect of apigenin on vitiligo may be related to enhancing antioxidant activity, activating Nrf2 pathway, inhibiting the phosphorylation of p38, JNK and Akt, and activating  $K^+ - Cl^-$  cotransport (KCC).

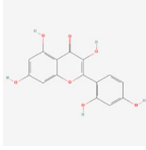
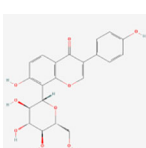
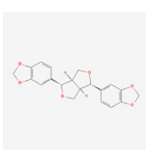
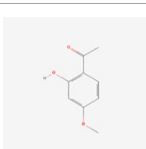
Baoxiang Zhang et al. (38) experimentally demonstrated that apigenin-treated melanocytes showed improved viability. Apigenin also increased the expression of cellular antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while reducing the production of the oxidative stress biomarker malondialdehyde. Additionally, apigenin treatment increased the expression and nuclear localization of the Nrf2 transcription factor. Further validation revealed that Nrf2 knockdown cells failed to exhibit significant apigenin-mediated effects on cell viability and oxidative stress, indicating the critical role of apigenin in Nrf2 modulation. The non-toxicity of apigenin and its positive effects on parameters associated with oxidative

TABLE 1 List of polyphenols targeting multiple molecular targets and pathways and chemical structures of polyphenols.

Classification	Compounds	Sources	Molecular targets and pathways	Effect on Melanogenesis	Refs.	Chemical structures	
Flavonoids	Flavones	Apigenin	Nrf2/ARE↑	Induction	(38)		
			p38 MAPK↓; JNK↓; Akt↓	Induction	(39)		
			K <sup>+</sup> -Cl <sup>-</sup> co-transport (KCC)	Induction	(40)		
		Baicalein	Scutellaria baicalensis, Rhizoma Coptidis, Rhizoma Cyperus, Eucalyptus	Nrf2/ARE↑	Induction	(41)	
				mitochondria-dependent caspase↓; p38 MAPK↓	Induction	(42)	
		Vitexin	Zingiber officinale, hawthorn, wood bean, mung bean, bamboo	MAPK-Nrf 2/ARE↑	Induction	(43)	
	Flavonols	Quercetin		oxidative stress↓; ROS↓	Induction	(44)	
				tyrosinase↑; TRP-2↑	Induction	(45)	
				endoplasmic reticulum dilation↓; tyrosinase↑	Induction	(46)	
		Quercetin 3-O-β-D-galactopyranose	Apples, cranberries, red onions, grapes, cherries, citrus fruits, asparagus, radishes	MITF/TYR/ TYRP1/TYRP2	Induction	(47)	
				PI3K/AKT and MAPK(p38)	Induction	(48)	
		Quercetin 3-O-(6"-O-E-caffeoyl)-β-D-glucopyranoside		MAPKs and Akt/GSK3β/β-catenin	Induction	(49)	
		Kaempferol	Vegetables, fruits, herbs	oxidativestress↓; ROS↓	Induction	(44)	
				MAPK (ERK1/2)	Induction	(50)	
				Nrf2/ARE	Induction	(51)	
	p38 MAPK/MITF			Induction	(52)		
	Silibinin	The seeds and fruits of Silybum marianum	PKA and p38 MAPK	Induction	(53)		
	Fisetin	Strawberries, apples, persimmons, grapes, onions, cucumbers	GSK3β/β-catenin	Induction	(54)		
Morin	Figs, mulberries, guavas, onions, apples	MAPK	Induction	(55)			

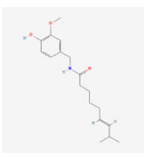
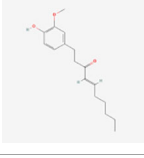
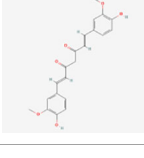
(Continued)

TABLE 1 Continued

Classification	Compounds	Sources	Molecular targets and pathways	Effect on Melanogenesis	Refs.	Chemical structures
						
Flavanols	EGCG	Green tea	IFN- $\gamma$ /JAK/STAT/ CXCL10 $\downarrow$	Induction	(56–59)	
Flavanones	Hesperetin	Citrus fruits	Wnt/ $\beta$ -catenin	Induction	(60)	
	Naringenin		Wnt/ $\beta$ -catenin	Induction	(61)	
Isoflavones	Puerarin	Pueraria mirifica	ERK1/2	Induction	(62)	
			cAMP/MITF-M	Induction	(63)	
	Icariin	Epimedium	MAPK/ERK1/2 $\uparrow$	Induction	(64)	
Lignans	Honokiol	Huperzine	SIRT3-OPA1 $\uparrow$	Induction	(65)	
	Sesamin	Flaxseed, sesame	cAMP $\uparrow$	Induction	(66)	
Phenolic acid	Paeonol	Paeonia suffruticosa, birch, juniper, jute plants	Nrf2/ARE $\uparrow$	Induction	(67)	
			cAMP $\downarrow$	Inhibition	(68)	

(Continued)

TABLE 1 Continued

Classification	Compounds	Sources	Molecular targets and pathways	Effect on Melanogenesis	Refs.	Chemical structures
Others	Capsaicin	Capsicum fruits	Smac/DIABLO, p53, NF-kB, and MAPK	Induction	(69)	
	6-Shogaol	Ginger	Nrf2/ARE	Induction	(70)	
	Curcumin	Curcuma longa	p38↓; NF-kB p65↓; p53↓; Smac/DIABLO ↓	Induction	(69)	

stress hold promise as a valuable therapeutic approach for the treatment of vitiligo. Mao Lin et al. (39) found that apigenin reduced the apoptosis of melanocytes induced by dopamine, a trigger of oxidative stress, by inhibiting the phosphorylation of p38, JNK and Akt, suggesting its potential as a drug candidate for vitiligo treatment. It was found that apigenin stimulated melanin synthesis in B16 mouse melanoma cells in a dose-dependent manner and regulates melanin production by activating KCC. This suggests that apigenin could promote melanogenesis by activating KCC, a membrane ion transporter in B16 cells, offering a potential therapeutic option for the treatment of vitiligo (40).

### 2.1.1.2 Baicalein

Baicalein (5,6,7-trihydroxy-flavone) is the predominant active constituent in *Scutellaria baicalensis*, which is also distributed in *Rhizoma Coptidis*, *Rhizoma Cyperus*, and *Eucalyptus*.

Baicalein exhibits various effects, including anticancer (80, 81), improved perfusion (82), inhibition of ferroptosis (83), activation of mitochondrial autophagy (84), antimicrobial (85), and anti-inflammatory properties (86). Baicalein also enhances skin injuries such as vitiligo, skin malignancy (87), and ultraviolet damage (88). The inhibitory effect of baicalein on vitiligo may be achieved through activation of Nrf2, inhibition of oxidative stress, downregulation of the p38 MAPK pathway, and inhibition of mitochondria-dependent cystatinase activation.

Baicalein, as observed by Jingjing Ma et al. (41), effectively suppressed H<sub>2</sub>O<sub>2</sub>-induced cytotoxicity and apoptosis in human vitiligo melanocytes (PIG3V), facilitated Nrf2 nuclear translocation, and enhanced the expression of Nrf2 along with its target gene heme oxygenase-1 (HO-1). Knockdown of Nrf2 abolished the protective effect of baicalein against H<sub>2</sub>O<sub>2</sub>-induced cell injury, apoptosis and mitochondrial dysfunction. This demonstrates that baicalein boosts the antioxidant defense mechanism of PIG3V cells by activating the Nrf2 signaling pathway, providing valuable evidence for its application in the

treatment of vitiligo. Bangmin Liu et al. (42) observed that baicalein exerted a notable protective effect against H<sub>2</sub>O<sub>2</sub>-induced apoptosis in human melanocytes by inhibiting mitochondria-dependent cystatinase activation and p38 MAPK pathway. Meanwhile, baicalein was able to reduce Bax/Bcl-2 ratio, cytochrome c release, cystatin-3 activation and p38 MAPK phosphorylation. These findings suggest that baicalein holds promise for treating vitiligo and can shield melanocytes from oxidative stress-induced damage via antioxidant and apoptosis inhibition pathways.

### 2.1.1.3 Vitexin

Vitexin (apigenin-8-C-glucoside), a C-glycosylated natural flavonoid compound, is commonly present in plants including *Zingiber officinale*, hawthorn, wood bean, mung bean, and bamboo (89). Vitexin exhibits antioxidant (90, 91), diabetes-inhibiting (92), antibacterial (93), neuroprotective (94, 95), anti-inflammatory (96), and hepatoprotective (97) properties.

Xiao-Sha Li et al. experimentally demonstrated that vitexin inhibited H<sub>2</sub>O<sub>2</sub>-induced apoptosis of melanocytes, promoted cell proliferation, decreased intracellular reactive oxygen species levels, and suppressed the expression of inflammatory factors IL-1β and IL-17A. Additionally, oysterin activated the MAPK-Nrf2/ARE signaling pathway and induced the expression of antioxidant genes, including HO-1 and SOD. Knockdown of the Nrf2 gene reversed the protective effects of oysterin, resulting in increased expression of IL-1β, IL-17A, and ROS, and decreased expression of HO-1 and SOD. Thus, ouabain protects melanocytes from oxidative stress by activating the MAPK-Nrf2/ARE signaling pathway, providing a potential strategy for the treatment of vitiligo (43).

## 2.1.2 Flavonols

### 2.1.2.1 Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonol compound present in plants with potent oxidizing properties and

various biological activities (98). It is abundant in various foods including apples, cranberries, red onions, grapes, cherries, citrus fruits, asparagus, and radishes (99, 100). Quercetin has been proved to have a variety of biological activities, such as antioxidant, anti-inflammatory, anti-apoptotic, anticancer, and immunomodulatory effects (101–103).

Ziqian Xu et al. (44) observed that quercetin decreased H<sub>2</sub>O<sub>2</sub>-induced apoptosis in PIG1 cells and concurrently lowered ROS levels induced by H<sub>2</sub>O<sub>2</sub>, indicating its potential in protecting melanocytes from oxidative stress. It has been demonstrated that H<sub>2</sub>O<sub>2</sub> induces expansion of the endoplasmic reticulum in melanocytes, inhibiting tyrosinase (TYR) output, whereas quercetin markedly mitigates these effects (46). Yun-Mi Jeong et al. (104) found that quercetin and green tea extract exhibited strong cytoprotective effects on H<sub>2</sub>O<sub>2</sub>-treated melanocytes, and various combinations of quercetin, green tea extract, and folic acid synergistically prevented cellular damage. This indicates the potential value of antioxidant combinations in vitiligo treatment and introduces a novel approach for its management. Susumu Takekoshi et al. (45) reported that quercetin promoted melanin production in the buccal follicular tissue of C3H/HeN-Jel mice by stimulating the synthesis of TYR proteins and TRP-2 proteins. With the increase of quercetin concentration, the production of melanin and the expression level of TYR protein also increased correspondingly. This suggests the potential of quercetin in treating vitiligo, though further validation through additional studies is warranted. Changhai Liu et al. (49) found that quercetin 3-O-(6'-O-E-caffeoyl)-β-D-glucopyranoside promoted melanogenesis in B16 cells. By activating the expression of MITF, TYR, tyrosinase-related protein-1 (TRP-1) and 2 (TRP-2) via the MAPKs and Akt/glycogen synthase kinase 3-beta (GSK3β)/β-catenin signaling pathway, it plays a regulatory role in melanogenesis. Experimental findings indicate that quercetin 3-O-β-d-galactopyranoside significantly elevates protein levels of TYR, MITF, tyrosinase-associated protein 1 (TYRP 1), and tyrosinase-associated protein 2 (TYRP 2). Knockdown of MITF attenuates the effect of quercetin 3-O-β-d-galactopyranoside on melanin content, suggesting its involvement in stimulating melanogenesis through the MITF/TYR/TYRP1/TYRP2 signaling pathway. In addition, quercetin 3-O-β-d-galactopyranoside can stimulate melanogenesis and melanocyte migration, and increase melanin content by inducing the expression of MITF and its downstream target genes in human primary melanocytes. Quercetin 3-O-β-d-galactopyranoside has potential efficacy in treating vitiligo (47). Quercetin 3-O-β-d-galactopyranoside has the ability to protect human melanocytes from oxidative damage, possibly through activation of AKT, inhibition of p38 phosphorylation, and suppression of mitochondrial apoptotic signaling, which offering a novel avenue for the treatment vitiligo (48).

### 2.1.2.2 Kaempferol

Kaempferol is a natural flavonoid present in various vegetables, fruits, and herbs, exhibiting diverse pharmacological activities such as anti-inflammatory, antioxidant, antimicrobial, anticancer, anti-apoptotic, and neuroprotective effects (105, 106).

Ziqian Xu et al. (44) observed that kaempferol reduced H<sub>2</sub>O<sub>2</sub>-induced apoptosis in PIG1 cells while concurrently decreasing ROS

levels induced by H<sub>2</sub>O<sub>2</sub>. This suggests that kaempferol is able to reduce ROS in melanocytes, thereby protecting them from oxidative stress. Yihui Xie et al. (50) found that kaempferol promoted melanin synthesis in PIG1 cells by enhancing ERK1/2 phosphorylation and reduced apoptosis by inhibiting H<sub>2</sub>O<sub>2</sub>-induced ROS generation through up-regulation of HO-1 expression, as well as preventing H<sub>2</sub>O<sub>2</sub>-induced melanin reduction. Eunsun Jung et al. found that afzelin (kaempferol-3-O-alpha-L-rhamnoside) may inhibit GSK3β by activating the Nrf2/ARE signaling pathway, potentially serving as a therapeutic agent for mitigating oxidative stress-induced dermatoses (51). Research revealed afzelin upregulated the expression of MITF gene by activating the p38 MAPK pathway, subsequently promoting melanogenesis in human epidermal melanocytes (52).

### 2.1.2.3 Silibinin

Silibinin is the main bioactive flavone extracted from the seeds and fruits of *Silybum marianum* (107), exhibits various biological effects such as antioxidant, anti-inflammatory, anticancer, and hepatoprotective properties (108–111).

Takuhiro Uto et al. found that silibinin significantly increased the melanin content in mouse B16-F1 and human HMV-II melanoma cells. Silibinin activated intracellular TYR activity and upregulated the expression of TYR, TRP-1, TRP-2, and MITF. Additionally, silibinin enhanced the phosphorylation of cyclic AMP response element binding protein (CREB), PKA and p38 MAPK. This proves that silibinin effectively stimulates melanogenesis by increasing the protein expression of melanogenesis enzymes via PKA and p38 pathways, leading to the phosphorylation of CREB and expression of MITF (53).

### 2.1.2.4 Fisetin

Fisetin (3,3',4',7-tetrahydroxyflavone) is a naturally occurring flavonol widely distributed in fruits, vegetables and nuts, such as strawberries, apples, persimmons, grapes, onions, cucumbers and so on. It has pharmacological effects such as antioxidant, anti-inflammatory, anti-apoptosis and anticancer properties (112–116).

Menu Molagoda et al. (54) found that fisetin promoted melanogenesis by inhibiting GSK3β, activating the β-catenin signaling pathway, and upregulating MITF, TRP-1 and TRP-2. In addition, in zebrafish larval experiments, fisetin potentially promoted melanogenesis through the Wnt/β-catenin signaling pathway. These findings suggest that fisetin may be a potential herbal extract for treating vitiligo.

### 2.1.2.5 Morin

Morin, as a dietary flavonol, widely exists in fruits and vegetables consumed daily, such as figs, mulberries, guavas, onions, apples and so on. Morin has been shown to have antioxidant, anti-inflammatory, anti-apoptotic, anticarcinogenic, and neuroprotective properties (117–121).

SeoYeon Shin et al. found that morin promotes melanogenesis by activating the ERK and p38 signaling pathways and upregulating MITF, TRP-1 and TRP-2 in B38-F16 mouse melanoma cells (55).



## 2.1.3 Flavanols

### 2.1.3.1 Epigallocatechin-3-gallate

EGCG is an important component of Catechins, which has been proved to possess anticancer (122), antiviral and antioxidant effects (123).

EGCG can regulate autoimmunity by reducing the number of leukocytes and CD8<sup>+</sup> T cells, inhibiting the adhesion of T lymphocytes to melanocytes, suppressing inflammatory responses by downregulating TNF- $\alpha$ , IFN- $\gamma$ , and IL-6, while simultaneously inhibiting the expression of CXCL3, CXCL5, C-FOS, CXCR4, S100B, Rab27A, TGF-Br2 genes and upregulating the expression of PI3k and EGFR genes. This process plays a role in delaying the development of vitiligo and promoting the formation of melanocytes in lesion tissues (56–58). The IFN- $\gamma$ /JAK/STAT/CXCL10 pathway has been proved to be related to the occurrence and development of vitiligo, and the role of EGCG in modulating immunity and downregulating inflammatory factors may be accomplished by intervening IFN- $\gamma$ /JAK/STAT/CXCL10 pathway. Weixuan Ning et al. found that EGCG directly inhibited the phosphorylation of JAK2, STAT1, and STAT3 in IFN- $\gamma$ -induced human melanocytes. Additionally, the intervention of EGCG decreased the expression of CXCL10 in human melanocytes induced by IFN- $\gamma$  and the protein levels of receptors such as CD11a, CXCR3, and CCR2 in T cells, ultimately inhibiting the adhesion of T cells to human melanocytes induced by IFN- $\gamma$  (59). Meanwhile, downregulation of the IFN- $\gamma$ /JAK/STAT/CXCL10 pathway also reduced the production of inflammatory factors such as IFN- $\gamma$ .

Per-acetylated epigallocatechin-3-gallate (AcEGCG), a fully acetylated derivative of EGCG, is considered effective in protecting melanocytes from oxidative damage. Wenting Hu et al. reported that topical application of 0.5% AcEGCG cream twice daily on two patients with vitiligo resulted in controlled skin repigmentation and halted progression of pigment loss by the sixth and eighth weeks, respectively (124). In another randomized controlled trial, Wenting Hu et al. compared a group using topical EGCG to a control group treated with pimecrolimus, ultimately finding both agents effective in pigment repigmentation, with no statistically significant difference in the Vitiligo Area Scoring Index between lesions treated by the two drugs. Additionally, no severe side effects of EGCG were observed during the study (125).

## 2.1.4 Flavanones

### 2.1.4.1 Naringenin and hesperetin

Both naringenin and hesperidin are citrus flavanones known for their diverse biological activities, including antioxidant, anti-inflammatory, anti-mutagenic, and anticancer properties (61, 126–129).

Yu-Chun Huang et al. (61) found that naringenin enhanced melanin synthesis and TYR activity in B16-F10 cells by promoting the expression of TYR, MITF, and  $\beta$ -catenin, and enhancing the phosphorylation of Akt or GSK3 $\beta$ . This suggests that naringenin induces melanogenesis signaling through activation of the PI3K/Akt or Wnt/ $\beta$ -catenin pathways. It was found that hesperidin increased the phosphorylation of GSK3 $\beta$  by activating CREB and

MAPK in the Wnt/ $\beta$ -catenin pathway, consequently enhancing melanogenesis (60).

## 2.1.5 Isoflavones

### 2.1.5.1 Puerarin

Puerarin, a major isoflavonoid extracted from *Pueraria mirifica*, exhibits pharmacological effects including antioxidant, anti-inflammatory, anticancer, neuroprotective, and analgesic properties (130–134).

Xiaoxia Ding et al. found that Puerarin promoted melanogenesis by inhibiting the phosphorylation and activation of the ERK1/2 signaling pathway and upregulating MITF, TRP-1 and TRP-2. Puerarin also exhibits antioxidative stress effect, which can increase the level of cAMP in cells and further promote the synthesis of melanin (62). It was found that puerarin effectively prevented vitiligo by activating the cAMP/MITF-M signaling pathway and up-regulating the expression of cAMP, MITF and its downstream pathways TYR, TRP-2 and Bcl-2, thereby stimulating melanin synthesis and increasing melanocyte survival (63).

### 2.1.5.2 Icariin

Icariin, the primary active compound in traditional Chinese medicine *Epimedium*, exhibits a wide array of beneficial effects, including neuroprotection, anti-osteoporosis, anti-inflammatory, and antioxidative stress properties (135–140). Additionally, icariin shows promise in alleviating vitiligo.

Chen Hong et al. found that *Epimedium* extract, including icariin, could promote TYR activity, upregulate the protein expression of TYR family, thereby facilitating melanin biosynthesis via activation of the MAPK/ERK1/2 signaling pathway. In addition, *Epimedium* extract EFE effectively increased the number of melanosomes, accelerated melanosome maturation, and induced the transfer of melanosomes from melanocytes to keratinocytes for pigmentation via cytoplasmic transport facilitated by the growth/extension of melanocyte dendrites (64). Yan Ye et al. observed that icariin showed potent melanogenic activity, albeit without impacting the expression of regulatory factors in melanin synthesis pathways, such as TRP-1 and TRP-2. It only marginally increased the expression of TYR (140), necessitating further investigation into its specific mechanism.

## 2.2 Lignans

### 2.2.1 Honokiol

Honokiol, as a compound with anti-inflammatory (141), anticancer (142, 143), anti-depressant (144), neuroprotective (145) properties, mainly exists in the phytomedicinal herb *Huperzine*. Its potential in dermatological therapy has been identified (146).

Xiuli Yi et al. (65) experimentally found that oxidative stress impairs the expression and activity of mitochondrial deacetylase sirtuin 3 (SIRT3) in vitiligo melanocytes. SIRT3 deficiency promotes melanocyte apoptosis induced by oxidative stress via the SIRT3/OPA1 pathway. Honokiol significantly increased the expression of

SIRT3 at mRNA and protein level, and decreased the acetylation of SOD2. This indicates that honokiol can prevent the apoptosis of vitiligo melanocytes under oxidative stress by activating the SIRT3/OPA1 pathway, offering a novel potential avenue for the treatment of vitiligo.

### 2.2.2 Sesamin

Sesamin, a natural compound present in sesame oil and classified as a lignan, was initially isolated from flaxseed and subsequently extracted from sesame. It has gained considerable interest due to its antioxidant properties and its role in regulating blood lipid levels (147), hypertension (148), and blood glucose levels (149), among other pharmacological effects.

Zejun Jiang et al. (66) found that sesamin increased the melanin content and TYR activity in B16 melanoma cells in a dose-dependent manner. Furthermore, sesamin treatment enhanced the mRNA and protein levels of TYR. Western blot analysis showed that sesamin induced and consistently upregulated MITF. Moreover, sesamin activated CREB and PKA through a cAMP-dependent pathway. These findings demonstrate that sesamin stimulates melanogenesis in B16 cells by activating cAMP signaling and upregulating MITF and TYR.

## 2.3 Phenolic acid

### 2.3.1 Paeonol

Paeonol, a natural compound present in the root bark of peony (*Paeonia suffruticosa*) and other plants, is primarily extracted from peony roots, notably in traditional Chinese medicine. Additionally, paeonol can be found in several other plant species, including certain birch, juniper, and jute plants. Studies have demonstrated that paeonol exhibits antioxidant, anti-inflammatory, antimicrobial, and antitumor activities.

Shanshan Guo et al. (67) found that salvinorin protected melanocytes from oxidative stress by activating Nrf2. They experimentally found that the intervention of paeonol can increase the cell vitality and melanogenesis of PIG1 cells treated with H<sub>2</sub>O<sub>2</sub>, and it can also relieve oxidative stress by restoring the activities of SOD, CAT and GPx. However, after knockdown of Nrf2 using siRNA, the protective effect of paeonol on antioxidant damage of PIG1 cells was eliminated. This proves that paeonol may protect melanocytes from oxidative stress by activating Nrf2, which in turn plays a role in treating vitiligo.

Interestingly, it has also been reported that paeonol can downregulate the production of melanin by reducing the phosphorylation of cAMP response element binding protein (phospho-CREB), downregulating the expression of MITF and reducing the mRNA and protein levels of TYR (150). Paeonol also inhibited melanin transfer and PAR-2 activating peptide SLIGRL-induced melanin transfer during co-culture of melanocytes and keratinocytes (68). These findings suggest that not only does paeonol fail to benefit vitiligo patients, but it may also exacerbate their symptoms. Thus, further research is necessary to elucidate the effect of paeonol on vitiligo.

## 2.4 Others

### 2.4.1 Capsaicin

Capsaicin, a unique alkaloid primarily found in *Capsicum* fruits (151), has been extensively investigated for its antioxidant, anti-inflammatory, analgesic, and anticancer properties (152–155).

Matteo Becatti et al. found that capsaicin prevented apoptosis and mitochondrial damage by regulating signaling pathways in keratinocytes of vitiligo patients, including inhibiting the activation of Smac/DIABLO and NF- $\kappa$ B, inhibiting p38 phosphorylation and increasing ERK activity, thus improving cellular antioxidant capacity. Therefore, capsaicin shows promise in mitigating the damage of keratinocytes in vitiligo skin and halting the progression of vitiligo (69).

### 2.4.2 6-Shogaol

6-Shogaol (6-SG) is an active compound extracted from ginger with a variety of antioxidant, anti-inflammatory, anticancer, anti-angiogenic, and neuroprotective effects (156–160).

Lingli Yang et al. (70) found that 6-Shogaol(6-SG) reduced the damage of oxidative stress to human epidermal melanocytes by activating the Nrf2/ARE pathway. In addition, 6-SG upregulated the expression of antioxidant enzymes HO-1 and quinone oxidoreductase-1, further enhancing their antioxidant effects. Therefore, 6-SG is expected to be used to prevent melanocyte loss in vitiligo.

### 2.4.3 Curcumin

Curcumin ((E,E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), the primary active compound in the dietary spice *Curcuma longa*, has been utilized in Indian and traditional Chinese medicine to treat various ailments. These include pain disorders, digestive issues, menstrual challenges, skin ailments, sprains, wounds, and liver disorders (161). Due to its antioxidant properties, curcumin can potentially serve as a food preservative (162). Laboratory studies have confirmed curcumin's antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer properties (163–165). Recent case reports indicate that oral administration of turmeric powder (abundant in curcumin) combined with honey promotes melanin deposition and reverses vitiligo (166).

Matteo Becatti et al. (69) found that curcumin inhibited melanocyte apoptosis by increasing phosphorylation of ERK, increasing total antioxidant capacity, inhibiting intracellular ROS production and lipid peroxidation, and increasing mitochondrial activity. Matteo Becatti et al. initially observed elevated levels of activated p38, NF- $\kappa$ B p65 subunit, p53 and Smac/DIABLO, and low levels of phosphorylation of ERK in keratinocytes around vitiligo lesions. In contrast, intervention with curcumin significantly reduced mitochondrial superoxide production and restored mitochondrial membrane polarization compared to untreated controls. Meanwhile, curcumin decreased the expression of p38, NF- $\kappa$ B p65 subunit, p53 and Smac/DIABLO, increased the phosphorylation of keratinocytes around the lesion, and significantly inhibited the apoptosis of melanocytes. However, it is

worth noting that curcumin has been shown to cause oxidative stress in Asian patients with acute vitiligo (167). Therefore, whether curcumin can benefit vitiligo patients still needs further clinical studies.

### 3 Conclusion and future perspectives

Vitiligo, a global autoimmune skin disorder, has a complex etiology involving factors such as autoimmunity, melanocyte dysfunction, and interactions between genetic and environmental elements. This condition not only raises significant aesthetic concerns but also carries potential psychological and social implications for the affected individuals. Therefore, continuous improvement in understanding and treating vitiligo is essential for enhancing the quality of life of patients.

Recent advancements have spotlighted the potential role of natural compounds, particularly polyphenols, in vitiligo management, owing to their unique antioxidative, anti-inflammatory, and immunomodulatory properties. These compounds are theorized to exert beneficial effects by modulating melanogenesis pathways, alleviating oxidative stress, and regulating immune responses, thus offering a complementary approach to conventional therapies. For example, the combination of curcumin cream with targeted narrow-spectrum UVB phototherapy showed slightly greater effectiveness compared to targeted narrow-spectrum UVB alone. However, there was no significant difference in the improvement of hyperpigmentation between the two groups, likely due to the small sample size (161).

Currently, research on the clinical efficacy of polyphenols in treating vitiligo remains relatively scarce, possibly due to the inherent low bioavailability of polyphenolic compounds, which is primarily determined by their chemical properties. Polyphenols are readily absorbed through the intestinal tract, but they are rapidly metabolized in the body and easily cleared by the liver, resulting in typically low plasma concentrations. Additionally, polyphenols are unstable within the body, prone to degradation in the intestinal environment, which further reduces their bioavailability. These factors limit the effective concentration of polyphenols in the body, thus affecting the efficacy and reliability of their clinical application (168). However, recent studies have demonstrated that enhancing the bioavailability of polyphenols can unlock significant potential in treating diseases like vitiligo. Various strategies to enhance the bioavailability of polyphenols have been discovered. For example, nanotechnology, which involves encapsulating polyphenols in nanocarriers to protect them from degradation in the gastrointestinal tract and enhance their absorption rates. Research indicates that nanotechnology can significantly increase their concentration and stability in the body, thereby enhancing their biological activity (169). Composite formulations can also enhance the bioavailability of polyphenols by combining them with absorption-enhancing substances such as lipids, proteins, or other enhancers. These formulations help increase their solubility and stability, thus enhancing their bioavailability. Moreover, modifying the administration route of polyphenols can increase their bioavailability. Studies have found

that administering polyphenols via the skin can directly affect the skin of vitiligo patients and might be more effective than oral administration in utilizing the local therapeutic effects of polyphenols (170). With the improvement in the bioavailability of polyphenols, the potential and breadth of their clinical research are also increasing. In the future, we can anticipate more clinical trials targeting specific diseases with polyphenols, where their antioxidant and anti-inflammatory properties may be further utilized.

Despite the promising applications of polyphenolic compounds in the treatment of vitiligo, current research still has some shortcomings and problems. Due to the diversity and complexity of the structure and properties of polyphenolic compounds, the study of their pharmacological and toxicological mechanisms is more challenging. Currently, we have limited understanding of the mechanism of action of polyphenolic compounds in hypomelanosis treatment, and more in-depth studies are needed to reveal their precise molecular mechanisms. Meanwhile, the lack of systematic pharmacokinetic and pharmacodynamic studies prevents us from accurately assessing the metabolic mechanisms of polyphenolic compounds *in vivo*. Additionally, the lack of standardized methods for extracting and purifying polyphenolic compounds results in their purity and stability not being guaranteed. Moreover, the bioavailability and tissue distribution properties of polyphenolic compounds have not been clarified, which limits their use in hypomelanosis treatment. Given the safety and toxic side effects of polyphenolic compounds, their clinical efficacy needs to be verified by more large-scale clinical trials to ensure their effectiveness and safety in clinical applications. Furthermore, the mechanism of interaction between polyphenolic compounds and existing treatments is not fully understood, and further studies are needed to determine rational combination regimens.

In response to these limitations, future research should aim to address the following questions. 1) Integrative therapy and molecular mechanisms: Future research should explore the synergistic effects of combining polyphenolic compounds with established pharmacological agents, such as corticosteroids, to enhance treatment efficacy for vitiligo. This includes identifying specific polyphenols like Apigenin, Baicalein, Kaempferol, and Paeonol that may have the most promising anti-inflammatory and hypomelanotic properties, and understanding their complex molecular interactions to develop more targeted therapies. 2) Chemical structure and drug development: There is a need for a deeper understanding of how the chemical structure of polyphenolic compounds influences their biological activity. This research should aim to discover compounds with improved potency, reduced side effects, and better targeting capabilities, ensuring both the efficacy and safety of these agents in treating vitiligo. 3) Formulation science and drug delivery: The development of effective drug delivery systems is essential to enhance the bioavailability of polyphenolic compounds. This includes innovations in production, quality control, and formulation science, as well as the application of advanced technologies such as nanotechnology to protect and enhance the absorption of these compounds, thereby improving their therapeutic potential. 4) Clinical evaluation and holistic management: Future research must include comprehensive clinical evaluations to assess the efficacy and safety of polyphenolic treatments in vitiligo, including large-scale trials to determine optimal dosages, administration routes,

and potential drug interactions. Furthermore, given the psychological and social impact of vitiligo, therapeutic strategies should be developed to address both the physical and mental health aspects of the condition, ensuring a holistic approach to patient care.

In summary, this review aimed at summarizing the mechanisms of natural polyphenols in the treatment of vitiligo. A clear conclusion is that these compounds have a positive effect on the treatment of vitiligo, mainly due to their antioxidative properties, immunomodulation, promotion of melanin production, and reduction of cellular apoptosis. It is crucial to further investigate the precise molecular mechanisms of these compounds in the treatment of vitiligo and explore the potential of combining them with existing therapies to enhance efficacy. We hope that this review will offer new insights for future research on utilizing natural polyphenols to target multiple pathways and targets in combating vitiligo.

## Author contributions

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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