Advances in the function of traditional medicine for vitiligo treatment

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Author contributions
Li HY and Yuan ST provided the ideas; Li HY edited the original draft; Liu J wrote the initial draft; Xu JJ, Cheng W, and Zhang W provided data; Li JY and Li LG revised the manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
cAMP, cyclic adenosine monophosphate; MITF, microphthalmia-associated transcription factor; CREB, cAMP response element; ROS, reactive oxygen species; Trm, resident memory T cells; CXCL12, CXCL chemokine ligand 12; CXCL10, CXCL chemokine ligand 10; KZE, Kaliziri extract; ISL, Isoliquiritigenin; EGCG, epigallocatechin gallate; COME, C. officinalis methanol extract; KZE, Kaliziri extract; IFN-γ, generate interferon-γ.

Citation

Abstract
Vitiligo has a significant impact on a substantial number of individuals worldwide. Traditional Chinese medicine has a long history of serving as a therapeutic treatment for vitiligo. Nevertheless, given the increasing volume of research on the utilization of traditional Chinese medicine for vitiligo treatment, it is imperative to conduct a comprehensive review that elucidates the efficacy of Chinese traditional medicine and other active ingredients in the treatment of vitiligo. This paper presents a comprehensive overview of the clinical preparations used to treat vitiligo, while also highlighting the potential monomers and extracts derived from traditional Chinese medicine for vitiligo treatment. A thorough analysis of the pharmacological effects of traditional Chinese medicine on vitiligo treatment will provide valuable insights and reliable information for the development of new treatment strategies.

Keywords: vitiligo; traditional Chinese medicine; melanogenesis
Vitiligo, a common skin disease, is characterized by piecemeal skin depigmentation that can occur on any part of the body. It is estimated that vitiligo affects approximately 1.3% of the adult population [1]. The presence of vitiligo exerts a detrimental impact on the overall well-being of individuals, manifesting in diminished self-esteem and considerable psychological anguish. Consequently, the decline in quality of life parallels the challenges experienced by individuals with burdensome skin ailments like psoriasis and eczema [2].

Traditional Chinese medicine has a wide range of sources and low cost, on the other hand, at present, the small molecule compounds used in the treatment of vitiligo have unstable efficacy and are prone to recurrence after discontinuation of the drug. Therefore, a summary of monomers or extracts from traditional Chinese medicine that may treat vitiligo can help in the development of new drugs to treat vitiligo, which are positive implications for the field.

The Role of traditional Chinese medicine preparations in vitiligo

According to the theory of traditional Chinese medicine, vitiligo is commonly associated with inadequate function of the liver and kidney. It is believed that liver and kidney deficiencies result in the liver's inability to store and circulate blood, while also causing a deficiency in kidney essence (a syndrome in traditional Chinese medicine. Generally manifested as deafness, hair loss, dizziness, retardation). As a result, the mutual production of blood is disrupted, leading to inadequate nourishment of the skin and the formation of white patches. Therefore, in traditional Chinese medicine, replenishing the liver and kidney (a common traditional Chinese medicine treatment, which means to provide energy to the liver and kidneys), promoting blood circulation, and dispelling wind (traditional Chinese medicine believe that wind plays an important role in the occurrence and development of many illness, and dispelling wind means to eliminate the triggers of diseases) are vital components of the treatment process for vitiligo. Traditional Chinese medicine preparations with the effect on melanogenesis were shown in Table 1. In addition, Table 2 showed that the efficacy of traditional Chinese medicine preparations for vitiligo treatment.

Oral traditional Chinese medicine preparations

Bailing tablet. Bailing tablet (Z44022280), a traditional Chinese medicine preparation, is believed to possess properties that promote blood circulation, resolve blood stasis (according to the theory of traditional Chinese Medicine, “abnormal flow of the blood is blood stasis”, so resolve blood stasis means addressing this phenomenon of abnormal blood flow), and dispel wind according to Chinese medicine principles. Through network pharmacology and molecular docking, Jinming Li et al. found that the main compound of bailing tablet contains quercetin, baicalin, luteolin, kaempferol, arachidonic acid, calycosin, formononetin, prangendin, phellipterin, and 7-o-methylisoxylitol and reported that the mechanism of bailing tablets in the treatment of vitiligo is multicomponent, multtarget, and multichannel, of which bailing tablet might regulate the main signaling pathways of melanogenesis, such as MAPK, PI3K, and AKT pathways [3]. Additionally, another study by Wu Guochun demonstrated that combining bailing tablets with compound Shouwu Tribulus decoction treatment was more effective than compound Shouwu Tribulus decoction treatment alone, implying that bailing tablets may enhance the efficacy of compound Shouwu Tribulus decoction [4].

Vitiligo capsule. Vitiligo capsules (Z20053739) contain key ingredients such as psoralen, astragalus, saffron, and puncturevine. These capsules are known to have the ability to activate tyrosinase activity and enhance melanocyte production. Notably, Jiang Ping et al. found that on the basis of local irradiation of narrowband ultraviolet-B and topical application of captopril ointment, the therapeutic effect of the treatment group with the addition of vitiligo capsules was more obvious [5].

Total glucosides of paony capsule (H20055058). The main active ingredient of the capsule is paeoniflorin, which is extracted from the dried root of Paeonia lactiflora, and can regulate immune response, suppress autoimmune response in multiple ways, and have anti-inflammatory effects. Previous studies have shown that Paeonia lactiflora capsules can regulate the CD4+ T lymphocyte/CD8+ T lymphocyte ratio in the peripheral blood of vitiligo patients. Besides, total glucosides of paony capsule can combine with narrowband ultraviolet-B or 308 nm excimer laser for vitiligo treatment [6].

Topical traditional Chinese medicinal preparations

Compound kaliziran tincture (Z65020003). Vernonia anthelmintica Willd. is the main component ingredient of the compound kalikrein tincture, which is one of the most commonly Uyghur medicine for the treatment of vitiligo. Ainur Abduresim et al. evaluated the clinical efficacy of the compound kalikrein tincture in the treatment of stable vitiligo and found that among 100 patients with stable vitiligo, 28.0% were cured, 52.0% were effective, and 18.0% were improved, which can initially confirm the effect on vitiligo treatment [7]. Moreover, Xiaoyan Chen et al. found that treating vitiligo with compound Kaliziran Tincture combined with compound Shouwu Tribulus soup can increase the level of tyrosinase and pigmentation. Narrow white spot area. The total effective rate of the combination group was 85.96%, which was much higher than the control group [8].

Compound psoralen tincture. Psoraleae fructus is the main component ingredient of the compound psoralene tincture. Modern pharmacological research revealed that the main components of psoralen include psoralen, iso-psoralen, and psoralen. Psoralen mainly acts on tyrosinase enzyme to promote hydroxylfation of tyrosine, which further stimulates o-phenol 3,4-di-hydroxyphenylalanine formation and subsequent oxidation to form melanin. Moreover, topical psoralen plus UVA therapy was already recognized as an effective therapy at the end of the last century [9, 10]. A previous study showed that fire needle combined with compound psoralene tincture can narrow white spot area and improve the pigment scores [11].

The role of Chinese traditional medicine monomer and extract in vitiligo

It is widely acknowledged that the efficacy of Chinese traditional medicine in treating diseases is attributed to its active ingredients. Many active ingredients found in Chinese medicines have been shown
Table 1 Traditional Chinese Medicine preparations with the effect on vitiligo

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Classification</th>
<th>Ingredients</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailing tablet</td>
<td>Oral preparation</td>
<td>Angelica sinensis (Oliv.) Diels, Radix Astragali, Panax pseudo-ginseng Wall. var. notoginseng (Burkill) Hoo &amp; Tseng, Cortex Moutan, Portulaca oleracea Linn.</td>
<td>Upregulate PI3K/Akt pathway, enhance photosensitivity</td>
<td>[3]</td>
</tr>
<tr>
<td>Compound kali ziran tincture</td>
<td>Topical preparation</td>
<td>Vernonia anthelmintica (Linn.) Willd., Psoralea corylifolia Linn., Fallopia multiflora (Thunb.) Harald., Angelica sinensis (Oliv.) Diels, Sinapis alba Linnaeus</td>
<td></td>
<td>[7]</td>
</tr>
<tr>
<td>Compound Psoralen Tincture</td>
<td>Topical preparation</td>
<td>Psoralea corylifolia Linn., Cascusta chinensis Lam., Gardenia jasminoides Ellis</td>
<td>enhance photosensitivity</td>
<td>[8, 9]</td>
</tr>
</tbody>
</table>

Table 2 The efficacy of Traditional Chinese Medicine preparations for vitiligo treatment

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Ways of treatment</th>
<th>Efficacy of treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailing tablet</td>
<td>combine with compound Shouwu Tribulus soup</td>
<td>73.5%</td>
<td>[4]</td>
</tr>
<tr>
<td>Vitiligo capsule</td>
<td>combine with local irradiation of NB-UVB and topical application of captopanol ointment</td>
<td>82.61%</td>
<td>[5]</td>
</tr>
<tr>
<td>Total Glucosides of Paeony Capsule</td>
<td>combine with NB-UVB or 308 nm excimer laser</td>
<td>84.83%</td>
<td>[6]</td>
</tr>
<tr>
<td>Compound kali ziran tincture</td>
<td>combine with compound Shouwu Tribulus soup</td>
<td>85.96%</td>
<td>[8]</td>
</tr>
<tr>
<td>Compound Psoralen Tincture</td>
<td>Combine with fire needle</td>
<td>86.7%</td>
<td>[11]</td>
</tr>
</tbody>
</table>

The color of skin, hair and eyes in determined by melanin which is a complex pigment. Therefore, increasing the content of melanin in vitiligo lesions is a good treatment to ameliorate vitiligo. The skin pigmentation involves melanocytes and keratinocytes. First of all, melanin is produced by specialist skin cells within the epidermis called melanocytes. Melanocytes are the places where melanosomes become mature. The process of melanosome mature can be divided into four stages. Specifically, both stage I and II melanosomes lack pigment, but stage II melanosomes deposit PMEL fibrils on which melanogenesis takes place. And then the fibrils with melanin get thicker and blacker with melanosomes come to stage III. It is come to stage IV when the intercellular structure in melanosomes is masked [20-22]. Melanocytes are branched cells with finger like projections. As the melanosomes mature, the stage IV melanosomes in epidermal melanocytes migrate to the tips of the projections and are transferred into the surrounding keratinocytes. The regulation of melanogenesis and skin pigmentation is shown in Figure 1. The primary cause of depigmentation in vitiligo is the loss of melanocytes from the skin. Considering the pathogenesis of vitiligo, the key point of vitiligo treatment is ameliorating melanin loss. The melanin loss results from the reduced ability of melanocytes to produce melanin and the decrease in the number of melanocytes. As a result, the treatment of vitiligo involves two main strategies: (1) promoting melanogenesis (2) protecting melanocytes. On the one hand, promoting melanogenesis is a wise way to increase melanin content and improve the ability of melanocytes to produce melanin. On the other hand, antioxidant and anti-autoimmune can protect melanocytes from death and increase the number of melanocytes.

Acacetin. Acacetin, a di-hydroxy and mono-methoxy flavone, is

therapeutic effects for vitiligo through various mechanisms, including regulation of melanin production, antioxidant properties, and immunomodulation. Table 3 shows these active ingredients from plants that may play an important role in the treatment of vitiligo.

Monomer and extract with effects of promoting melanogenesis

Melanogenesis is the process by which melanin, a pigment responsible for skin, hair, and eye color, is synthesized. One key regulator of melanogenesis is melanocyte-stimulating hormone, which acts as an agonist of melanocortin receptors. Melanocyte-stimulating hormone activates adeny late cyclase, resulting in an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. This in turn activates PKA [12]. PKA then phosphorylates CAMP response element (CREB), which serves as a transcription factor in the microphthalmia-associated transcription factor (MITF) [13]. Next, increased CAMP levels further upregulate the expression of CREB, which binds to the CRE domain in the MITF gene promoter and initiates the expression of MITF. Of particular importance is the upregulation of tyrosinase expression by MITF, which promotes melanin synthesis [14, 15]. Previous studies have shown that many signaling pathways are involved in the regulation of melanogenesis, such as the Wnt signaling pathway, and the CAMP signaling pathway [16]. Another pathway that has been found to participate in melanogenesis is mitogen-activated protein kinase (MAPK) pathway [17]. The MAPK family consists of several members, including ERK, JNK, and p38 MAPK. These members can be activated in response to various external stimuli, such as UV radiation. Besides, reactive oxygen species (ROS), acting in the pathways of ERK and JNK activation, also leads to the regulation of melanogenesis [18, 19].

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Table 3 The effects of active ingredients from plants

<table>
<thead>
<tr>
<th>Monomers/Exra</th>
<th>Plants</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoting melanogenesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acacetin</td>
<td><em>Robinia pseudoacacia</em> Linn.</td>
<td>Upregulate the activity of TYP, increase pERK1/2</td>
<td>[24, 25]</td>
</tr>
<tr>
<td>Isoliquiritigenin</td>
<td><em>Glycyrrhiza uralensis</em> Fisch.</td>
<td>Upregulate the activity of TYP, increase the expression of TYR</td>
<td>[27]</td>
</tr>
<tr>
<td>Geniposide</td>
<td><em>Gardenia jasminoides</em> Ellis.</td>
<td>Increase pERK1/2</td>
<td>[29]</td>
</tr>
<tr>
<td>Quercetin</td>
<td><em>Lindera obtusiloba</em> Bl.</td>
<td>Upregulate the activity of TYP, increase the expression of TYR</td>
<td>[32, 33]</td>
</tr>
<tr>
<td>Cirsimaritin</td>
<td><em>Lithocarpus dalbatus</em> (J. D. Hooker et Thomson ex Miquel) Rehder</td>
<td>Increase the expression of TYR, TRP1, MITF</td>
<td>[34]</td>
</tr>
<tr>
<td>Naringenin</td>
<td><em>Citrus maxima</em> (Burm.) Merr.</td>
<td>Activate PE3K/Akt, Wnt/β-catenin pathways</td>
<td>[35]</td>
</tr>
<tr>
<td>Glycyrrhizin</td>
<td><em>Glycyrrhiza glabra</em> Linn.</td>
<td>Increase the expression of TYR, increase intracellular cAMP levels, activate CREB pathway</td>
<td>[36]</td>
</tr>
<tr>
<td>C. officinalis</td>
<td></td>
<td>Upregulate the activity of TYP, increase the expression of TYR, TRP1, MITF</td>
<td>[37]</td>
</tr>
<tr>
<td>Cassia alata</td>
<td></td>
<td>Increase the expression of MITF</td>
<td>[38]</td>
</tr>
<tr>
<td>Psoralea corylifolia L</td>
<td></td>
<td></td>
<td>[39]</td>
</tr>
<tr>
<td>Kaliziri</td>
<td></td>
<td>Increase the expression of TYR, MITF</td>
<td>[24]</td>
</tr>
<tr>
<td>Antioxidant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baicalin</td>
<td><em>Scutellaria baicalensis</em> Georgi</td>
<td>Inhibit caspase activation and the p38 MAPK pathway</td>
<td>[44]</td>
</tr>
<tr>
<td>Apigenin</td>
<td><em>Apium graveolens</em> L.</td>
<td>Inhibit p38 MAPK pathway and ROS accumulation</td>
<td>[46]</td>
</tr>
<tr>
<td>Paeoniflorin</td>
<td><em>Paeonia suffruticosa</em> Andr.</td>
<td>Activate JNK/Nrf2/HO-1 Pathways</td>
<td>[48]</td>
</tr>
<tr>
<td>Capsaicin</td>
<td><em>Capsicum annum</em> Linn.</td>
<td>Repressed intracellular ROS generation; enhance the ERK pathway; reduce caspase-9 activation</td>
<td>[50]</td>
</tr>
<tr>
<td>Epigallocatechin Gallate</td>
<td><em>Camellia sinensis</em></td>
<td>Reduce ROS generation</td>
<td>[51]</td>
</tr>
<tr>
<td>Baicalein</td>
<td><em>Scutellaria baicalensis</em> Georgi</td>
<td>Decreased ROS and iron ion levels</td>
<td>[55]</td>
</tr>
<tr>
<td>Anti-autoimmune</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGB 761</td>
<td><em>Ginkgo biloba</em> Linn.</td>
<td>Reduce the secretion of IL17A and increase IL22 secretion</td>
<td>[72]</td>
</tr>
<tr>
<td>Demethylzeylasteral</td>
<td><em>Tripterygium wilfordii Hook. f.</em></td>
<td>Inhibit JAK/STAT pathway</td>
<td>[74]</td>
</tr>
</tbody>
</table>

**cAMP**, cyclic adenosine monophosphate; **ROS**, reactive oxygen species; **MITF**, microphthalmia-associated transcription factor; **CREB**, cAMP response element.

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Figure 1 The regulation of melanogenesis and skin pigmentation. The expression of MITF is regulated by several signaling pathways, such as cAMP/PKA, Wnt, PI3K/AKT, and MAPK signaling pathways. The process of melanosomes mature can be divided into four stages. From stage I to stage IV, the content of melain is increasing and then the mature melanosomes were transferred to keratinocytes. cAMP, cyclic adenosine monophosphate; MITF, microphthalmia-associated transcription factor.
isolated from various plants, such as Robinia pseudoacacia Linn., Turnera diffusa Willd., and Grevillea robusta A. Cunn. ex R. Br. [23]. Flavonoids, because of their function such as antioxidative, anti-inflammatory, and anticancer activities and low toxicity, have been used in the treatment of many diseases. Interestingly, Ipppei Horibe et al. noticed that flavonoids have controversial effects on melanogenesis: promotion and inhibition. They found that the 4-O-methyl group of flavonoids, diosmetin, kaempferide, and acacetin can induce melanin synthesis in B16F10 cells. Especially, among these flavonoids, 20 μM acacetin has the highest effect on increasing the melanin contents [24]. Moreover, the activity of tyrosinase and phosphor-ERK1/2 was also upregulated by acacetin [24].

Isoliquiritinigenin (ISL). The roots and rhizomes of Glycyrrhiza uralensis Fisch. have been used as Chinese traditional medicine for a long time. ISL, isolated from the roots of Glycyrrhiza, has promising pharmacological effects such as anti-inflammatory, antioxidative, antitumor, and immunomodulatory [25]. Xiaoyu Chen et al. reported that ISL could not only stimulate melanin biosynthesis, increase TYR activity and the mRNA expression of TYR, but also significantly increase the accumulation of ROS with ISL treatment, which can promote melanocyte proliferation and melanogenesis [26].

Geniposide. Geniposide, isolated from the fruit of Gardenia jasminoides Ellis., has been used to treat vitiligo. There are many researches on its pharmacological effects such as anti-inflammatory, anti-oxidative, anti-diabetic, neuroprotective, hepatoprotective, and cholangic effects [27]. Lan et al. discovered that the geniposide can enhance melanogenesis by using NE-induced normal human epidermal melanocyte or normal human epidermal keratinocyte as an invitro model. Moreover, geniposide reduced the repression effect of NE on melanogenesis in normal human epidermal melanocyte in the presence of stem cell factor, however this effect was abrogated by selective Glucagon-likepeptide-1-Receptor antagonist and inhibition of c-kit, which indicated that geniposide promotes melanogenesis by activating Glucagon-likepeptide-1-Receptor-dependent c-kit receptor signaling [28].

Quercetin. It was reported that quercetin can inhibit melanogenesis, however, Nagata Hidetaka et al. illustrated that 20 μM quercetin increased tyrosinase activity and enhanced melanogenesis in both human melanoma cells and human melanocytes [29, 30, 31]. Moreover, Susumu Takekoshi et al. found that quercetin could upregulate the expression of tyrosinase protein to induce melanogenesis without influencing the mRNA expression of TRP2 [32].

Cirsimaritin. Previous studies revealed that cirsimaritin, isolated from the branches of Lithocarpus dealbata (J. D. Hooker et Thomson ex Miquel) Rehder, possesses activation of antioxidiant. Based on these studies, Hyo Jung Kim et al. examined the hyperpigmentation effect of cirsimaritin and found that cirsimaritin upregulates melanin synthesis through cAMP/PKA-dependent CREB activation and upregulation of MITF, tyrosinase, and TRP1 expression in melanoma cells [33].

Naringenin. With the in-depth research of flavonoids, naringin, the main flavonoid in Citrus maxima (Burm.) Merr., has attracted more attention. Yu-Chun Huang et al. focused on the mechanisms of naringenin and its glycosides on melanogenesis and found that naringenin increased melanin content and tyrosinase activity in a concentration-dependent manner. Moreover, naringenin upregulated the expression of MITF and β-catenin and promoted phosphorylation of Akt or GSK3β, which suggested that naringenin enhanced melanin synthesis through activating the PI3K/Akt or Wnt/β-catenin signaling pathways [34].

Glycyrrhizin. Glycyrrhizin, isolated from the roots and rhizomes of Glycyrrhiza glabra Linn., has pharmacological effects such as anti-oxidative, anti-viral, and interferon-γ inducing activities. Jongung Lee et al. found that glycyrrhizin promotes melanogenesis by increasing the expression of tyrosinase at the mRNA and protein levels, which works by increasing intracellular CAMP levels and activating the CREB pathway [35].

C. officinalis methanol extract (COME). Coriis officinalis is known as a medicine for liver and kidney invigoration in China. Previous studies showed that hot water and ethanol extracts of C. officinalis had an activity of free-radical-scavenging and inhibited melanogenesis. Nevertheless, Yun Ah An et al. revealed that COME significantly increased melanogenesis and tyrosinase activity at concentrations above 3.125 μg/mL. COME could also upregulate the mRNA expression of tyrosinase and increase the expression of MITF, TRP1, and TRP2 [36].

Cassia alata. Considering the effects of an herbal extract on the differentiation and migration of melanoblast cells, Sumathy Babitha et al. obtained 13 herbal candidates and found that the leaf extract of Cassia alata, a plant of the genus Cassia, causes a dose-dependent increase in melanin content in mouse melanocytes, induces tyrosinase activity and directly stimulates the migration of melanocytes [37].

Melia azedarach L. Different parts of Melia azedarach L. (Meliaceae) have been used for the treatment of ulcers, diabetes, and skin disease. Mi-Ok Kim et al. figured out that the ethanol extract of Melia azedarach L. induces melanogenesis by upregulating the MITF gene through the cAMP-PKA-CREB signaling pathway [38].

Psoralea corylifolia L. For more than a thousand years, Ammi majus, Psoralea corylifolia, and Ficus carica have been used to enhance skin pigmentation in India, Egypt, and other countries. It has been demonstrated that coumarins have strong photosensitivity and can be used for long-wave UV irradiation for vitiligo. Besides, A study reported that 16 coumarins were isolated from Umbelliferae herbs, among which, psoralen (Psoralen, 7), 8-methoxypsoralen (Methoxsalen, 8-MOP, 8), and 5-methoxypsoralen (Bergapten, 9) had strong stimulatory effects on melanogenesis in mouse B16 melanoma cells [39].

Kaliziri. Kaliziri extract (KZE) has been serving as a traditional Ugyhur medicine for the treatment of vitiligo for a long time. Adila Tuexuntay et al. analyzed components of KZE by liquid chromatography-mass spectrometry and found KZE consists of 15 compounds and eight of them are flavonoids. Next, they revealed that KZE can significantly increase melanin synthesis and upregulated MITF and TYR protein expression at a concentration of KZE for 20 μg/mL [40].

Monomers with antioxidant effects
The theory of oxidative stress is widely recognized as a key factor in the pathogenesis of vitiligo. One of the main causes of vitiligo is the excessive accumulation of hydrogen peroxide (H2O2) in the epidermis, which results from oxidative stress. In addition to its role in promoting cellular dysfunction, H2O2-induced oxidative stress is also known to contribute to cell death through various pathways in melanocyte. Apoptosis, a kind of regulated cell death, is one of the most prevalent ways of melanocyte death in vitiligo. Ferroptosis, a type of nonapoptotic cell death, could be induced by oxidative stress. It is reported that interferon gamma released from CD8+ T cells participated in tumor cell lipid peroxidation and ferroptosis, and interferon gamma is integral in vitiligo pathogenesis [41, 42]. Therefore, anti-ferroptosis might be a promising strategy in vitiligo treatment.

Baicalin. Baicalin, isolated from the root of Scutellaria baicalensis Georgi, has been used as Chinese traditional medicine for a long time. The functions of baicalin include anti-inflammatory, anticytotoxicity, antiviral, and antitumor. Bangmin Liu et al. first found the antioxidant activity of baicalin in the presence of H2O2. It was shown that pretreatment with baicalin decreased H2O2-induced oxidative stress and apoptosis in human melanocytes by inhibiting caspase activation and the p38 MAPK pathway [43]. Besides, Wen-shin Chang et al. noticed the effects of baicalin on UBV-suppressed cell viability and found that the cell apoptosis result from UBV can be rescued by treatment of baicalin at doses of 75 and 50 μg/mL [44].

Apigenin. Apigenin, a plant-derived flavonoid, exists in a variety of vegetables. Because of its effective antioxidant activity, apigenin was considered to have the potential to treat vitiligo. Mao Lin et al. noted that apigenin could protect melanocytes from apoptosis by inhibiting the accumulation of ROS and relative signaling pathways about
oxidant stress such as JNK, p38 MAPK, and Akt as well as the activation of caspase 3 and PARP [45]. Next, Baoxiang Zhang et al. found that the activities of several important enzymes participating in antioxidant defense, including SOD, CAT, and GSH-Px, were significantly enhanced by apigenin in H2O2 treatment cells. Moreover, the mRNA and protein expression levels of Nrf2 were significantly upregulated after the treatment of apigenin. Apigenin improved cell viability and elevated SOD and CAT activities in H2O2 treated cells whereas not in Nrf2 knockdown cells, which suggested that apigenin may have a potential therapeutic effect on vitiligo through reducing oxidant damage [46].

**Paenoflorin.** Paenoflorin, extracted from the roots of *Paonia suffruticosa* Andr., is the main ingredient of the total glucosides of the paeony capsule. Jinping Yuan et al. found that paenoflorin had the function of protecting melanocytes from H2O2-induced oxygenation stress damage by activating the c-Jun N-terminal kinase (JNK)/Nrf2/heme oxygenase-1 (HO-1) pathways [47].

**Capsaicin.** Capsaicin, extracted from *Capsicum annuum* Linn., is one of the active ingredients of *Capsicum* spp. Based on previous research that declared that capsaicin has anti-inflammatory, antioxidant activities, and other activities, it may play a role in the treatment of vitiligo. Matteo Becatti et al. found that pretreatment with capsaicin can suppress intracellular ROS generation, enhance the ERK pathway, and reduce caspase-9 activation, thereby providing antioxidant protection to keratinocytes [48, 49].

**Epigallocatechin gallate (EGCG).** EGCG is one of the most abundant active compounds in green tea, which has strong antioxidant and anti-inflammatory activities and can regulate immune responses mediated by T lymphocytes. Considering the low bioavailability and stability of EGCG, W. Ning et al. put the spotlight on peracylated EGCG, a derivative of EGCG, and found that both peracylated EGCGa and EGCG showed strong antioxidant effects in primary human melanocytes by reducing ROS generation, restoring lost mitochondrial potential, protecting melanocytes from H2O2-induced toxicity through inhibiting the p38 signaling pathway [50]. Besides, the animal experiment also proved that EGCG creams with different concentrations (2%, 5%, 10%) showed the effects of reducing oxidative stress and modulating immune function in mono-benzophenone-induced depigmentation mice [51].

**Baicalein.** Previous studies have showed that baicalein, a major flavonoid in *Scutellaria baicalensis* Georgi, could inhibit H2O2-induced oxidative damage and apoptosis [52, 53]. Meng Yang et al. focused on the effect of baicalein of protecting melanocytes from ferroptosis and found that baicalein can prevent growth inhibition, mitochondrial dysfunction and decreased ROS and iron ion levels in R517-induced melanocytes through increasing GPX4 and declining TFR1 expression, which suggested that baicalein could serve as an available drug in the treatment of vitiligo [54].

**Monomers with anti-autoimmune effects**

Vitiligo has been frequently associated with autoimmune diseases, and it has been observed that the majority of vitiligo patients show the presence of anti-melanocyte antibodies [55–57]. Similar immunological responses have also been identified in animal models of vitiligo, and there is evidence to suggest that about 4% of melanoma patients who undergo immunotherapy may develop vitiligo symptoms [58–60]. Based on these findings, a hypothesis has emerged suggesting a relationship between vitiligo and autoimmunity. According to this hypothesis, an autoimmune response is involved in the pathogenesis of vitiligo. Further research has shed light on the role of specific immune cells, such as CD8+ T cells, regulatory T cells, and resident memory T cells (Trm) in the progression and maintenance of vitiligo [61–65]. Both innate immunity and adaptive immunity play significant roles in the progression of vitiligo. Innate immunity is thought to occur in the early stages of vitiligo when melanocytes are subjected to internal and external stress [66]. ROS overproduction causes melanocytes to secrete exosomes which contain melanocyte-specific antigens, miRNAs, heat shock proteins, and damage-associated molecular patterns. Stressed melanocytes release HSP70s to activate dendritic cells and induce dendritic cells into effective antigen-presenting cells [67, 68]. Moreover, previous studies demonstrated that CD8+ T cells are both necessary and sufficient for the elimination of melanocytes, and an amount of CD8 + T cells with anti-melanocyte cytotoxic were found in vitiligo lesions [69]. The CD8+ T cells in vitiligo lesions can generate interferon-γ (IFN-γ), which is indispensable in the process of disease. Not only can IFN-γ increase the accumulation of autoreactive CD8+ T cells in the lesions,
but IFN-γ can also upregulate the expression of CXC chemokine ligand 9 (CXCL9), CXC chemokine ligand 10 (CXCL10) through activating JAK/STAT1 signaling pathway. The expression of CXCL9 and CXCL10 exacerbates the progression of the disease. CXCL9 facilitates the recruitment of autoreactive T cells to the lesions, while CXCL10 is important for their effector function and localization within the skin [70]. Notably, both CXCL9 and CXCL10 act through the same receptor, CX-C motif chemokine receptor 3, suggesting the presence of a positive feedback loop that promotes the progression of vitiligo. Regarding the recurrence of vitiligo in the same area, it is believed that Trm cells were not completely eliminated from the lesions during therapy. In a vitiligo mouse model, it was demonstrated that Trm cells retained the ability to recognize antigens and produce IFN-γ, CXCL9, and CXCL10, even after a significant period of time [65]. Thus, Trm may be a key factor in the maintenance and recurrence of vitiligo. Figure 2 illustrates the role of CD8+ T cells and resident memory T cells in vitiligo pathogenesis.

EGb 761. Ginkgo biloba Linn. has been serving as a traditional medicine in China for a long time. There are multiple reports of promising results for Ginkgo biloba Linn. in the treatment of vitiligo. The function of EGb 761, an extract of G. biloba leaves, on modulating the AhR pathway was vague. Therefore, Baoyi Liu et al. kept an eye on the production of IL17A and IL22 in CD4+ T cells in vitiligo and discovered that EGb 761 reduced IL17A and increased IL22 secretion in the CD4+ T cells, which may have therapeutic potential for vitiligo [71].

Demethylzylyzeralateral. Demethylzylyzeralateral (T-96), apart from Tripterygium wilfordii Hook. f., showed various pharmacological activities, such as anticaner, anti-inflammatory, immune suppression, anti-fertility, antivirus, antimicrobial [72]. Considering these promising effects, Yuqiang Chang et al. revealed that T-96 reduced the proliferation, activation, and function of activated CD8+ T cells by inhibiting JAK3-STAT5 signaling pathway. Moreover, T-96 can block the migration of CD8+ T cells by suppressing the expression of CXCX3 on CD8+ T cells [73].

Conclusions

In this review, we have summarized various clinically therapeutic drugs, compounds and extracts that have shown potential for vitiligo treatment during preclinical studies. Additionally, we observed that many of the compounds associated with vitiligo treatment are primarily studied for their antioxidant effects, suggesting that targeting drugs or compounds with antioxidant properties may be a promising approach for the treatment of vitiligo. However, there are some limitations to these studies. Firstly, considering the multifactorial nature of vitiligo pathogenesis, it would be ideal if a single drug could target and elucidate the treatment mechanism of vitiligo from multiple angles. Secondly, most studies primarily focus on assessing the cytotoxicity of the drugs, but it remains unclear whether long-term medication use may lead to unwanted effects such as hyperpigmentation and allergies. Lastly, the majority of clinically used traditional Chinese medicines for vitiligo treatment are administered orally or topically, and more research is needed to explore the optimal method of application for the monomers or extracts.

In China, vitiligo was initially called for “bai chu” in the book named “Wu shi er bing fang” (Formularies for 52 Kinds of Disorders), which is one of the oldest Chinese medicine books. Then, the name of vitiligo, and its etiology and symptoms were first proposed in a book named “zhu bing yuan hou lun” written by Yuanfang Chao, a famous medical practitioner of the Sui Dynasty. Recently, as people pay more and more attention to traditional Chinese medicine, many herbs based on the theory of Chinese medicine and modern medicine have been discovered and play an important role in the treatment of vitiligo.

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