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Review Article

Phytochemical-based vesicular system for the treatment of vitiligo: A review

Pooja Udhav Pardeshi[1], Chinmay Rajendra Kapile[1], Abhijeet Dattatraya Kulkarni[2]✉*, Vishal Subhashchand Gulecha[2], Amar Gangadhar Zalte[2], And Shweta Shailesh Gedam[3]

[1]Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, P.O. Box 423603, Maharashtra, India
[2]School of Pharmaceutical Sciences, Sandip University, Nashik P.O. Box 422213, Maharashtra, India
[3]Department of Pharmaceutics, Sandip Institute of Pharmaceutical Sciences, Nashik P.O Box 422213, Maharashtra, India

ABSTRACT

Vitiligo is a depigmenting disorder that causes white patches on the skin and mucosa. It has an impact on a patient's mental well-being, physical well-being, and human lifestyle. These depigmented macules were originally mentioned in pre-Hindu, Vedic, and ancient Egyptian manuscripts more than 3,000 years ago. In recent years, there has been a growing interest in using phytochemicals over synthetic compounds in the pharmaceutical field. To better understand the effectiveness of natural products in the fight against vitiligo, large-scale clinical trials are required. Here, in this study, we summarize a list of vesicular formulations, with and without phytochemicals, that have been used and will be utilized in the future to treat vitiligo. To assist further progress in this vitiligo review we hereby mention an overview of pathophysiology, recent updates on clinical trials, and patents.

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1. Introduction

Vitiligo, the term derived from the Latin word «vitium,» name «blemishing fault,» causes white patches just on the skin. It affects the patient's self-esteem and is still the social stigma (Kopera,1997; Khaitan and Sindhuja, 2022). These benign white spots can be exceedingly distressing mentally, even leading to suicidal ideation (Garg et al., 2016). The origins of vitiligo have been for a long time a source of controversy (Speeckaert et al., 2015). In 1765, Claude Nicolas Le Cat was the first to describe the condition that is today known as vitiligo (Spritz and Andersen, 2017). Vitiligo is a pigmentary condition that affects melanocytes mostly in the skin and mucous membrane shown in Fig. 1. It's caused by a dynamic interaction of hereditary and environmental factors, resulting in the autoimmune destruction of melanosomes, *i.e.*, loss of melanin pigment (Khaitan and Sindhuja, 2022). Melanin refers to a group of natural pigments that play an important role in skin pigmentation and photoprotection. After migrating from melanocytes, it is deposed in keratinocytes, where it is formed from tyrosine by several oxidation reactions triggered by the enzyme tyrosinase (Gugleva et al., 2021). Vitiligo affects around 0.5-1% of the world population (Ezzedine et al., 2012; Sun et al., 2020). Even though both genders are afflicted with vitiligo, women are more inclined to publicly express and face the condition for cosmetic purposes, as well as seek medical treatment. Vitiligo strikes 50% of the patients before they become 20, and about 70% to 80% before they turn 30 (Ezzedine et al., 2015). India has the greatest recorded prevalence (up to 8.8%), next to Mexico (2.6-4.0%) and Japan (1.68%) (Sehgal et al., 2007; Sun et al., 2020). Vitiligo's pathophysiology is complex and unclear, however, it is likely to be caused by a mix of immunological, inherited, and environmental causes (Mahmoud et al.,

✉ Corresponding author: Abhijeet Dattatraya Kulkarni
Tel: 02594-222542; Fax: 02594-220162
E-mail address: kulkarniabhijeet11@gmail.com, **doi: 10.30495/tpr.2022.1955013.1249**

2008). Vitiligo isn't a cosmetic disease, so treatment can and should be offered to patients (Rodrigues et al., 2015) and has been given a diagnosis code (L80) by the World Health Organization (WHO) in its international statistical classification of diseases,10th revision. This is similar to other disorders like acne and alopecia areata, which were previously considered cosmetic diseases. Vitiligo results in autoimmunity disorders like type 1 diabetes, multiple sclerosis, psoriasis, and inflammatory bowel disease. It is also considered as a chronic, organ-specific autoimmune disorder that specifically attacks the epidermis, destroying melanocytes in its wake. In human skin, autoreactive cytotoxic T cells are both necessary and sufficient to cause vitiligo, indicating that vitiligo is predominantly caused by an immune-mediated attack on melanocytes. Autoreactive T cells are recruited to the skin by cytokines and destroy melanocytes, similar to other autoimmune diseases, and anti-inflammatory treatments are beneficial (Rodrigues et al., 2015). Acne as well as psoriasis (a chronic inflammatory skin disorder characterized by inflammation in the dermis and epidermis, keratinocyte hyperproliferation, and leukocyte infiltration) are the other common inflammatory skin diseases that have severe psychological implications (Amigo et al., 2007; Pejin et al., 2008; Tommonaro et al., 2016). Although psoriasis may cause arthritis and other systemic effects, these are not required for fully reimbursable medical treatment, which requires only moderate to severe skin involvement (Ezzedine et al., 2015). In the traditional Chinese medicine, a variety of natural substances and extracts have been utilized to treat vitiligo. The exact mechanism of action of these compounds is still unknown, but it appears to be related to their anti-inflammatory, immunomodulatory and antioxidant properties. Taking into account this point, antioxidant and anti-inflammatory natural molecules could be potential candidates for vitiligo therapy, due to their efficacy and safety (Mir-Palomo et al., 2019).

1.1. Classification

Vitiligo can be divided into various clinical forms, in accordance with a review published by the Vitiligo Global Issues Consensus Conference in 2012 (Table 1) (Ezzedine et al., 2012).

1.1.1. Non-segmental vitiligo (NSV)

Acrofacial, mucosal (varifocal), generalized, and global kinds of non-segmental vitiligo (NSV) are among the clinical subgroups (Ezzedine et al., 2012).

a. Acro-facial: Mostly affects the face, forehead, scalp, hands, and lower legs, with the orofacial area as well as digit appendages being the most commonly affected areas.

b. Mucosal: It affects the mucosae of the mouth and genital tract. Additionally, mucosal sites may also be afflicted in people with acrofacial, general, or universal types; when just a single mucosal region is affected, it is referred to as ambiguous.

c. Generalized (common): Mostly affects the region of the outer layer of the whole skin, however, it is most common in the hands, face, and injury sites.

d. Universal: This is the most prominent variety in adulthood, affecting the biggest portion of the outer thick layer of skin (85% of the skin surface). This is frequently preceded by the generalized type.

1.1.2. Segmental vitiligo (SV)

It may have an impact on just one or all of the segments. The most common form is unisegmental, which comprises one side of the body. There are one or more white macules, usually parallel to the body midline, with body hair involvement (leukotrichia) and the quick dawning of disorder.

1.1.3. Unclassifiable vitiligo

a) Focal: Whitish spots isolated through the entire body with no segmental distribution. This form has the potential to grow into SV or NSV forms.

b) Mucosal: There is only one mucosa impacted.

1.1.4. Mixed

When both SV and NSV are present at the same time, this condition arises. NSV is usually preceded by a segmental form.

1.2. Pathophysiology of vitiligo

Vitiligo's etiopathogenetic pathways are yet unknown. The autoimmune theory is the most widely accepted of the various explanations suggested. The autoimmune death of melanocytes causes vitiligo, which is caused by a dynamic combination of hereditary and environmental factors. In vitiligo, defects in melanocyte adhesion and increased oxidative stress amplify the immunological response. Because of the essential involvement of cutaneous mosaicism in segmental vitiligo, it is also noticed that the beginning, natural course, and response to treatment differ from non-segmental vitiligo (Khaitan and Sindhuja, 2022).

1.3. Role of oxidative stress and environment

Vitiligo patients' melanocytes may be unable to neutralize the increased reactive oxygen species produced by environmental stressors like as UV light and chemicals. The majority of investigations reveal higher oxidative stress indicators *in vitro*, although their relevance in disease pathogenesis is still debatable. High levels of oxidative stress markers [H_2O_2 superoxide dismutase, malondialdehyde, reactive oxygen species (ROS)], and reduced protective mechanisms against these oxidative stressors (catalase, glutathione) were documented in the skin and blood of vitiligo patients. Melanocytes in the perilesional skin had a dilated endoplasmic reticulum (ER), aberrant mitochondria, and melanosomes that were all dysfunctional. As a result

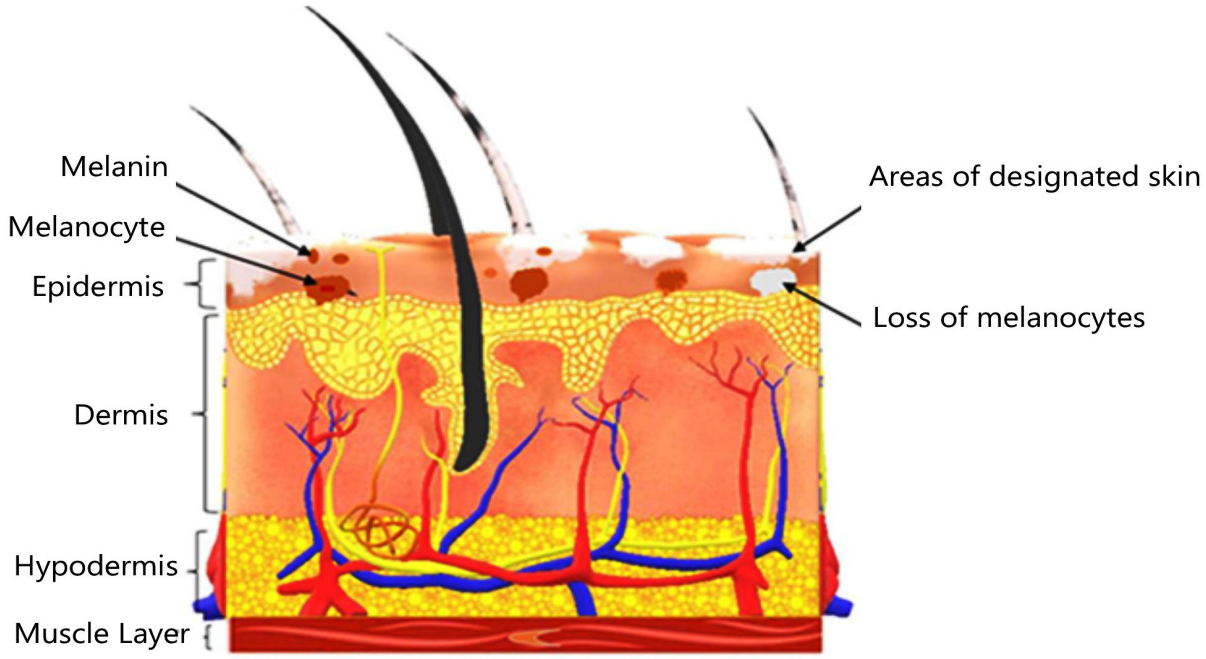


Fig. 1. Schematic diagram of vitiligo skin cross-section.

Table 1
Vitiligo classification (Ezzedine et al., 2012; Faria et al., 2014).

Types	Subtypes
Non-segmental	Acrofacial, mucosal (one or more regions affected), generalized, universal
Segmental	Unisegmental, bi or multisegmental
Unclassified	Focal at onset mucosal (One site)
Mixed (NSV+SV)	As reported by the severity of SV

Adapted from: Revised classification/nomenclature of vitiligo and related issues: The Vitiligo Global Issues Consensus Conference- 2012 & Vitiligo- Part 2- classification, histopathology, and treatment (Ezzedine et al., 2012).

of increased intracellular oxidative stress, melanocytes produce pro-inflammatory cytokines [interleukin (IL)-6, matrix metalloproteinase 3 (MMP3), cyclooxygenase (COX)-2, insulin-like growth factor-binding protein (IGFBP)-3 and 7] and chemokines (CXCL 12 and CCL 5), which activate and recruit T cell (Khaitan and Sindhuja, 2022).

1.4. Genetics of vitiligo

1.4.1. Genes and autoimmunity

The hazard of vitiligo in patient's immediate relatives (6.0% in siblings and 23% in identical twins), as well as its connection to other autoimmune diseases like Hashimoto's thyroiditis, hypocortisolism, insulin-dependent diabetes and Addison's anemia were utilized to demonstrate its low heredity and autoimmune-like character (Rezaei et al., 2007; Khaitan and Sindhuja, 2022). There are many vulnerability genes that code for non-specific immunity, *e.g.*, NLRP1, CASP7, IFIH1, COMT, TRIF, TICAM1, and others along with specific immune systems, *e.g.*, FOXP3, XBP1, CCR6, PTPN22, IL2R, HLAA2, -DR4, -DR7, CTLA4, CD80, GZMB, and others. Immune systems have been found by genome-wide association studies (Rodrigues et al., 2017b; Khaitan and Sindhuja, 2022). A limited collection of risk alleles (TYR, OCA2, and MC1R) is only expressed in melanocytes, implying that melanocytes have a role in disease initiation. Furthermore, XBP1 has been associated with the unfolded protein response (UPR) cellular stress pathway, which may contribute to the onset of inflammation (Khaitan and Sindhuja, 2022).

1.4.2. Genome-wide analysis

By selecting genes for investigation, candidate gene analyses have an inherent a priori bias. Genome-wide

analyses of polygenic, multifactorial disorders, on the other hand, are theoretically impartial beyond the assumption that genetic factors play an important role. Genome-wide genetic analysis can be done in three ways. Genome-wide linkage analysis looks for disease cosegregation of polymorphic markers within and across families with various affected relatives. Such families are infrequent, linkage resolution is low genetically, and genetic investigations depend on several key assumptions that may or may not be right (Spritz and Andersen, 2017).

1.4.3. Genome-wide linkage analysis

Genome-wide linkage and association analysis are much less susceptible to technical faults than individual gene methods since they're not influenced by a priori biological hypotheses. Genetic linkage studies are better for discovering disease vulnerability alleles with substantial effects that are relatively uncommon, such as those seen in multiplex families (Czajkowski and Mecińska-Jundziłłet, 2014). Even though, most genetic linkage analyses look at the entire genome, the very first sequence analysis (linkage analysis) for GV (Generalized Vitiligo) was such null research that looked at the linkage of a suspect gene, MITF (Melanocyte Inducing Transcription Factor) (Tripathi et al., 1999). The first study to reveal a strong relationship among vitiligo as well as AIS1 loci on genetic code 1p31.3-p32.2 had been carried out on a single familial complex of twenty-four individuals, fourteen of those had autoimmune disorders (Alkhateeb et al., 2002). A group of 71 families with multiple vitiligo instances in both Northern America and the UK took part in the next investigation. AIS1 on chromosome 1p31 matched the criteria for highly substantial linkage in this investigation, demonstrating its significance as a vitiligo susceptibility locus (Fain et al., 2003).

1.4.4. Genome-wide association studies

Genome-wide association studies (GWAS) look at a group of genetic polymorphisms over the entire genome to find the most frequently associated genetic markers with a disorder. It's also utilized to find out which genetic quantitative features are linked to the development of a disease (Hirschhorn et al., 2005; Czajkowski et al., 2014). The very first GWAS study was undertaken among the residents of a remote Romanian village. In this population, generalized vitiligo and other autoimmune disorders (Hashimoto's thyroiditis, rheumatism, insulin-dependent diabetes) were shown to be more common (Czajkowski et al., 2014). The GWAS is the «benchmark» for discovering complex phenotypic genetic variants and is most useful for detecting relatively common disease susceptibility genes (Spritz 2012).

2. Phytochemicals with vesicular system

Phytochemicals are compounds derived from natural plant species that have been proved to have good effects on human health, prevention, and therapy in recent decades (Mouhid et al., 2017). Different skin and mucus disorders can be caused by pathological diseases. A wide spectrum of compounds with anti-inflammatory and antioxidant properties can be found in nature to help prevent skin and mucous membrane disorders. Plant-derived compounds and their transformation into pharmaceutical designs are important in the therapy of skin problems because manufactured medicines may create drug resistance. The «green concept» is a growing concept in which biocompatible preparations with phytoconstituents included in lipid matrix are produced, ensuring patient care with low or no adverse reactions when used on body surfaces. Lipid nanoformulations and lipid membrane acknowledge a strong contact between the lipid matrix and the body surface, resulting in long-term production and great potency of herbal compounds loaded in the nano-system (Khan et al., 2021).

2.1. Phytochemical formulation-based on a vesicular system

Traditional medicine has been practiced since the birth of civilization. It is the use of written or oral knowledge, as well as our predecessor's experience, beliefs, and knowledge, in the treatment of human and animal diseases. Traditional medicinal treatment relies on a variety of resources, but the use of plants is especially significant (Almoshari, 2022). Formulations incorporating phytochemicals derived from a variety of botanical sources are shown to have good skincare activity with no side effects. Extracts in topical preparations can help to reduce oxidative stress in the skin, which has been linked to a slower ageing process. Many natural products such as arbutin (melanin inhibiting), azulene (antioxidant and anti-inflammatory), carnosic acid (antioxidant), glycyrrhizin (skin whitening), rutin (antioxidant), squalene (emollient) and rosmaric acid (antioxidant) are extensively used in various skin related formulations. These active compounds are designed to improve skin elasticity, reduce wrinkles, protect against UV radiation with antioxidant properties, and prevent collagen degradation, among other things (Gyawali et.al., 2016; Habeeba and Siddiqua, 2022). In the future, developing new natural products to combat autoimmune damage will be a spotlight and also provide a new direction to elucidate the pathogenesis of vitiligo (Pang et al., 2021). NDDS makes an effort to improve the medicinal value of existing pharmaceuticals, while also ensuring the secure and reliable distribution of novel therapeutics to fulfill the body's space-time requirements. In vesicular carriers, phosphatides, cholesterin, and/or other surfactants are frequently utilized to entangle a fluid core and separate it from the surrounding fluid (Singh et al., 2016).

2.1.1. Liposome

Liposomes, which are made up of phospholipids and have spherical, vesicular structures, can encapsulate

drugs that are both hydrophilic and lipophilic. Because of their compact size and lipidic composition, they can also be delivered to specific locations (Kamra et al., 2017; Khan et al., 2021). Because liposomes and epidermal membranes have comparable lipid compositions, they can penetrate deeper into the epidermal barrier, potentially increasing drug absorption and reducing side effects. Liposomal encapsulated drugs are found to be effective medicament of acne, eczema, psora, and vitiligo (Kamra et al., 2017). Sinico et al. (2006) used a film hydration technique to develop an 8-methoxy psoralen-loaded liposomal therapy. Psoralens are a group of naturally occurring chemicals that have been used to treat a variety of skin disorders characterized by hyperproliferative characteristics or an absence of melanin pigment with photochemotherapy. After a series of purges, the resulting vehicles' dimensions ranged from 100-500 nm, demonstrating remarkable permeation behaviour as compared to controls loaded with the hydroalcoholic mixture. Most nanotransporters demonstrated remarkable endurance in terms of 8-MOP production and penetration-absorption in the layers of the epidermis. Mir-Palomo et al. (2019) developed baicalin-berberine samples with ultra-deformable vesicles to show their efficacy as vitiligo combination therapy. Baicalin-berberine are natural chemicals that have antioxidant, anti-inflammatory, and proliferative effects. Preparation increased the penetration of drugs and antioxidants *in vitro,* according to the literature (Sun et al., 2020). Co-loaded vesicles increase pigmentation activity, according to photoprotective impact assessments. Doppalapudi et al. (2017) reported that psoralen (PSR) and resveratrol (RSV) loaded with ultra-deformable liposomes (UDL) have anti-vitiligo properties. Bangham method (thin film hydration method) was used to make UDL (Trucillo et al., 2020). Psoralen stimulates both melanin and tyrosin production in melanosomes when combined with ultraviolet-A (PUVA). Resveratrol, a sirtuin activator and suspected antioxidant which is claimed to reduce melanocyte cell damage which might be the mechanism to prevent the progress of vitiligo. Optimally co-loaded UDL (Ultra-deformable liposomes) were produced with vesicles size varying between 120-130 nm, a zeta potential of +46.20 mV, and entrapment efficiencies range from 74 to 76 percent of psoralen and resveratrol, respectively. PSR and RSV skin penetration are additionally aided by the co-loaded UDL's unique deformable nature. The drug dose is reduced by increasing encapsulation of mounted compounds, and the prolonged release of PSR and RSV from co-loaded UDL eliminates the need for frequent drug administration. Cell absorption experiments revealed that the encapsulated moiety penetrated the produced UDL more effectively. A combined effect of PUVA and RSV works to cure vitiligo through two modes of action: Pigmentation improvement and redox balance restoration via free radical scavenging activity.

2.1.2. Transferosome

Phosphatidylcholine and highly efficient edge activators make up transferosomes, which are a unique sort of liposome. They are trademarks of IDEA AG, a German industry that uses them to describe its patented medicine delivery system. The name comes from the word "transfere," which means "to carry across," and the "soma," which means "body". Transferosomes surpass the barrier to skin permeation by pressing themselves along the stratum corneum's internal encapsulating lipids (Rajan et al., 2011). Vinod et al. (2012) developed a transferosome integrated with piperine and targeted the melanocytes found in the skin layers by the film hydration technique. Piperine vesicles in soabean-phosphatidylcholine were produced with mean size in μm (67.11 ± 0.22) to (70.55 ± 3.62) and entrapment efficiency % (60.12 ± 1.04) to (80.43 ± 0.14). The particles appeared to protrude through pores smaller than their own and restore their form under external pressure. This demonstrates that vesicles have extreme flexibility, deserving the title "transferosomes". Depending on the composition of the vesicular system, dose, and form, the kinetic parameters, efficiency, and transferosome-mediated transporter can be altered for trans-epidermal, deeper layers, and system-wide transport (Table 2).

2.1.3. Nanoemulsion

Nanoemulsions are thermodynamically stable clear oil-water emulsions held by an interfacial coating produced by surfactant and cosurfactant molecules. The mean droplet size is between 10 to 140 nm (Singh et al., 2016). Nanoemulsion formulations have been shown to have better topical and cutaneous delivery qualities including both *in vitro* and *in vivo* experiments (Shafiq et al., 2007; Singh et al., 2016). Shivasaraun et al. (2018) developed a new drug complex loaded lipid-based nanoemulsion gel. The combination of flavonoid (hesperidin) and phytochemotherapy agent (trimethylpsoralen) for psoralen therapy is beneficial. When compared to the commercial formulation, TMP + hesperidin in nanoemulgel caused no adverse reactions or side effects. As a result, the innovative flavonoid TMP combination would be a preferable combination strategy for the prevention of leukoderma.

2.1.4. Other than phytochemicals

2.1.4.1. Niosome

Niosomes are a form of new drug delivery technology that envelopes the medication in a vesicle. Niosomes can enhance therapeutic molecule performance. By simply protecting medicine from the biological environment, it becomes more available to the specific site (Makeshwar et al., 2013). Manosroi et al. (2010) created an elastic-cationic niosome, loaded with human tyrosinase plasmid pMEL34 by chloroform film method. In EC niosomes, the highest filled with pMEL34 was 150 mg/16 mg of the niosomal formulations. They also prepared elastic cationic niosomes (PE) and Tat/human tyrosinase plasmid/EC niosomes (TPE) combinations

loaded with human tyrosinase plasmid. EC niosomes were produced through the freeze-dried empty liposomes (FDELs) technique. The carrier's zeta potential and vesicular size showed that it is still within the region of a stable dispersion. This type of preparation has been demonstrated to increase tyrosinase gene expression as well as melanin production *in vitro* with almost no deleterious side effects.

2.1.4.2. Cubosome

Cubosomes are bicontinuous cubic phase liquid crystals having several features that make them potentially useful as a medication delivery system (Garg et al., 2007). Cubosomes are a potential carrier for effective topical drug administration with improved skin penetration and minimal potential for irritation (Gaballa et al., 2020). Using an emulsification method, Sanjana et al. (2022) prepared a unique dexamethasone (DMS) loaded cubosomal formulation. To treat vitiligo, cubosomes were integrated through a hydrogel for extended DMS administration. Dexamethasone-loaded cubogel had an *in vitro* drug release of 83% at the half-day hours, showing that it could be used as a longer-lasting vitiligo medication delivery mechanism.

2.1.4.3. NLC (Nanolipid carriers)

In topical preparations, NLCs are employed extensively. Because liquid and solid lipids are present in NLCs, they can pass throughout cells and keep them hydrated (Khan et al., 2021). Nanolipid carriers are made up of less pernicious biological and ecological lipids with a wider coverage area in close enough proximity to the skin surface, allowing more drugs to be absorbed by the skin (Singh et al., 2016). Ashtiani et al. (2021) prepared topical simvastatin-loaded NLCs. They used a simplistic and repeatable technique(ultra-sonication) to create simNLC. The drug entrapment efficiency was found to be 98.99% and the drug loading capacity was found to be around 4.1%. The addition of simvastatin to NLCs did not affect skin biophysical parameters, according to human safety findings.

2.1.4.4. Microemulsion

Microemulsions are isotropic dispersions that are thermodynamically stable. In biphasic dispersions, an interface coating of surfactant atoms in interaction with a cosurfactant stabilizes immiscible liquids (Singh et al., 2016). Microemulsions are transparent, with globules varying over the range size of 10-100 nm and having no agglomerates (Lawrence et al., 2000). Microemulsion, as a promising topical delivery carrier, has garnered a lot of studies due to its nano-scale particle size and certain additives that act as penetration enhancers (Zhao et al., 2014). Patel et al. (2013) formulated a gel-based microemulsion loaded with clobetasol propionate which overcome clobetasol propionate's poor solubility. The preparation's efficiency was determined by the fact that the stratum corneum has swollen as a result of the gel formulation's fluid retention, allowing clobetasol to penetrate deeper into the skin. In vitiligo patients, *in vivo* experiments showed rapid repigmentation, improved skin location, and treatment outcomes.

2.1.4.5. Ethosome

Ethosomes, are a type of novel vesicles in transdermal drug administration, that have a significant effect on drug penetration across biological membranes. Ethosomes are high-ethanol-content phospholipid-based elastic nanovesicles (20-45%). Concerning size and scope, ethosomal systems surpass either typical liposomes or hydroalcoholic products when it comes to delivering substances to the skin (Nandure et al., 2013). Garg et al. (2016) prepared methoxsalen hydrogel composition-based on ethosomes that improved transdermal administration for vitiligo treatment. The ethosomes-based formulation was discovered to have been a potential drug target strategy, with better methoxsalen percutaneous penetration and lower photoirritation and skin redness, resulting in improved patient adherence for vitiligo diagnosis. Concerning the gel formulation, Patel et al. (2019) formulated topical transfersomal drug delivery in the form of thin film using rotary evaporation technique. If given in a transfersomal gel, tacrolimus can restore melanocytes. The major prevalent adverse effects of tacrolimus are skin irritation and incinerating which can be alleviated by combining it with a transfersomal transporter. Shadab et al. (2020) converted Safoof-e-Bars has been transformed to the simplest and most desirable new dosage form called 'emulgel,' which has similar content as SB and may be used by patients without any adverse effects. Safoof-e-Bars (SB) is a significant granular dosage form frequently used in the treatment of vitiligo. Emulgel's non-greasy nature allows for improving the release of drugs when subjected to other transdermal drug delivery systems. Habeeba and Siddiqua (2022) carried out a case study on babchi Unani marketed formulation to fight vitiligo. In this connection, an 11-year-old male had chalky white patches with hypopigmentation without itching over the hand, legs, stomach, or on the back for 1 year, gradually spreading over the chest. The patient was treated with wunaninani oral medication (nobar tablet) and applied ointment, and babchi oil locally. After treatment, there was repigmentation of the skin without any side effects. The treatment modility showed color changes of patches from chalky white to brown and it was concluded that the Unani formulation is effective in the treatment of vitiligo.

3. Vitiligo and plant-derived compounds as potential therapeutics

Vitiligo has been treated with herbal preparations of various natures and effects since antiquity (Gianfaldoni et al., 2018). There are several traditional herbal treatments for pigment deficiency in traditional medicine. The compounds originating from plants are listed in Table 3 and shown in Fig. 2 (Pang et al., 2021).

Table 3
Plant-derived compounds as potential therapeutics in vitiligo.

Category/Class	Compound(s)	IUPAC Name
Glycosides	Geniposide (**1**): It is a sort of iridoid glycoside. The mechanism of geniposide promoting melanogenesis was through activating t GLP-1R/c-kit receptor signal to enhance the expression of the c-kit receptor, to eliminate the depigmentation caused by norepinephrine. In the melanocytes induced by H_2O_2, geniposide increased the activities of SOD and CAT, and reduced the accumulation of ROS, thus increasing the antioxidant capacity of melanocytes and preventing melanocyte apoptosis by upregulating the Bcl-2/Bax ratio, while increasing cell viability. This process involves the activation of the PI3K/Akt signaling pathway (Zhou et al., 2019).	Methyl (1*S*,4a*S*,7a*S*)-7-(hydroxymethyl)-1-{[2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-1,41.5.7a-tetrahydrocyclopenta[c]pyran-4-carboxylate
	C-3-G (**2**): It is a kind of anthocyanin flavonoid widely found in vegetables and fruits. Pharmacological actions include anti-inflammatory, antifatigue, antioxidation, anti-tumor behaviors, etc. (Pang et al., 2021).	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxychromenylium-3-ylβ-D-glucopyranoside
	THSG (**3**): THSG exerts antioxidant effects by protecting cells from oxidative damage caused by H2O2 through increasing superoxide dismutase (SOD) activity, reducing malondialdehyde (MDA) content, and inhibiting ROS production (Pang et al., 2021).	2-[2,4-Dihydroxy-6-[2-(4-hydroxyphenyl)ethenyl]phenoxy]-6-(hydroxymethyl)oxane-3,4,5-triol
	Glycyrrhizin (**4**): It is natural triterpene saponin. Jung et al. (2001) were the first to find that GLC induced melanin production in B16 melanoma cells in a dose-dependent manner by upregulating the tyrosinase and Trp-2 gene.	(3β,20β)-20-Carboxy-11-*oxo*-30-norolean-12-en-3-yl 2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid
	Paeoniflorin (**5**): *In vivo* and *in vitro*, paeoniflorin has a wide range of pharmacological activities, including the anti-inflammatory, antioxidant, immunomodulatory, analgesic, anticonvulsant, antithrombotic, neuroprotective, cardioprotective, hepatoprotective, antitumor and antidepressant effect (Pang et al., 2021).	[(1*R*,2*S*,3*R*,5*R*,6*R*,8*S*)-6-Hydroxy-8-methyl-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-9,10-dioxatetracyclo[4.3.1.02,5.03,8]decan-2-yl]methyl benzoate
	Madecassoside (**6**): It is a natural triterpenoid saponin, isolated from Centella asiatica (L.) Studies have found that Madecassoside and asiatic acid has a wide range of pharmacological activities, such as anti-apoptotic, anti-inflammatory, and antioxidative features (Pang et al., 2021).	[6-[[3,4-Dihydroxy-6-(hydroxymethyl)-5-(3,4,5-trihydroxy-6-methyloxan-2-yl)oxyoxan-2-yl]oxymethyl]-3,4,5-trihydroxyoxan-2-yl] 8,10,11-trihydroxy-9-(hydroxymethyl)-1,2,6a,6b,9,12a-hexamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylate
Coumarins	Psoralidin (**7**): Diabetic complications, oxidative stress, obesity, osteoporosis, apoptosis, autophagy, and cell proliferation all benefit from psoralidin. For color restoration, psoralidin is utilized in traditional Uyghur medical products (Pang et al., 2021).	3,9-Dihydroxy-2-(3-methylbut-2-enyl)-[1]benzofuro[3,2-c]chromen-6-one
	Isofraxidin (**8**): Isofraxidin-related derivatives have been found to have anti-inflammatory, antioxidant, neuroprotective, and other biological activity (Pang et al., 2021).	7-Hydroxy-6,8-dimethoxy-2H-1-benzopyran-2-one
	Scopoletin (**9**): Scopoletin has been reported to have anti-inflammatory and antioxidant effects (Pang et al., 2021).	7-Hydroxy-6-methoxychromen-2-one
	7-Isopentenyloxycoumarin (**10**): 7-isopentenyloxycoumarins have antifungal, antioxidant, anticancer, neuroprotective, and anti-inflammatory properties (Pang et al., 2021).	3-(3-Methylbut-3-enoxy)chromen-2-one

Table 3 Continued

Category/Class	Compound(s)	IUPAC Name
Phenolic compounds	EGCG (**11**): Having many pharmacological effects, including anti-inflammatory, anti-atherosclerotic and anti-cancer effects. In a mouse model of monobenzone-stimulated vitiligo, EGCG reduced the incidence of hyperpigmentation while also delaying the time to depigmentation and the area of depigmentation. The suppression of CD8 + T cell migration and inflammatory cytokine expression were the underlying mechanism. In the meantime, EGCG reduced serum levels of IFN-, TNF-, and IL-6. 5%EGCG cream is the optimal concentration for the treatment of vitiligo (Zhu et al., 2014).	[(2*R*,3*R*)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate
	1,5-dicQA (**12**): 1,5-diCQA has a wide range of pharmacological effects, such as antioxidant, neuroprotective, antifibrotic, and other biological activities. Plant seeds containing 1,5-diCQA are used in traditional medicine to treat vitiligo (Pang et al., 2021).	(1R,3R,4*S*,5*R*)-1,3-Bis[3-(3,4-dihydroxyphenyl)prop-2-enoyloxy]-4,5-dihydroxycyclohexane-1-carboxylic acid
	3,5-diCQM (**13**): Caffeoylquinic acid derivatives have been used in the eastern traditional medicine to treat a variety of diseases and show a diversity of pharmacological effects, such as liver protection, anti-inflammatory and antimicrobial features. In the experiment of B16F10 melanoma cells treated with 0-50 μm 3,5-dicCQM, the results demonstrated that 3,5-diCQM might induce pigmentation (Pang et al., 2021).	(3*S*,5*S*)-3,5-Bis[[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]-1,4-dihydroxycyclohexane-1-carboxylic acid
	Morin (**14**): Having antitumor, antihypertensive, antioxidant, anti-inflammatory, antidiabetic, neuroprotective, antibacterial, and other pharmacological effects (Pang et al., 2021).	2-(2,4-Dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one
Flavonoids	Baicalein (**15**): Representing anti-cytotoxic, anti-inflammatory, and anti-tumor properties. Baicalein increased the expression of Nrf2 and its downstream gene HO-1 in human vitiligo melanocytes (PIG3V) induced by hydrogen peroxide, and promoted the translocation of Nrf2 from the cytoplasm to the nucleus, indicating that the protective effect of baicalein on melanocytes is dependent on the Nrf2 signaling pathway. Baicalein has an antioxidant impact on keratinocytes, so developing a baicalein topical preparation for vitiligo treatment could be a viable option (Pang et al., 2021).	5,6,7-Trihydroxy-2-phenylchromen-4-one
	Quercetin (**16**): Possessing several biological functions, including antioxidant and free radical scavenging properties. Cultured melanoma cells or NHEM treated with quercetin enhance melanin production and tyrosinase activity. Treatment of HMVII cells with quercetin at various dosages (1,5, 10, 20 m) and for various times (1, 3, 5, 7 days) resulted in a dose and time-dependent rise in melanin content in a cell experiment (Pang et al., 2021).	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
	Kaempferol (**17**): Being used to combat cardiovascular disease, cancer outbreaks, immune dysfunction, diabetes, oxidative stress and other diseases (Pang et al., 2021).	3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one
	Apigenin (**18**): Compared with other flavonoids, apigenin is relatively non-toxic and non-mutagenic, and has significant effects on normal and cancer cells. Therefore, apigenin may be a relatively safe remedy for the treatment of vitiligo (Pang et al., 2021).	5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

Table 3 Continued

Category/Class	Compound(s)	IUPAC Name
Flavonoids	Galangin (**19**): Possessing a variety of biological activities, including antibacterial, antiviral, anti-inflammatory, anti-obesity, and anti-antioxidant activities (Pang et al., 2021).	3,5,7-Trihydroxyflavone 3,5,7-Trihydroxy-2-phenyl-4H-chromen-4-one
	Naringenin (**20**) and hesperetin (**21**): The flavonoids in sweet orange peel include flavonoid glycosides, flavones, and flavonols, among which flavanones exist in the form of glycosides, e.g., hesperidin and naringenin or aglycones e.g., hesperidin and naringenin. Citrus fruits increase the creation of cell melanin and the expression of tyrosinase, which protects skin against the UV damage (Pang et al., 2021).	(2*S*)-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-4,5-Dihydroxy-6-(hydroxymethyl)-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-2-yl]oxy-5-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one And (2*S*)-5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one
	Afzelin (**22**): Afzelin markedly alleviated ultraviolet-induced oxidative stress in human skin, damage to mitochondrial membrane potential and mitochondrial permeability (Pang et al., 2021).	5,7-Dihydroxy-2-(4-hydroxyphenyl)-3-{[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy}-4H-1-benzopyran-4-one
	Fisetin (**23**): Fisetin has anti-allergic, anti-arthritis, and neuroprotective effects. Interestingly, it has a two-way regulatory effect on melanin production (Pang et al., 2021). Takekoshi et al. (2014) first reported that fisetin could promote Tyr activity and melanin content of human melanoma cells. However, Shon et al. (2016) found that fisetin inhibited the melanin content in and out of mouse B16F10 melanoma cells mediated by α-MSH.	2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4H-1-benzopyran-4-one
	Puerarin (**24**): Exhibiting a wide range of antioxidant activities in cardiovascular diseases, diabetes, obesity, osteoporosis, and other diseases. This natural compounds also displays obvious pharmacological activities against vitiligo *in vitro* and *in vivo* (Pang et al., 2021). Park et al. (2014) found that puerarin could increase the melanin content of melanocytes in vitro, and topical application could improve the melanin content of mouse skin tissue, the mechanism is via activation of the cAMP pathway, followed by elevation of MITF, tyrosinase, Trp-2, and Bcl-2 to increase melanocyte survival and melanin content.	7-Hydroxy-3-(4-hydroxyphenyl)-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-4H-1-benzopyran-4-one
	Butin (**25**): Showing a wide range of pharmacological activities for the treatment of aging, diabetes, liver diseases, and cancer. A recent study found that butin induced melanin production both in vivo and in vitro when the concentration was 40 μmol/L, while tyrosinase activity peaked. Meanwhile, in an H_2O_2-induced zebrafish model, butin reduced the levels of reactive oxygen species *in vivo* (Lai et al., 2021).	(2*S*)-2-(3,4-Dihydroxyphenyl)-7-hydroxy-2,3-dihydrochromen-4-one
	Liquiritin (**26**) and liquiritigenin (**27**): Representing a number of biological activities, such as antiviral, anti-inflammatory, antioxidation, anti-tumor, and so on. LQ and LQG were used to treat mouse melanoma B16-F1 cells and human melanoma hmvii cells with different doses for 72 h. The results showed that both natural drugs significantly increased the content of melanin in melanocytes in a dose-dependent manner and had no effect on cell viability (Pang et al., 2021).	(2*S*)-7-Hydroxy-4-(4-{[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}phenyl)-2,3-dihydro-4H-1-benzopyran-4-one and (2*S*)-7-Hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one

Table 3 Continued

Category/Class	Compound(s)	IUPAC Name
Flavonoids	Vitexin (**28**): Having many pharmacological activities, anti-inflammatory, antiviral, anticancer and antihypertensive impacts. In H_2O_2-induced human melanocyte PIG1. Vitexin inhibited hydrogen peroxide-induced apoptosis and promoted cell proliferation by activating the MAPK-Nrf2/ARE pathway, including decreasing IL-1β. The expression of IL-17A, Bax, caspase-3, and ROS, up-regulated the expression of p53, Bcl2, Nrf2, HO-1, NQO-1, and SOD (Li et al., 2020).	5,7-Dihydroxy-2-(4 hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-4H-1-benzopyran-4-one
	Hyperoside (**29**): It has been demonstrated to have antioxidant, anticancer, antifibrotic, antiallergic, anti-inflammatory, and other properties in studies. *In vitro*, hyperoside significantly boosted melanocyte proliferation in a dose- and time-dependent manner. In the H_2O_2-induced melanocyte model, hyperoside protected melanocytes from oxidative damage by regulating the PI3K/ Akt pathway, inhibiting p38 phosphorylation, and suppressing mitochondrial apoptotic signaling, which included upregulation of the Bcl-2/Bax ratio and expression of Akt, and downregulation of caspase 3, p38 (Yang et al., 2016).	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-{[(2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy}-4H-1-benzopyran-4-one

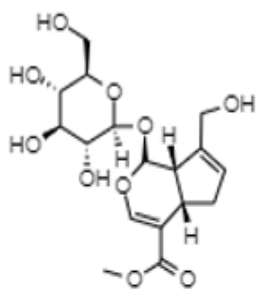
4. The economic burden of vitiligo

Treatment for vitiligo comes with a hefty price tag, both directly and indirectly, which is born by clients, carers, 3rd party funders, government institutions, *e.g.*, healthcare, and medical associations. Prescribed medicine, medical center visits, phototherapy, missed working days, social avoidance, and lowered quality of life (QOL) should all be evaluated because they influence patient's finances, duration, and sources of energy (Ongenae et al., 2005; Bickers et al., 2006; Ezzedine et al., 2015). One way for determining the disease's burden is to use standardized questionnaires to assess the effect of the disease on the patient's physical, psychological, and social functioning and well-being (Al-Niaimi et al., 2017). When leucoderma is treated it may improve results in terms of repigmentation as well as the quality of life (Lee et al., 2010). Furthermore, early identification of related autoimmune disorders will allow for more effective treatment of these conditions. Patients with policyholders are more probable to obtain treatment, therefore acknowledging such realities and ensuring coverage by 3rd party payers would help to reduce the burden of vitiligo.

Finally, the authors of a recent study employed burden of diseases measures to analyze the priority of dermato study sponsored by the National Institutes of Health (NIH) is a federal government agency, like many other nations that are eager to include disease burden in policy and funding considerations (Hagstrom et al., 2015). For young, unmarried women, the condition has a significant psychological impact. Vitiligo reduces the number of options for marriage in arranged marriage systems. Furthermore, vitiligo increases the probability of divorce among married women who develop the disease (Parsad et al., 2003). As a result, vitiligo should no longer be regarded as a cosmetic problem, but rather as a disfiguring, mentally debilitating skin illness that necessitates medical intervention (Ezzedine et al., 2015).

5. Teledermatology

Teledermatology is a rapidly growing field. Patients benefit from online interactions supported by websites and mobile applications since they save time while also filling a need for skin treatment. In the United States, the waiting time to see a dermatology specialist is 29 days, and the need for dermatological treatments keeps increasing (Rubin et al., 2015). Physicians are unable to access vital data in a patient's clinical record and family history because virtual care services allow inquiries to be conducted confidentially often with no authentication for identification (Peart and Kovarik, 2015). Limit your virtual appointments to your specialized practise area; physicians should offer a clear strategy for follow-up if additional treatment is required. Physicians should collect the patient's medical history which contextualizes the dermatologic symptoms. Also, they require verification of identity because there are certain teledermatology applications that don't demand identity confirmation but it is essential to make sure the



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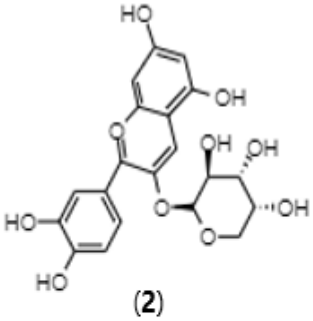

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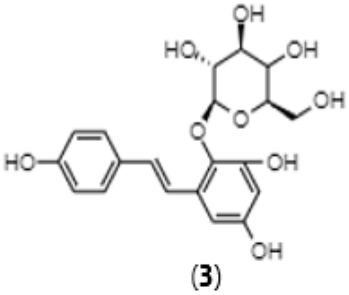

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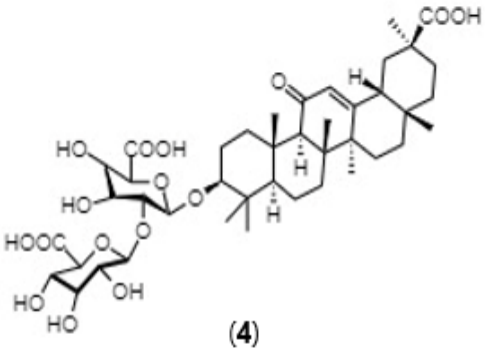

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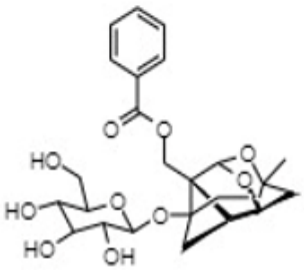

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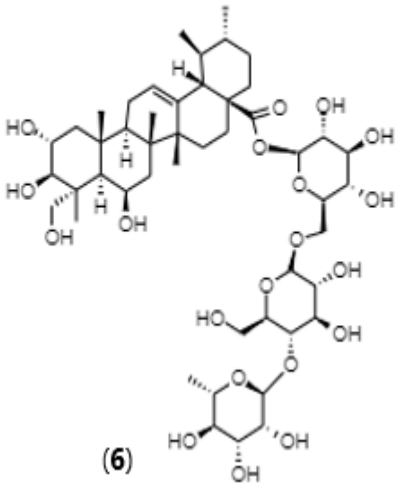

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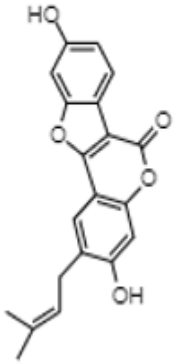

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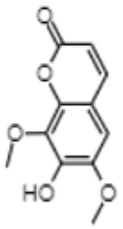

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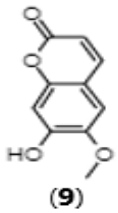

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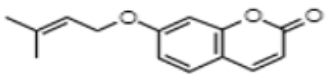

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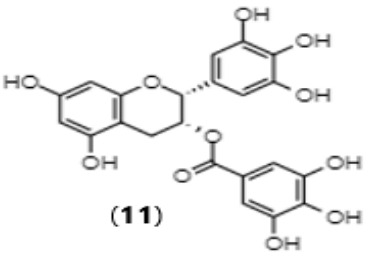

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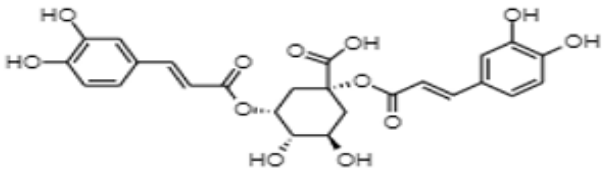

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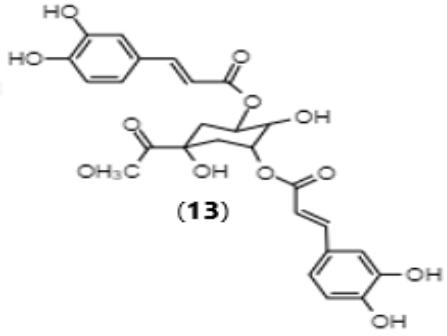

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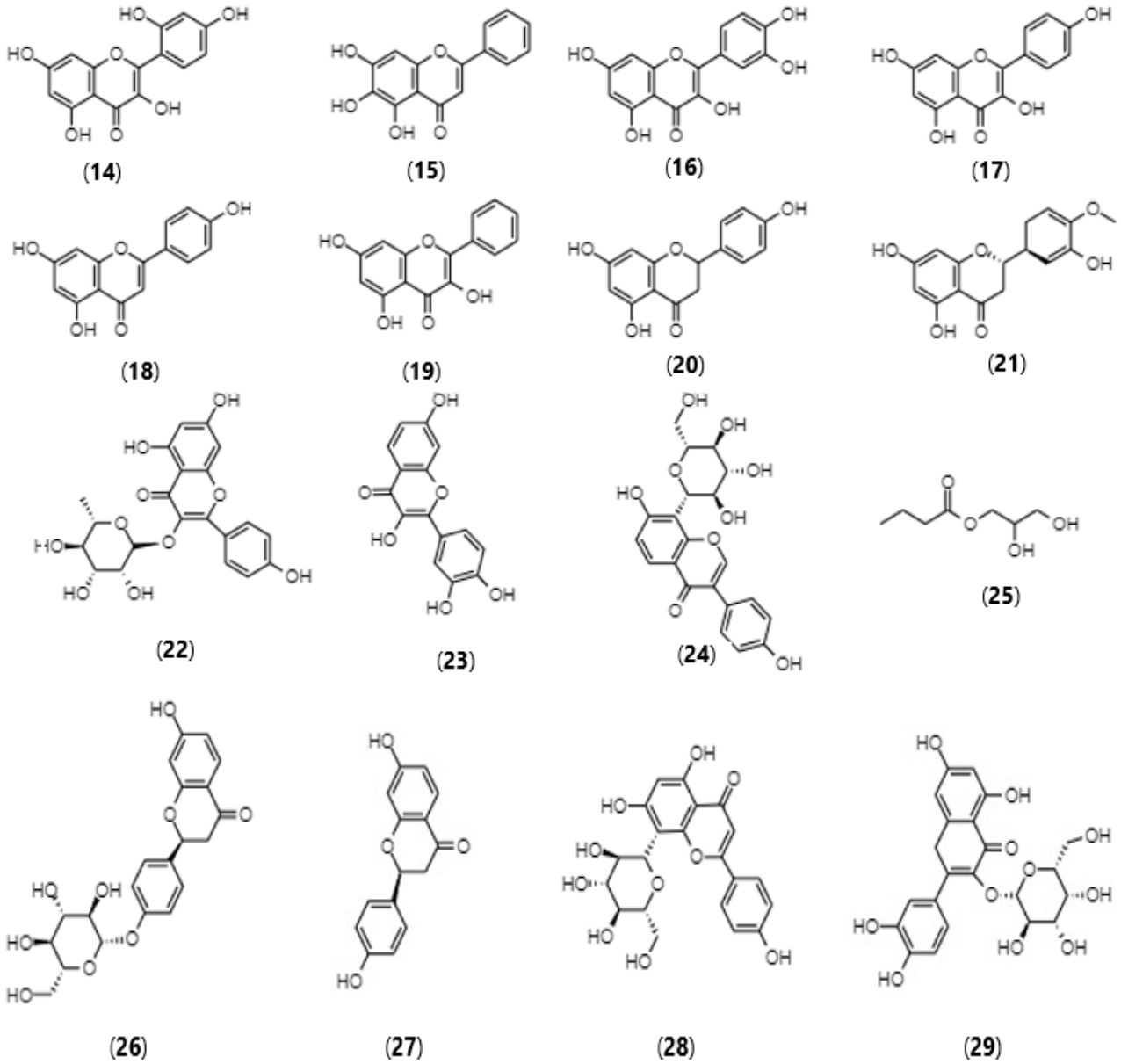

Fig. 2. Chemical structures of the characterized compounds (**1-29**) as potential therapeutics of vitiligo.

individual retrieving a prescription is the same as the one who files the inquiry when writing a prescription online, other people misusing prescription medication could result in difficulties like drug interactions and side effects. They should use teledermatology software that is integrated with your EMR (Electronic medical records), this will ensure that primary physicians can continue to coordinate the patient's care, and remain informed of the patient's newest diagnoses and medications. Teledermatology programs and virtual treatment could bring additional benefits to patients, such as extended chances for skin-related care, faster diagnosis, and possibly improved results if these suggestions are taken into consideration (Rubin et al., 2015).

6. Clinical trials

Adequately designed clinical trials are required to better understand the effectiveness of natural products in the fight against vitiligo. We've discussed a few clinical trials (Table 4) that are relevant to vitiligo treatment.

7. Recent patents

Since 2000, the number of patents has grown by 30% annually, parallel to the recent rise in the popularity of

Table 4
Recent clinical trials for the treatment of vitiligo.

Sr. No	Title of the study	Current status	Purpose	Intervention/ Treatment
1	Feasibility study to evaluate RECELL and melanocyte keratinocyte transplantation procedure for repigmentation of stable vitiligo lesions	Active	Device Feasibility	Procedure: Melanocyte-keratinocyte transplantation and Ultraviolet Lamp (UVB) Device: RECELL 1:5 and Ultraviolet Lamp (UVB) Device: RECELL 1:10 and Ultraviolet Lamp (UVB) Device: RECELL 1:20 and Ultraviolet Lamp (UVB)
2	A study to evaluate the mechanism of action of ruxolitinib cream in subjects with vitiligo (TRuE-V MOA)	Active	Treatment	Drug: Ruxolitinib cream Drug: Vehicle cream
3	Comparison between systemic steroids, topical steroids, or calcineurin inhibitors with mini punch grafting in treatment of stable non-segmental vitiligo	Active	Treatment	Procedure: Autologous mini punch grafting
4	Punch mini graft versus transverse needling or combination of both in treatment of non-segmental vitiligo	Active	Treatment	Autologous punch mini grafts, transverse needling, punch minigrafts followed by transverse needling, oral pulse steroid with narrow band
5	Evaluating the efficacy of the melanocyte keratinocyte transplantation procedure in the treatment of vitiligo	Active	Treatment	Procedure: MKTP with surgical blade device: MKTP with negative pressure instrument Device: Suction blister grafting without cell dissociation
6	A study to evaluate the efficacy of micro-needling as a stand-alone treatment for vitiligo	Active	Treatment	Device: Skinpen precision system
7	Evaluation of AMG 714 for vitiligo (REVEAL)	Active	Treatment	Biological: AMG 714 Biological: Placebo Procedure: nbUVB phototherapy
8	Diphenylcyclopropenone (DPCP) as a depigmenting therapy in extensive vitiligo	Active	Treatment	Drug: diphenylcyclopropenone (DPCP)
9	Effect of microneedling, bimatoprost, and excimer for the treatment of vitiligo	Active	Treatment	Drug: Bimatoprost Device: Excimer laser Device: Microneedling with a dermaroller
10	Assess the efficacy and safety of SHR0302 ointment in adult patients with vitiligo	Active	Treatment	Drug: Low Dose SHR0302 Ointment BID Drug: High dose SHR0302 ointment BID Other: Placebo Comparator: Vehicle
11	Study to evaluate adverse events and changes in disease activity with oral tablets of upadacitinib in adult participants with non-segmental vitiligo	Active	Treatment	Drug: Upadacitinib Drug: Placebo
12	The evaluation of vitiligous lesions repigmentation after topical administration of methotrexate in patients with active vitiligo	Active	Treatment	Drug: 1% Methotrexate gel Drug:0.5% Methotrexate gel
13	Pilot study assessing the effect of tildrakizumab in vitiligo (TILDVIT-1227)	Active	Treatment	Drug: Tildrakizumab
14	Combined effect of acitretin and narrow band ultraviolet B on vitiligo repigmentation	Active	Treatment	Drug: Acitretin Other: Narrow band ultraviolet B

nanotechnology. A summary of the relevant patents has been provided that were published in the period 2010-2021 aiming to treat vitiligo (Table 5). These patents comprise herbal compounds formed from the interaction between different herbal plants and crude extracts which are inventions for treating vitiligo. Present inventions provide a pharmaceutical come back towards dermatological skin conditions.

Table 5
Recent patents in the last decades with herbal drug extract for the treatment of vitiligo.

Title	Type and Patent Number	Reference
Phytotherapeutic formulation for vitiligo treatment	Brazil BR102013013736A2	Jose Humberto (2013)
Composition for alleviating vitiligo symptoms and preparation method thereof	WIPO(PCT) WO2020032297A1	Min Yeon-hong (2018)
One treats leukodermic Chinese medicine composition and preparation thereof	China CN106074778A	Tong et al. (2016)
Phytotherapeutical formulation for the treatment of vitiligo	WIPO(PCT) WO2016123682A1	Jose Humberto. (2015)
Composition comprising extracts of Longanae arillus for prevention and treatment of vitiligo	South Korea KR101349746B1	Kim et al. (2011)
External preparation for treating vitiligo and preparation method thereof	China CN106421249A	Li Wengli (2016)
External traditional Chinese medicine preparation for treating leucoderma and preparation method thereof	China CN108714167A	Teng et al. (2018)
Composition for preventing and treatmenting gray hair and leukoplakia containing pueraria genus plant extracts or puerarin	South Korea KR20110100393A	Kim et al. (2010)
Pharmaceutical composition for preventing or treating vitiligo comprising extract of Ricinus communis as an active ingredient	South Korea KR20200048305A	Kim et al. (2018)
Plant-source anti-leucoderma compound spray	China CN103655739A	King (2012)
Traditional Chinese medicine for treating leukoderma and preparation method for traditional Chinese medicine	China CN105326899A	Cui Yihong (2015)
Methods and systems for treating vitiligo using phloroglucinol and related compositions	United States US20210260001	Nicholas et al. (2021)
Traditional Chinese medicine for treating leucoderma	China CN103893558A	Yu (2014)
Traditional Chinese medicine liniment for treating leukoderma	China CN105616536A	Lu Shuai et al. (2016)

8. Concluding remarks

Vitiligo is a pigmentary disorder that affects melanocytes mostly in the epidermis and mucous membrane. It is a widespread disorder that affects approximately 1.0% of the global population. It's caused by a dynamic interaction of hereditary and environmental factors, resulting in the autoimmune destruction of melanocytes. Some natural compounds may be considered a potential treatment option for vitiligo. Concerning future prospects, we mentioned some ongoing clinical trials and patents for vitiligo. To better understand the effectiveness of natural products in the fight against vitiligo, appropriately designed clinical trials are required. This review article attempts to argue briefly has been about the state of the art of vesicular formulations that have been used to treat vitiligo. Nanoparticles mixed with phytoconstituents are known as nano-phytomedicine, which is surely going to appreciate the value of the current drug delivery system in the upcoming era. It has a lot of potential for improving the efficacy of herbal medications by removing the absorption and stability-related issues associated with them. Many limitations of the potential bioactive phytochemicals related to their bioavailability and biological activity have been improved manifold by the application of a nano-vesicular system. Liposomes, niosomes, ethosomes, and phytosomes are the newer generation of vesicular systems which augments the innate capacity of naturally-derived chemicals to treat various chronic inflammatory diseases like vitiligo. In addition, the cost associated with nanotherapeutics will be significantly lowered with the advent of phytochemical-based vesicular system. People's health will be vastly improved by nano-phytomedicine in the future. Authors are optimistic that upcoming future will definitely witness the presence of nano-phytopharmaceuticals derived vesicular systems on the market at affordable cost. In the current review, a variety of vesicular formulations, both with and without

phytochemicals, that have been and will be utilized to treat vitiligo are reviewed.

Abbreviations

NSV: Non-segmental vitiligo, SV: Segmental vitiligo, ROS: Reactive oxygen species, ER: Endoplasmic reticulum, IL: Interleukin, MMP3: Matrix metalloproteinase 3, COX-2: Cyclooxygenase, IGFBP: Insulin-like growth factor- binding protein, MITF: Melanocyte inducing transcription factor, GWAS: Genome-wide association studies, FDELs: Freeze-dried empty liposome method, DMS: Dexamethasone, NLC: Nanolipid carriers, C-3-G: Cyanidin-3-*O*-β-glucopyranoside, THSG: 2,3,5,49-Tetrahydroxystilbene-2-*O*-glucoside, EGCG: Epigallocatechin-3-gallate, 1,5-dicQA: 1,5-Dicaffeoylquinic Acid, 3,5-diCQM: 3,5-Dicaffeoylquinic acids, NIH: National Institutes of health, QOL: Quality of life, EMR: Electronic medical records, BARVIT: Baricitinib vitiligo, METVI: Methotrexate vitiligo, ERASE: Early repigmentation approach for stopping the evolution, DPCP: Diphenylcyclopropenone, PRP*: Platelet-rich plasma,* VITILIMEL: *Vitiligo and Melanoma,* TILDVIT: Tildrakizumab in vitiligo, Vitisod: Vitiligo *superoxide dismutase*.

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Conflict of interest

The authors declare that there is no conflict of interest.

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