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Insights into the role of Nrf2 in vitiligo pathogenesis: a target for herbal medicine

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Vitiligo (skin depigmentation) affects approximately 2% of the global population. It is characterized by a decrease in the number of pigment-forming cells known as melanocytes in the skin. Vitiligo is classified according to its extent and distribution into segmental (affecting one side of the body) and non-segmental (affecting both sides of the body). Vitiligo is an autoimmune disease characterized by complex and multifactorial genetic and non-genetic factors. The genetic factors are related to gene defects on HLA regions that code the histocompatibility complex, creating autoimmune response. Non-genetic factors include the exposure of melanocytes to oxidative stress and environmental factors. Conventional therapies include corticosteroids, immunomodulators, vitamins, phototherapy, surgery, and laser therapy. The use of complementary medicines such as plants, their extracts, and natural compounds in managing vitiligo has consistently been shown in many studies to be effective in the management and treatment of vitiligo. This review summarizes the most recent advances in understanding the pathogenesis of vitiligo, with an emphasis on the role of the Nrf2 pathway machinery and the effectiveness of herbal medicines and their extracts in vitiligo management and treatment. Plants such as *Ginkgo biloba*, *Olea europaea*, *Cucumis melo*, *Camellia sinensis*, and *Allium sativum* exhibit activity against vitiligo. The possible mechanisms by which these plants act are summarized in this review.

KEYWORDS

vitiligo, ROS, Nrf2 pathway, oxidative stress, HO-1, HLA, herbal plants, ginkgo

1 Introduction

Vitiligo is an acquired asymptomatic autoimmune disease that affects skin pigment (melanin)-forming cells (melanocytes), resulting in the appearance of white (depigmented) patches on the skin, hair, eyes, inner ear, and mucous membranes of the mouth, nose, and eyes (Ortel et al., 1988; Picardo et al., 2015). In its early stages, vitiligo starts as a patch that is paler than the skin and gradually becomes completely white (Ezzedine et al., 2012; Picardo et al., 2015). Vitiligo can develop at any age and affects both sexes equally, with women complaining of it earlier and more frequently (Alikhan et al., 2011; Rodrigues et al., 2017).

Vitiligo prevalence among the world's population ranges from 0.5% to 2% (Alikhan et al., 2011; Kruger and Schallreuter, 2012; Zhang et al., 2016) with some areas in India and Africa having a higher incidence, reaching up to 9% (Shah et al., 2008; Zhang et al., 2016). In

a recent report by Valle (2019), the total number of people with vitiligo worldwide was estimated to range from 65 to 95 million (Valle, 2019). Although the incidence of vitiligo is relatively low, it often has devastating effects on patients' psychology and quality of life (Alikhan et al., 2011).

The etiology of vitiligo remains unknown (Manga et al., 2016). Many theories have explained the destruction of melanocytes in vitiligo. These theories include metabolic abnormalities, oxidative stress, endoplasmic reticulum stress, environmental factors, and autoimmune processes (Iannella et al., 2016; Picardo et al., 2015). Vitiligo is classified into two types: segmental and non-segmental. Segmental vitiligo affects one side of the body and is less common than non-segmental vitiligo, which affects both body sides (Ezzedine et al., 2012).

Vitiligo is not a life-threatening disease; however, it can alter life because it affects patients' lives both biologically and psychologically. Hearing loss and ocular problems are the main physical impairments associated with vitiligo. Hearing loss is detected in up to 20% of patients with vitiligo because of the loss of functional melanocytes of striavascularis (Alikhan et al., 2011). Ocular abnormalities such as iritis (inflammation of the iris) and uveitis (inflammation of the middle layer of the eye) are reported in almost 40% of patients with vitiligo. Psychologically, many patients experience serious depression, low self-esteem, anxiety, and problems with confidence; they often feel embarrassment and shame and have to deal with social stigma due to misunderstandings of vitiligo (Sawant et al., 2019). A questionnaire-based study involving 73 British adults with vitiligo reported an increase in bereavement, sleep disturbance, and changes in eating habits compared with other dermatological diseases (73 control patients) (Papadopoulos et al., 1998). Another study conducted in 2003 involving 31 adults with vitiligo reported a decrease in social support and acceptance and an increase in anxiety compared to 116 other patients who experienced other dermatologic diseases (Picardi et al., 2003).

Several studies suggest oxidative stress as a hallmark of vitiligo pathogenesis with particular interest of the elevated level of the reactive oxygen species (ROS) in melanocytes and its role in triggering inflammation, autoimmunity and susceptibility to apoptosis (Chang and Ko, 2023; Colucci et al., 2015). An increase of H₂O₂ is detected in epidermis from vitiligo patients (Schallreuter et al., 1999) while marked decrease of the antioxidant enzymes have been reported (Zedan et al., 2015). The nuclear factor erythroid 2-related factor 2 (Nrf2) is a master cellular sensor of oxidative stress and a key regulator of the cellular redox state. Once activated, Nrf2 enhance the expression of endogenously antioxidant, detoxification and cytoprotective enzymes that provide cell protection and survival (Jian et al., 2014). The dysfunction of Nrf2 was reported in many studies amplifying melanocyte destruction (Jian et al., 2014). On the contrary, Nrf2 activation by several inducers such as DMF, Sulforaphane and plant extracts present a promising strategy in vitiligo management (Li et al., 2020; Lin et al., 2020; Liu et al., 2007). Recently, there has been an increasing interest in understanding the pathophysiology of vitiligo and the use of complementary herbal treatments. This review aims to summarize the current advances in vitiligo pathophysiology, with an emphasis on oxidative stress affecting melanocytes, and identify the underlying role of Nrf2 pathway as a

possible target for herbal plants and natural products involved in vitiligo management.

2 Classification of vitiligo

Vitiligo is classified into two major categories according to its extent and distribution: segmental vitiligo (SV) and non-segmental vitiligo (NSV) (Table 1). Segmental vitiligo accounts for (5%–27.9%) of all vitiligo cases and characterized by its unilateral distribution, stable size, low association with autoimmune diseases, and a tendency to affect younger patients (87% of cases are <30 years old). In some cases, two segments may appear on opposite sides of the body, and vitiligo is called dissegmental; if these segments appear on the same side, it is called multisegmental (Picardo et al., 2015; van Geel and Speeckaert, 2017).

Non-segmental vitiligo is the most common type, characterized by symmetrical bilateral depigmented macules, an unpredictable course and activity that increases in size over time, and is associated with autoimmune diseases. It includes all forms of vitiligo that are not classified as segmental (Ezzedine et al., 2012) such as acrofacial, universal (generalized), mixed, and rare cases. In acrofacial cases, lesions primarily affect the distal fingers, facial orifices, face, hands, feet, and head. It can later progress to a universal form, involving lesions in multiple parts of the body in a symmetrical pattern on 80%–90% of the body surface (Alikhan et al., 2011; Ezzedine et al., 2012).

Mucosal vitiligo involves the oral or genital mucosae, or both. When it is associated with other sites of skin depigmentation, it is classified as NSV. However, it can involve only mucosal site for a long time of diagnosis—at least 2 years—and it classified under the undetermined category (Table 1).

The mixed type of vitiligo is characterized by the presence of segmental and non-segmental types; it most often starts with segmental vitiligo and then develops into non-segmental vitiligo, so it is considered the NSV subtype.

2.1 Risk factors and disease association

Individuals at risk of acquiring vitiligo include those with a family history of certain autoimmune diseases, such as type 1 diabetes, alopecia areata, pernicious anemia, rheumatoid arthritis, and autoimmune thyroid diseases (Alikhan et al., 2011; Alkhateeb et al., 2003; Nejad et al., 2013), suggesting the existence of shared common molecular pathways in the development of various autoimmune disorders.

Thyroid diseases are the most prevalent autoimmune diseases associated with vitiligo and are reported in 20% of vitiligo cases. Their prevalence is at least three times higher than that in the normal population (Nejad et al., 2013). In one study, 34.9% (538/1541) participants with vitiligo had comorbid autoimmune disorders (Gill et al., 2016). Similarly, in another study, 34% of patients with vitiligo had a history of thyroid disease (Yaghoobi et al., 2011). These findings are similar to those obtained by Baldini et al. (2017), who reported a higher incidence of thyroid disorders and thyroid hormone antibodies in vitiligo patients and their family members (Baldini et al., 2017).

TABLE 1 Vitiligo classification including features of each category.

Type	Subtype	Features
Non-segmental	Acrofacial	Depigmentation of distal fingers and facial orifices
	Universal	Depigmentation of 80%–90% of body skin and hair
	Generalized	Bilateral, symmetrical lesion in multiple parts of the body
	NS Mucosal	Present of a lesion in mucosal part associated with other part of skin
	Mixed	The presence of SV and NSV together
Segmental	Unisegmental	One or more lesions on one side of the body. It is most common type of SV.
	Bisegmental	Two or more lesions on the opposite side of the body
	Multisegmental	Two distinct lesions on the same side of the body
Undetermined	Focal	Small isolated hypo-pigmented lesion that does not fit a typical segmental distribution, and not evolved into NSV after 1–2 years
	Mucosal	The presence of segment on one mucosal site

NSV: non segmental vitiligo, SV: segmental vitiligo.

Several physical and psychological factors are associated with vitiligo pathogenesis. These factors include exposure to sunburns, cuts, radiation, chemicals, and trauma (Rodrigues et al., 2017). Psychological factors, including a high frequency of stressful life events and preceding vitiligo onset, are associated with the development of vitiligo. A questionnaire-based study included 1541 vitiligo patients reported that 56.6% of participants experienced at least one stressor within 2 years prior to vitiligo onset; the stressor was mainly death of a loved one, and other stressors included financial problems, family problems, or end of long-term relationships.

3 Vitiligo pathogenesis

The pathogenesis of vitiligo is poorly understood. However, they are believed to be genetic (Nath et al., 1994; Spritz and Andersen, 2017) and non-genetic factors (Wang et al., 2014; Wang et al., 2016).

3.1 Genetic factors in the pathogenesis of vitiligo

The earliest evidence implicating genetic factors in the pathogenesis of vitiligo was reported by Nath et al., in 1994 (Spritz and Andersen, 2017). Vitiligo affects 1% of the general population (Abreu et al., 2015), but the risk of patients' siblings (immediate relatives of patients with vitiligo) developing the disease is 12%, approximately 7% for parents (Majumder et al., 1993), and 23% among monozygotic twins (Nath et al., 1994).

Vitiligo is a complex disease that cannot be explained by Mendelian patterns. It is characterized by multi-factorial polygenic inheritance, incomplete penetrance, and multiple susceptibility loci (Shen et al., 2016). Mutations and single nucleotide polymorphisms in genes involved in both innate and adaptive immunity and non-immune genes increase the risk of vitiligo.

Genome-wide association studies (GWAS) are the gold standard for identifying genetic variations in complex diseases. Using this approach, a set of SNP across the whole genome is examined to identify the most relevant variants associated with the disease (Spritz, 2012). Richard Spritz et al. conducted the largest GWAS on Caucasian populations and identified several genetic locations linked to vitiligo. Genes linked to vitiligo pathogenesis are categorized into five groups: transcription factors/co-regulators, adaptive immunity, innate immunity, cellular signaling/adaptor proteins/receptors, and nonimmune genes (Alkhateeb et al., 2005; Jin et al., 2016; Jin et al., 2012; Jin et al., 2010a; Jin et al., 2010b; Spritz, 2012). Other GWAS carried out in the Han Chinese identified candidate genes, including (CXCR5/DDX6 at 11q23.3, PMEL/IKZF4 at 12q13.2, and SLC29A3/CDH23 at 10q22.1) (Tang et al., 2013). In East Asia, the identified genes included (HLA-B and HLA-C at 6p21.33, RNASET2/FGFR1OP/CCR6 at 6q27, and ZMIZ1 at 10q22.3) (Quan et al., 2010). These differences were probably due to heterogeneity among the populations. The gene names, loci, functions, and risk allele positions are listed in (Table 2).

Genome-wide linkage studies are another unbiased approach used to identify genetic loci associated with complex human diseases. In this approach, a gene with multiple features is detected by scanning the entire genome (Dawn Teare and Barrett, 2005). Linkage studies of families from North America and the United Kingdom with multiple vitiligo have identified susceptible locus at chromosome 1p31 for the gene FOXD3 (Fain et al., 2003). Genetic variations associated with vitiligo, including those in HLA (Yang et al., 2005; Zamani et al., 2001; Zhang et al., 2004), PTPN22 (Cantón et al., 2005; Elmongy and Abu Khalil, 2013; LaBerge et al., 2008; Laddha et al., 2008; Rajendiran et al., 2018), NALP1 or NRLP1 (Jin et al., 2007a; Jin et al., 2007b), and XBP1 (Birlea et al., 2011; Ren et al., 2009).

The HLA region is a crosslinker between the genome and autoimmune diseases. This region encodes the histocompatibility complex (responsible for antigen presentation of antigens) (Matzaraki et al., 2017). Several genes associated with vitiligo are located in the HLA region, which induces an autoimmune response

TABLE 2 Genome loci association with vitiligo (Based on GWAS data).

Protein classification	Gene name/ Locus	Accession number (NCBI)	UniProtKB entry (ExPASy)	Function	Risk allele position or SNP
1. Transcription factors/co-regulators	RERE/1p36.23	NC_000001.11	Q9P2R6	Transcriptional repressor during development and play role in apoptosis	G at position 1: 8526142 Variant ID: rs4908760
	FOXP1/3p13	NC_000003.12	Q9H334	Essential transcriptional factor regulator of B-cell development	G at position 3: 71573135 Variant ID: rs17008723
	FOXD3/1p31.3	NC_000001.11	Q9UJU5	Transcriptional repressor and activator. A transcription factor that regulates Melano blast differentiation	–639G>T at the promoter region
	LPP/3q28	NC_000003.12	Q93052	Support cell adhesion and shape. May function as transcriptional co-activator	T at position 3: 188112554 Variant ID: rs1464510
	IKZF4/12q13.2	NC_000012.12	Q9H2S9	Transcription factor essential for the inhibitory function of regulatory T-cells	C at position 2: 56416928 Variant ID: rs2456973
	BACH2/6q15	NC_000006.12	Q9BYV9	Transcription factor of adaptive immunity. Key regulator of T-cell function and B-cell maturation	A at position 6: 90957463 Variant ID: rs3757247
2. Adaptive immunity	HLA-DRA/6p21.32	NC_000006.12	P01903	Presents antigen on the cell surface for recognition by the CD4 T-cells	T at position 6: 32373698 Variant ID: rs3806156
	HLA-A/6p22.1	NC_000006.12	P04439	Displays antigen for recognition CD8-positive T cells	T at position 6: 29942083 Variant ID: rs3823355
	UBASH3/21q22.3	NC_000021.9	P57075	Negatively regulate T-cell signaling	A at position 21: 43836186 Variant ID: rs11203203
	CD44/11p13	NC_000011.10	P16070	Cell-surface receptor that plays a role in cell-cell interactions, adhesion, migration, inflammation and T-lymphocytes Activation	G at position 11: 35280852 Variant ID: rs10768122
	CD80/3q13.33	NC_000003.12	P33681	Essential for T-lymphocyte activation, proliferation and cytokine production	C at position 3: 119288414 Variant ID: rs59374417
	PTPN22/1p13.2	NC_000001.11	Q9Y2R2	Negative regulator of T-cell receptor by dephosphorylation of Src family kinases	A at position 1: 114377568 Variant ID: rs2476601
	BTNL2/6p21.32	NC_000006.12	Q9UIR0	Negative T-cell regulator, decreasing T-cell proliferation and cytokine release	A at position. 6: 32345283 Variant ID: rs7758128
3. Innate Immunity	GZMB/14q12	NC_000014.9	P10144	Mediated immune responses and involved in cell lysis and apoptosis	G at position 14: 25102160 Variant ID: rs8192917
	IFIH/2q24.2	NC_000002.12	Q9BYX4		G at position 2: 163110536

(Continued on following page)

TABLE 2 (Continued) Genome loci association with vitiligo (Based on GWAS data).

Protein classification	Gene name/Locus	Accession number (NCBI)	UniProtKB entry (ExPASy)	Function	Risk allele position or SNP
				Innate immune receptor and cytoplasmic sensor of viral genome. Play role in induction of type I interferons and proinflammatory cytokines	Variant ID: rs2111485
4. Cellular signaling/adaptor proteins/receptors	IL2RA/10p15.1	NC_000010.11	P01589	Interleukin-2 receptor that controls regulatory T cells and immune tolerance	A at position 10: 6098824 Variant ID: rs706779
	CCR6/6q27	NC_000006.12	P51684	Chemotaxis of dendritic cells, T-cells and B-cells. Plays an important role in B-cell differentiation, skin homeostatic and inflammatory response	C at position 6: 167505791 Variant ID: rs6902119
	CLNK/4p16.1	NC_000004.12	Q7Z7G1	Regulation of immunoreceptor signaling. Positive regulator of T-cell receptor and natural killer T cell receptor signaling	C at position 4: 10726853 Variant ID: rs16872571
	SLA/8q24.22	NC_000008.11	Q13239	Adapter protein which negatively regulates T-cell receptor (TCR) signaling	G at position 8: 133929917 Variant ID: rs853308
	SH2B3/12q24.12	NC_000012.12	Q9UQQ2	Adaptor protein that Links T-cell receptor signaling to phospholipase C-gamma-1 and phosphatidylinositol 3-kinase	T at position 2: 111904371 Variant ID: rs4766578
	TICAM1/19p13.3	NC_000019.10	Q8IUC6	Adaptor protein for TLR3, TLR4 and TLR5 to mediate NF-kappa-B activation. Involved in innate immunity and induces apoptosis	T at position 19: 4830628 Variant ID: rs6510827
	TOB2/22q13.2	NC_000022.11	Q14106	Regulator of cell growth, differentiation. Involved in T cell tolerance	G at position 22: 41757647 Variant ID: rs4822024
5. Non-immune genes	OCA2/15q13.1	NC_000015.10	Q04671	Believed to be involved in the transport of tyrosine (melanin precursor) within the melanocyte	C at position 15: 28356859 Variant ID: rs1129038
	TYR/11q14.3	NC_000011.10	P14679	Catalyzes the rate limiting reaction in melanin biosynthesis from tyrosine	G at position 11: 89011046 Variant ID: rs1393350
	MC1R/16q24.3	NC_000016.10	Q01726	Encodes the receptor protein for a melanocyte-stimulating hormone which is important for human pigmentation	A At position 16: 89818089 Variant ID: rs9926296

Proteins were classified into five groups according to their functions. More information about genes and proteins features can be retrieved using the nucleotide NCBI accession number (<https://www.ncbi.nlm.nih.gov/>) and the UniProtKB entry numbers (<https://www.expasy.org/>), respectively. The risk allele position or SNP was retrieved from the NCBI (<https://www.ncbi.nlm.nih.gov/snp/>).

owing to self-antigens that activate T cells. Variations in this region indicate that patients with vitiligo are at a higher risk of developing other autoimmune diseases (Bowcock and Fernandez-Vina, 2012; Hayashi et al., 2016; Jin et al., 2019). PTPN22 increases the risk of vitiligo owing to its effect on protein tyrosine phosphatase, which plays a key role in signal transduction and controls the activity of the T-cell immune system. Affected PTPN22 proteins cause a loss of control of the immune system, which attacks melanocytes in the skin and contributes to vitiligo (Cantón et al., 2005). NALP1 is highly expressed in immune cells, especially in T cells and Langerhans cells.

NALP1 associates with other proteins (ASC, caspase 1 and caspase 5) to form NALP1 inflammasome. This complex activating the pro-inflammatory cytokine IL-1 β (Kummer et al., 2007), which is clearly elevated in vitiligo patients (Tu et al., 2003). XBP1 plays a central role in unfolded protein response (UPR) signaling. Upon the accumulation of misfolded proteins in the ER, the XBP1 mRNA undergoes specific splicing, generating the spliced XBP1 transcription factor (sXBP1), which subsequently translocates to the nucleus and drives the expression of stress-induced inflammatory genes.

3.2 Non-genetic factors in the pathogenesis of vitiligo

Nongenetic factors include environmental factors, alterations in autoimmune responses, and exposure of melanocytes to OS. Autoimmune responses can be divided into two categories: adaptive and innate (Das et al., 2019). In adaptive immunity the CD8 T cells, activated by binding of INF- γ to cytokine receptors, are considered as the most important cytotoxic T-cell inducing melanocyte injury (Wang et al., 2016).

The mechanism by which T-cells inducing melanocyte damage is mediated by binding of INF- γ to cytokine receptors causing JAK (intracellular Janus kinases) activation (Abdou et al., 2018), which will undergo autophosphorylation due to adenosine triphosphate (ATP) help. This cascade causes a conformational change in signal transducers and activators of transcription (STAT) to activate and bind to each other. This activation helps STAT enter the nucleus and induce the transcription of many mediators, which then activate cytokines, such as CXCL9 and CXCL10 (Ala et al., 2015), which are considered the most potent chemokines that activate other cytotoxic T-cells (Wang et al., 2016). The ratio of CD8/CD4 increases in blood samples obtained from vitiligo patients (Kaur et al., 2017), which is directly correlated with the severity and activity of the disease (Rashighi et al., 2014), and is considered a marker of poor treatment response.

3.2.1 Environment

Vitiligo is triggered by a combination of environmental and physical factors that disrupt melanocyte function, leading to skin depigmentation. Chemical compounds, such as phenols, commonly found in gloves, hair dyes, adhesives, and leather products, act as tyrosine analogs (Toosi et al., 2012). These chemicals interfere with melanin production by disrupting the activity of tyrosinase, a key enzyme involved in melanogenesis (Toosi et al., 2012). This disruption generates harmful free radicals known as semi-quinone radicals that induce cellular stress and trigger the UPR (Toosi et al., 2012). Additionally, physical trauma to the skin such as cuts, abrasions, or friction from clothing, sports equipment, or accessories can initiate or exacerbate vitiligo through the Koebner phenomenon (Sagi and Trau, 2011). This process is linked to oxidative or mechanical stress, which impairs the expression of E-cadherin, a calcium-dependent adhesion molecule critical for maintaining the connection between melanocytes and keratinocytes. When E-cadherin function is compromised, melanocytes detach from the epidermis and are lost in a process known as melanocytorrhagy. Together, these factors, including OS, immune responses, and disrupted melanocyte-keratinocyte adhesion, interact to drive vitiligo development and progression (Al-Shobaili and Rasheed, 2015).

3.2.2 Innate immunity

Melanocyte stress dysregulates the innate immune system, which comprises macrophages, natural killer cells (NK cells and white blood cells), and inflammatory dendritic cells (DC). Similar to the adaptive immune system, innate immunity rapidly initiates responses without specific antigen recognition as in the adaptive

immune system (Richmond et al., 2013). Through the activation of pattern recognition receptors (PRRs), such as NOD-like receptors (NLR), which comprise large multiprotein complexes known as inflammasomes. Inflammasomes are responsible for increasing the production and release of pro-inflammatory proteins and cytokines, including heat shock protein (HSP) (Abdou et al., 2013), IL6, and IL8, due to high levels of heat shock protein -70, which can induce inflammatory dendritic cell DC (carry melanocyte-specific antigen to T-cells in the lymph tissue to damage it) (Wang et al., 2014), melanocytes will be damaged, which may cause vitiligo. The destruction of melanocytes through T-cells is considered a cross-link between innate and adaptive immunity.

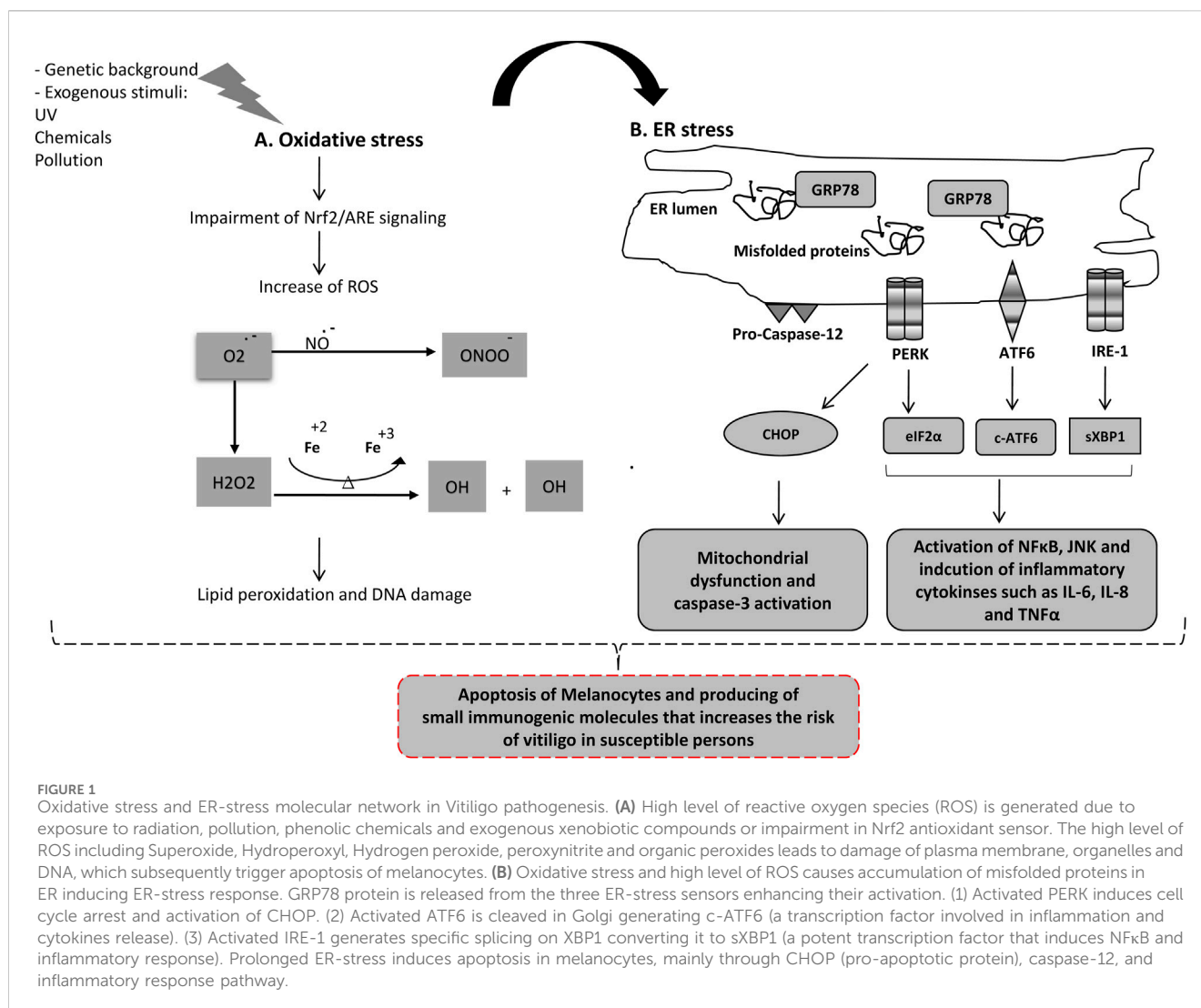
3.2.3 Oxidative stress

Melanocyte cells synthesize proteins according to genetic information from nucleus DNA, this protein (melanin-synthesis related proteins) become functional due to an appropriate oxidative folding process, in which oxidation of sulfhydryl groups to produce disulfide bridges in proteins is the main step to get a mature folded protein. The endoplasmic reticulum catalyzes disulfide bond formation in proteins through a family of chaperones that are responsible for disulfide bond formation (protein disulfide isomerase (PDI)), which uses a molecule of oxygen in oxidative folding; hydrogen peroxide (Alikhan et al.) is produced as a byproduct, and catalase and glutathione peroxidase eliminate it; in this way, ER homeostasis is maintained (Eletto et al., 2014).

However, high level of ROS (Alikhan et al., 2011) and free radicals, which are mainly produced in the mitochondria (which communicated with ER by mitochondrial associated membrane (MAM)), due to some conditions such as, exposure to UV radiation (290–320 nm) and chemicals that have phenolic groups (as monobenzyl ether of hydroquinone) (Canizares et al., 1958). They create OS (high level of hydrogen peroxide, and decrease the level of catalase enzyme and glutathione peroxidase enzyme) (Agrawal et al., 2004), which leads to ER imbalance (Guan et al., 2015), caused by damage to poly unsaturated fatty acids of the cell membrane and break the disulfide bonds in proteins, that cause an accumulation of unfolded proteins in the ER.

The accumulation of misfolded proteins, will exert mitochondrial stress (Dell'Anna et al., 2001), in which nucleus receives a signal and ultimately activates UPR (Harris, 2016), that help reestablish the ER homeostasis by increasing the protein folding capacity of the ER, and decrease the ER protein folding loads. However, prolonged activity of the UPR (indicating that ER stress cannot be managed) leads to cell apoptosis (melanocyte apoptosis in the case of vitiligo) (Malhotra and Kaufman, 2007). Moreover, stressed melanocytes undergo apoptosis and secrete melanocyte-specific antigens and immunostimulatory signals such as cytokines (IL-6 and IL8) (Bettigole and Glimcher, 2015), which attract autoimmune reactions toward melanocytes and cause disease progression (Colucci et al., 2015).

Some vitamins also play a major role in maintaining cellular homeostasis, such as lipophilic antioxidants, tocopherol (vitamin E), vitamin A, vitamin D, and COQ10. Moreover, hydrophilic antioxidants such as ascorbic acid (vitamin C), which stabilizes free radicals due to its delocalization around the chemical rings of vitamins (Jalel et al., 2009).



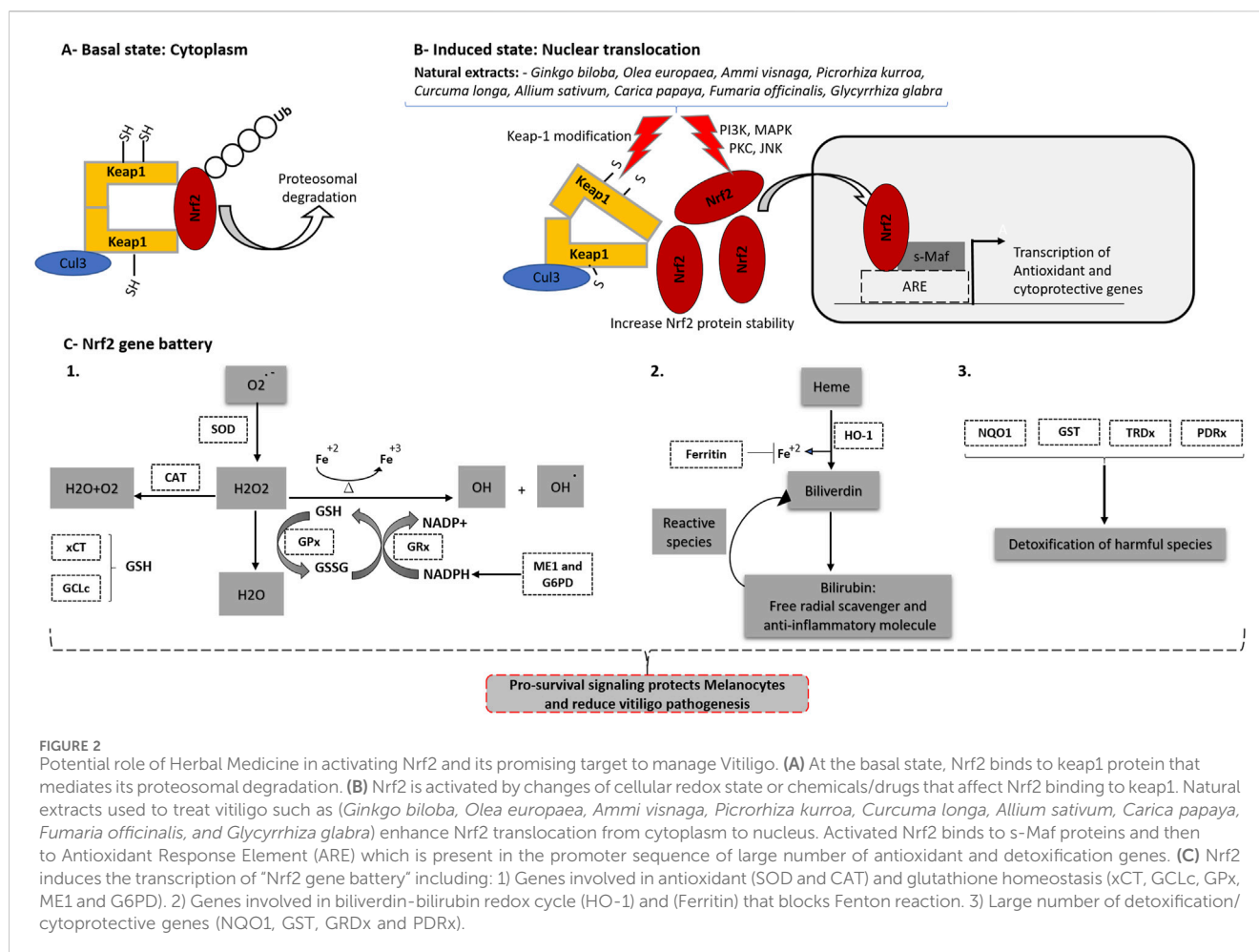
4 Oxidative stress and ER stress: central pathways in vitiligo pathogenesis

Vitiligo is associated with metabolic alterations, increased generation of ROS and increased susceptibility to mild exogenous stimuli in the epidermis. OS is a pathogenic event that affects melanocyte degeneration. OS triggers tissue damage and apoptosis, resulting in the production of small immunogenic molecules and an increased risk of autoimmune disorders in susceptible individuals. Endoplasmic reticulum is responsible for protein folding and is highly sensitive to changes in the cellular redox state. OS, ER stress, and the two events are linked (Figure 1) (Chaudhari et al., 2014; Malhotra and Kaufman, 2007).

ER stress occurs when the ER accumulates unfolded proteins, and cells initiate the UPR pathway. The UPR consists of three main signaling pathways, PERK, IRE-1, and ATF6, that normally bound by a chaperone called Grp78 and are inactive. ER stress results in the recruitment of GRP78 away from the UPR sensors and activates them. Activated PERK, phosphorylates eukaryotic initiation factor 2 (eIF2α) leading to cell cycle arrest and upregulates important transcription factors (ATF4, CHOP and Nrf2). Activated IRE-1 resulted in the

activation of the XBP1 transcription factor. ATF6 is processed in the Golgi to active the cleaved-ATF6 transcription factor. Prolonged ER stress leads to the activation of pro-apoptotic signaling (CHOP is a key player) (Almanza et al., 2019; Hetz, 2012). Chronic ER stress also activates the inflammatory response pathways. All UPR sensors participate in NF-Kappa B activation, increasing cytokine productions (IL-1, IL-6, IL-8, TNF-α and MCP1), activates JNK and induces inflammasome formation (Chaudhari et al., 2014; Garg et al., 2012; Hotamisligil, 2010; Mohan et al., 2019). Notably, UPR sensors are involved in regulating the development, differentiation, activation, cytokine production, and apoptosis of multiple immune cell types, including T cells, B cells, dendritic cells (DCs), macrophages, and myeloid-derived suppressor cells (MDSCs) (Cai et al., 2019; So, 2018).

Several studies have highlighted the important role of the UPR in vitiligo pathogenesis (Passeron and Ortonne, 2012; Rashighi and Harris, 2017; Toosi et al., 2012) and it could be a major link between OS and vitiligo autoimmunity (Manga et al., 2016; Park et al., 2019). Furthermore, single-nucleotide polymorphisms XBP1 in patients with vitiligo illuminate the importance of this pathway in the pathogenesis of vitiligo (Birlea et al., 2011).



5 Nrf2 – Antioxidant response pathway

Oxidative stress is considered as a major event in vitiligo pathogenesis (Chang and Ko, 2023). Nuclear factor erythroid-2 related factor 2 (Nrf2) is an important transcription factor and sensor of the cellular redox state. It belongs to the cap ‘n’ collar (CNC) family and has basic leucine zipper (bZip) domain that facilitates DNA binding (Li and Kong, 2009a). In the absence of stimuli, Nrf2 is tethered to the cytosol by its inhibitory partner, Keap-1 that regulates its binding and degradation through Cul3-ubiquitine ligase complex (Figure 2A). The Keap-1 contains three important domains in which BTB domain is required for homodimerization of Keap-1 and mediates the Cul3-ligase binding. IVR domain contains critical cysteine residues and regulate Nrf2/Keap-1 binding. The Kelch/DGR domain essential for Nrf2 binding (Canning et al., 2015). The classical model of Nrf2 activation involved the direct OS-induced Keap-1 modification (Itoh et al., 2004). Keap-1 contains several cysteine residues, among them, three were extensively studied and confirmed as redox sensitizing-cysteine (Cys151 in BTB domain, Cys273 and Cys288 in IVR domain) (Yamamoto et al., 2008). Under normal state, the thiol group of the cysteine residues are present in their reduced state (-SH), allowing complex with Cul3 and Nrf2, targeting the later for ubiquitination and proteosomal degradation. Oxidative

and electrophilic stress basically modify the cysteine residues state of Keap-1 causes a conformational change and Nrf2 release. The most common modifications occur on Cys151, Cys273 and Cys288 include: (1) S-oxidation generating sulfenic acid (-SOH) and sulfinic acid (-SO₂H) by oxidants (e.g., H₂O₂, sulforaphane and quinone) (2) S-nitrosylation (e.g., nitric oxide), and (3) S-alkylation induced by electrophiles (e.g., 4-octylitaconate and DMF). Furthermore, other post-translation modifications of Keap-1 (glycosylation, phosphorylation, glutathionylation and SUMOylation) is also reported indicating that the type of modifier is critical to determine how Keap-1 is chemically modified and Nrf2 is released (Song et al., 2023). Another model for Nrf2/Keap-1 activation is the indirect Nrf2 phosphorylation by OS-response kinases such as: PKC (Bloom and Jaiswal, 2003), ERK (Buckley et al., 2003), JNK MAP kinase (Keum et al., 2003), PI3K (Kang et al., 2002) and PERK (Cullinan et al., 2003). Upon activation, Nrf2 translocates to the nucleus, binds specifically to the Antioxidant Response Element (ARE) and induces transcription of downstream genes (Baird and Dinkova-Kostova, 2011) (Figure 2B).

Nrf2 regulates plethora of genes called “Nrf2 gene battery” that function together to restore redox homeostasis (Figure 2C). Several high-throughput microarray and CHIP/sequencing profiling approaches have been proposed, and several Nrf2 target gene

candidates have been identified. The first group function in glutathione homeostasis including amino acid uptake transporters (SLC7A11 and SLC6A9), GSH synthesizing enzymes (γ -GCLc and γ -GCLm), GSH metabolizing enzymes that eliminate ROS through GSSG/GSH oxidation-reduction cycle (GPx and GRx) and GSH complementary enzymes such as glutathione transferases (GST). The second group comprises the antioxidant/detoxification enzymes. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme in heme catabolism and is considered the main target of Nrf2 (Qaisiya et al., 2014). Cytoprotection by HO-1 against OS results from the generation of three products: carbon monoxide (CO), biliverdin-bilirubin, and ferrous iron (Fe^{2+}). These have important physiological roles against OS, inflammation, and apoptosis (Pae et al., 2008). The ferritin heavy chain (FTH) effectively sequesters pro-oxidative Fe^{2+} that would otherwise participate in the Fenton reaction (Vile and Tyrrell, 1993). The NADPH quinoneoxidoreductase-1 (NQO1) is a multifunctional flavoprotein capable of reducing or metabolizing a broad range of substrates in a single two-electron step, avoiding the generation of semi-reactive species (Dinkova-Kostova and Talalay, 2010). Superoxide dismutase (SOD) and catalase are essential for ROS elimination. The third group is involved in NADPH production and includes enzymes, such as ME1 and glucose-6-phosphate dehydrogenase. NADPH is an abundant antioxidant that acts as an electron donor for several oxidoreductase cycles, such as the GSSG-GSH cycle, biliverdin-bilirubin cycle, and the NQO1 detoxification process (Malhotra et al., 2010; Tonelli et al., 2018). Beside its classical role in regulation of the cellular antioxidant and detoxification processes, Nrf2 cross-talk with NF- κ B which is major regulator of inflammation and immune response (Barnabei et al., 2021). Nrf2 knockout animal models showed an increase in NF- κ B activity and upregulation of its downstream target genes (such as TNF- α , IL-1 β and IL-6 production) confirming the negative interplay between Nrf2 and NF- κ B (Gao et al., 2021).

5.1 Nrf2 signaling is impaired in vitiligo

The dysfunction of Nrf2 signaling is significant to vitiligo pathogenesis. Jian et al., shows that melanocytes from vitiligo patients have impaired Nrf2-ARE signaling, reduced Nrf2 translocation to nucleus, decreased induction of HO-1 antioxidant genes and lower activity of SOD and GPx (Jian et al., 2014). Knockdown of Nrf2 reduces melanocyte viability but not the viability of keratinocytes and fibroblasts, indicating that melanocytes are preferentially dependent on Nrf2 (Arowojolu et al., 2017). HO-1 suppresses T cell proliferation by inhibiting IL-2 production (Pae et al., 2004). The lower levels of HO-1 in patients with vitiligo are correlated with higher serum levels of IL-2, suggesting that serum HO-1 can be used indirectly to assess the antioxidant capacity of patients with vitiligo (Jian et al., 2014). Furthermore, serum bilirubin levels (the final product of HO-1) are significantly lower in vitiligo patients (Turkmen, 2020). Interestingly, genetic studies on the Han Chinese population have shown that variations in Nrf2 are associated with susceptibility to vitiligo (Guan et al., 2008; Song et al., 2016). In contrast, several studies demonstrated

that the Nrf2/HO-1 axis could be exploited as a therapeutic strategy to counter oxidative damage in melanocytes and treatment of vitiligo (Gęgotek and Skrzydlewska, 2015). Keap-1 siRNA and Nrf2 activation protects melanocyte cell lines from oxidative damage (Jian et al., 2011). On the contrary, Nrf2 downregulation increases H_2O_2 -induced melanocytes toxicity (He et al., 2017). Induction of HO-1 in cultured melanocytes from vitiligo patient was able to reduce cell death (Ellassiuty et al., 2011). Melanocytes treated with curcumin (an Nrf2 inducer) showed a reduced apoptosis and high level of NQO-1 Nrf2-target genes (Ellassiuty et al., 2011; Fang et al., 2020; Gęgotek and Skrzydlewska, 2015; He et al., 2017; Jian et al., 2011; Natarajan et al., 2010). Vitiligo melanocytes treated with H_2 induces Nrf2 and revers H_2O_2 -induced cell apoptosis (Fang et al., 2020; Fang et al., 2020). All these data and many others confirmed the crucial role of Nrf2 activation in protecting melanocytes from oxidative damage.

6 Management of vitiligo

No treatment ensures a complete cure for vitiligo owing to its complex and multifactorial pathogenesis (Cai et al., 2019). However, different methods of vitiligo management exist for stabilizing and repigmenting lesions. These include medical drugs (topical or systemic corticosteroids, topical immunomodulators, and vitamins), phototherapy, surgical techniques, lasers (Bleuel and Eberlein, 2018), and medicinal plants owing to their immunomodulatory and antioxidant properties. However, combination therapy may be more successful than monotherapy.

6.1 Therapeutic options in vitiligo management

Topical corticosteroids, immunomodulators, and phototherapy are effective in stable and localized cases. However, in cases of generalized rapid progression, oral corticosteroids are required to decrease disease progression.

Topical corticosteroids seem to be the first option for the treatment of vitiligo owing to their anti-inflammatory and immunosuppressive effects, which decrease the spread and progression of the disease, and have clear repigmentation effects on the face and neck, especially in recent lesions. However, the course of treatment should be at least 6 months to obtain good results, which may have side effects, including skin atrophy, telangiectasia (spider vein, dilation of blood vessels), and acneiform eruptions (in this case, it is advisable to switch to topical immunomodulators).

Tacrolimus is considered a prototype immunomodulatory drug because it inhibits calcineurin synthesis, decreases T-cell activity, and induces the production of proinflammatory cytokines. However, it also increases melanocyte migration and pigmentation. As mentioned for topical corticosteroids, topical tacrolimus also has an evident result, especially on the face, and it could be an alternative to topical corticosteroids in some cases, such as acneiform eruption, or when topical corticosteroids show no sign of recovery on the face (Choi et al., 2008).

TABLE 3 List of herbal medicine used in management of Vitiligo and their mechanism of action.

Latin Name	Family	Common Name	Part used	Form of Extracts Mechanism of Action	References
<i>Ginkgo biloba</i>	Ginkgoaceae	Ginkgo	Leaves	Protects human melanocytes from H ₂ O ₂ -induced oxidative stress by activating Nrf2 Extracts orally (40 mg) effective for arresting the progression of the disease in human	Liu et al. (2007), Parsad et al. (2003), Zhang et al. (2019)
<i>Olea europaea</i>	Oleaceae	Olive	Fruits	Antioxidant Oleuropein, oleocanthal and oleacein (OC) activate melanogenesis pathway in B16F10 cells and human epidermal melanocytes Oral OLE extracts (100 and 200 mg/kg) induce Nrf2/ARE pathway in rats kidney tissues	ALHaithloul et al. (2019), Cho et al. (2024), Nikiforidis et al. (1993)
<i>Cucumis melo</i>	Cucurbitaceae	Muskmelon	Fruits	Antioxidant due to SOD and catalase content Prevent melanocyte destruction	Buggiani et al. (2012), Gianfaldoni et al. (2018), Schallreuter et al. (2011)
<i>Ammi visnaga</i>	Apiaceae	Khella	Leaves	Visnagin upregulates antioxidant and anti-inflammatory genes Khellin (orally/topically) induces skin repigmentation in vitiligo patients Promotes melanocyte viability and reduces toxicity Extracts and visnagin induce Nrf2/ARE pathway	Arowojolu et al. (2017), Di Nardo et al. (2019), Ortel et al. (1988), Pasari et al. (2019)
<i>Picrorhiza kurroa</i>	Plantaginaceae	Kutki	Roots	Improve repigmentation in vitiligo patients Decrease the oxidative stress in macrophages cells Immunomodulatory effects anti-inflammatory Extracts induce Nrf2/ARE pathway	Bedi et al. (1989), Pasari et al. (2019), Soni and Grover (2019)
<i>Camellia sinensis</i>	Theaceae	Green tea	Leaves	Decrease oxidative stress in lymphocytes cells Antioxidant and anti-inflammatory due to the compound epigallocatechin-3-gallate (EGCG) in mice model of vitiligo	Ning et al. (2015), Zhu et al. (2014)
<i>Capsicum annuum</i>	Solanaceae	Chili pepper	Fruits	Capsaicin (10 mM for 24) has anti-inflammatory and antioxidant in keratinocytes from perilesional vitiligo skin Capsaicin (10 mM for 24) increases ERK phosphorylation in keratinocytes from perilesional vitiligo skin	Becatti et al. (2010), Males et al. (2019)
<i>Curcuma longa</i>	Zingiberaceae	Turmeric	Roots	Antioxidant (induces HO-1 expression in mouse epidermal JB6 cells) Curcumin inhibits melanocytes apoptosis by increasing ERK phosphorylation Anti-inflammatory Curcumin (10 µM) inhibits ferroptosis by regulating the Nrf2/HO-1 pathway to protect melanocytes Curcumin (1 µmol topically) increased Nrf2 protein expression <i>in vivo</i> in mice model and in mouse epidermal JB6 cells)	Ashrafizadeh et al. (2020b), Gupta et al. (2013), Liu et al. (2024), Shin et al. (2020), Yang et al. (2024)
<i>Allium sativum</i>	Amaryllidaceae	Garlic	Bulbs	Antioxidant Enhance natural killer's cell and lymphocyte activated killer cell activity Extracts (allicin) induce Nrf2/ARE pathway	Boo (2020); Eudy et al. (2017), Zhao et al. (2019)
<i>Phlebodium aureum</i>	Polypodiaceae	Golden polypody	Radical Leaves	Induces repigmentation when combined with phototherapy Activates Nrf2 pathway mice model Immunomodulatory activity Lowering hypothalamic oxidative stress and inhibiting polyclonal proliferation of mononuclear cells induced lymphocyte tissue	Chaiprasongsuk and Panich (2022), Males et al. (2019)
<i>Carpobrotus edulis</i>	Aizoaceae	Hottentot-fig	Leaves	Anti-inflammatory (inhibit lipoxygenase enzyme) Reduce oxidative stress <i>in vitro</i>	Bazzicalupo et al. (2021), Mulaudzi et al. (2019), Oliveira et al. (2024), Trigui et al. (2023), Zarrouk et al. (2019)

(Continued on following page)

TABLE 3 (Continued) List of herbal medicine used in management of Vitiligo and their mechanism of action.

Latin Name	Family	Common Name	Part used	Form of Extracts Mechanism of Action	References
				Reduce the DNA damage in H ₂ O ₂ -induced oxidative damage in HepG2 and Caco-2 cells	
<i>Carica papaya</i>	Caricaceae	Papaya	Fruit	Anti-inflammatory Increase the expression of antioxidant enzymes (GPx1 and GSH) in HepG2 Cells Extracts induce Nrf2/ARE pathway	Jarisarapurin et al. (2019), Nxumalo et al. (2024), Polat et al. (2008)
<i>Osmium basilicum</i>	Lamiaceae	Basil	Leaves	Anti-inflammatory in in vivo mouse model Reduce oxidative stress Decrease concentration of Cu while reduce cell damage	Kamelnia et al. (2023), Rodrigues et al. (2016), Sun et al. (2006)
<i>Juglans regia</i>	Juglandaceae	Walnuts	Fruit	Reduce oxidative stress Elevate CAT and SOD levels in mice model Activate the PI3K/Akt/Nrf2 signaling pathway in mice model	Chen et al. (2024), Jahanban-Esfahlan et al. (2019)
<i>Vitex agnus-castus</i>	Lamiaceae	Chaste tree	Seeds	Anti-inflammatory (decreases expression of IL-1 β and IL-17A) Vitexin protects human melanocytes from oxidative stress by activating MAPK-Nrf2/ARE Reduce oxidative stress Promoted melanocytes proliferation	Di Nardo et al. (2019), Li et al. (2020)
<i>Raphanus raphanistrum</i>	Brassicaceae	Radish	Seeds	Anti-inflammatory Reduce oxidative stress due to quercetin content	Iyda et al. (2019), Pang et al. (2021)
<i>Vernonia anthelmintica</i>	Asteraceae	Ironweed	Seeds	Promote melanogenesis Upregulate SOD and tyrosinase activity Reduces oxidative stress Upregulated the expression levels of Nrf2, HO-1, and NQO1 genes and proteins in human immortalized epidermal cells	Aobuli et al. (2018), Eibulayin et al. (2024), Lai et al. (2021), Zhong et al. (2019)
<i>Scutellaria baicalensis</i>	Lamiaceae	Baikal skullcap	Roots	Baicalein enhances cellular antioxidant defense in human vitiligo melanocytes Activates Nrf2 pathway	Ma et al. (2018)
<i>Glycyrrhiza glabra</i>	Fabaceae	Liquorice	Roots	Anti-inflammatory (inhibit IL-17 <i>in silico</i>) Reduce the DNA damage in Triptolide/H ₂ O ₂ -induced oxidative damage in HepG2 cells and melanocytes Induces Nrf2/HO-1 pathway	Cao et al. (2017), Kausar et al. (2023), Mou et al. (2019)
<i>Pyrostegia venusta</i>	Bignoniaceae	Flame vine	leaves	Topical (10%) and oral (300 mg/kg) administration induces repigmentation in mice models Anti-inflammatory (topical and oral administration decreases TNF- α in mice models of vitiligo)	Moreira et al. (2015)

Phototherapy, which includes ultraviolet A and B, is an efficient way to induce repigmentation in vitiligo owing to its ability to produce melanin and induce the differentiation of melanocytes (Farag et al., 2019). Patients should be aware of the treatment duration, expected results, and side effects of phototherapy (Esmat et al., 2016). This treatment results in partial repigmentation in the majority of cases, instead of complete repigmentation, which appears in only one or two cases, and is treated for 12 months by narrow-band UVB (NA-UVB), which is the best choice for phototherapy (Bordere et al., 2009). Nonetheless, the risk of vitiligo in repigmented skin after the discontinuation of therapy (relapse) has also been found; therefore, topical tacrolimus should be used after stopping phototherapy to decrease the risk of recurrent lesions (Bleuel and Eberlein, 2018).

Dexamethasone (2.5–10 mg) is an oral corticosteroid used in vitiligo treatment as an immunosuppressant and anti-inflammatory agent, and when administered twice weekly, it can prevent the progression and spread of disease (Dellatorre et al., 2020). However, common side effects of corticosteroids, such as weight gain, hypertrichosis (abnormal hair growth over the body), acne, and menstrual disturbances, occur during the treatment period, which limit the use of these drugs.

The combination of UVB and topical therapies, including dexamethasone or immunomodulators, is more effective at reducing disease progression and achieving rapid repigmentation (Dellatorre et al., 2020), than monotherapy alone. However, it is necessary to be careful about the long-term side effects of UVB in combination with systemic immunosuppressants or steroids.

6.2 Herbal medicine and natural product in management of vitiligo

The involvement of traditional medicine in vitiligo management has received considerable attention over the past 2 decades. This is largely due to the fact that vitiligo - until now - has no cure and herbal medicine or their purified natural compounds could provide safe alternative/supportive therapy for vitiligo in conjunction with existing pharmacological drugs (Table 3). Among the several herbal drugs implicated in the treatment of vitiligo are *Ginkgo biloba* and *Vernonia anthelmintica*—Chinese herb— (Pang et al., 2021; Zhang et al., 2019). In cell culture and animal models, both plants consistently exhibited melanogenesis and antioxidant capacity comparable to those of the positive controls (Huo et al., 2017; Lai et al., 2021; Zhang et al., 2019). In a recent study by Li et al., 2009 the ethanolic extracts of *V. anthelmintica* seeds (0.5 mg/mL) significantly promoted melanogenesis in B16 murine melanoma cells (Lai et al., 2021). However, in hydroquinone-induced vitiligo in mice, Butin (3',4',7'-Trihydroxyflavan-4-one) – major compound in the seed of *V. anthelmintica*—administration (4.25 and 45.5 mg/kg) significantly increases the basal layer melanocytes and melanin-containing epidermal cells (Huo et al., 2017). Lai et al. (2021) further confirmed previous findings on butin. In their study, butin (40 µmol/L) is reported to induce melanin production in B16 murine melanoma cells and in H₂O₂-induced zebrafish model at a concentration of 10, 40, 80 and 100 µmol/L (Lai et al., 2021). Another compound extracted from *V. anthelmintica*, cynarine (1,5-Dicaffeoylquinic acid) induced increased melanogenesis in B16 murine melanoma cells (Mamat et al., 2018). Although several studies using *in vitro* and *in vivo* models have implicated the role of *V. anthelmintica* and its derived metabolites in anti-vitiligo, no clinical studies have been conducted to confirm its effects on humans.

Ginkgo biloba is one of the few plants marketed in some countries owing to its ability to slow disease progression in humans with no side effects (Parsad et al., 2003; Szczurko et al., 2011). Two independent studies have consistently implicated *G. biloba* extract in slowing the progression of vitiligo in humans (Parsad et al., 2003; Szczurko et al., 2011). In Canada, in patients with vitiligo (n = 11), ingestion of 60 mg of *G. biloba* extract twice daily for a period of 12 weeks has been associated with a significant improvement, as assessed by measuring vitiligo area scoring index (VASI) and vitiligo European task force (VETF) spread (Szczurko et al., 2011). However, in another clinical study involving patients with gradually progressive (slow-spreading) vitiligo (focal, vulgaris, and acrofacial) divided into two groups, group A (receiving *G. biloba* extract 40 mg three times daily) and group B (receiving placebo). The progression of vitiligo in patients receiving *G. biloba* extracts (n = 27) was arrested in twenty patients and skin repigmentation was observed in ten patients. However, compared with placebo treated patients (n = 22) the progression of vitiligo was observed on only five patients with only two patients showed skin repigmentation (Parsad et al., 2003).

Consistent with the protective evidence implicating *G. biloba* extract (EGB761, standardized extract of dried leaves of *G. biloba* containing 24% ginkgo-flavonol glycosides, 6% terpene lactones such as ginkgolides A, B, C, J and bilobalides) as anti-vitiligo, applying EGB761 extracts (100 µg/mL) have also protected

human melanocyte cells pretreated with H₂O₂-induced OS and apoptosis. This protective effect has been associated with the activation of the Nrf2 pathway (Zhang et al., 2019). This effect has also been reported for baicalein (a flavonoid extracted from *Scutellaria baicalensis*), bilobides (terpenoid constituents of *Ginkgo biloba* extract), and methylcobalmine (activated forms of vitamin B12) (An et al., 2021; Lu et al., 2016; Ma et al., 2018).

Ammi species positively reduce vitiligo symptoms by inducing skin repigmentation in humans (Sidi and Bourgeois-Gavardin, 1952). The use of *Ammi majus* by older Egyptians for the treatment of skin conditions was supported by Sidi et al., in 1952. In a previous study, *A. majus* oral (tablet-containing Ammoidin 10 mg and Ammidin 5 mg—main active constituent in *A. majus*) and topical (Ammoidin and Ammidin, 7 and 2 mg/mL, respectively) administration followed by sun exposure or a combination of oral and topical administration caused remarkable skin repigmentation in all six patients tested, irrespective of the method of administration (Sidi and Bourgeois-Gavardin, 1952) although some reversible side effects such as skin burning were observed (Sidi and Bourgeois-Gavardin, 1952). These findings have triggered further research to identify safer options for *Ammi* species. *Ammi visnaga*, commonly known as Khella, was tested for its activity in the treatment of vitiligo *in vivo* by Egyptian scholars in 1982 (Abdel-Fattah et al., 1982). Khellin, the main active constituent of *A. visnaga*, administered orally (100 mg/day) for 4 months followed by exposure to sunlight for 15 min (45 min after khellin administration) effectively and variably induced stable skin repigmentation in 23 individuals out of 30 (Abdel-Fattah et al., 1982). In later clinical studies, administration of khellin, either orally or topically, followed by ultraviolet A or sunlight exposure, consistently achieved more than 70% skin repigmentation with minimal and often no side effects typically associated with other furanocoumarins present in *A. visnaga* (Orecchia and Perfetti, 1992; Ortel et al., 1988). Visnagin (an analog of khellin) has been reported to upregulate the Nrf2 pathway in rat models, attenuating OS (Abukhalil et al., 2021). Moreover, in *in vitro* model involving acinar cells, visnagin enhances expression Nrf2 leading to reduced inflammation in acute pancreatitis (Pasari et al., 2019). Although *A. visnaga* seems to have a positive impact on vitiligo, the underlying molecular mechanisms, targets, and markers, unlike *G. biloba*, are yet to be identified and require further investigation despite the involvement of the Nrf2 pathway.

Picrorhiza kurroa rhizomes (Scrophulariaceae) promote skin repigmentation in humans, likely due to their immunomodulatory and anti-inflammatory activities (Bedi et al., 1989). Administration of 200 mg *P. kurroa* rhizome capsules (picrolex) twice daily as a supplement with methoxsalen (a furanocoumarin drug), followed by exposure to light, significantly eliminated the vitiligo patches in 27 of the 30 patients involved in the study (Bedi et al., 1989). Although the underlying molecular pathways remain unclear, recent studies have implicated picrosides (iridoid glycosides in *P. kurroa* extracts) in activating Nrf2 pathways, leading to the increased expression of detoxifying enzymes (Soni and Grover, 2019).

Curcuma longa (turmeric) has been the subject of many dermatological studies because of its overwhelmingly positive impact on skin health and vitiligo (Guarneri et al., 2021; Jalalmanesh et al., 2022; Schallreuter and Rokos, 2006; Vaughn et al., 2016). In a recent clinical trial involving 30 patients with mild

to moderate vitiligo, turmeric cream application twice daily for 4 months reduced lesion size and skin pigmentation compared to the placebo group (Jalalmanesh et al., 2022). Several topical turmeric-based formulations have been developed and marketed in various countries (Narayanaswamy and Ismail, 2018). Turmeric exerts antivitamin effects through several mechanisms. Turmeric is demonstrated to inhibit the production of several key inflammatory cytokines such as IL-1, TNF- α promoting melanocytes death (Singh et al., 2021). Turmeric also reduced the OS associated with vitiligo pathogenesis. Curcumin, the main active constituent of turmeric, scavenges free radicals, increases the expression of antioxidant enzymes, and modulates Nrf2 expression by regulating antioxidant responses.

6.2.1 Plants contribute to reduced oxidative stress in vitiligo management

Antioxidants are substances that can prevent or inhibit damage to cells caused by free radicals that the body produces in response to environmental stress or other pressures (Basilicata et al., 2019). Antioxidants can be extracted from many herbs and plants, affect OS in vitiligo, and have been used either alone or in combination with sunlight/ultraviolet light (UV), which removes free radicals by donating an electron that protects the cells and organ systems of the body from OS by against free radical (Zhong et al., 2019). Cells naturally produce antioxidants such as glutathione peroxidase and catalase, which protect mitochondria from stress (Hosseinizadeh et al., 2019). Sometimes, the body cannot create antioxidants on its own, which can come from several different sources, such as plants in dietary supplements, and some antioxidants do not remove free radicals but enhance endogenous activity that may be classified as antioxidants (Mothana et al., 2019).

The most efficient enzymatic antioxidants are catalase, glutathione peroxidase (GPx) and superoxide dismutase (SOD). Non-enzymatic antioxidants include vitamins E and C, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), melatonin, carotenoids, and natural flavonoids (Nandi et al., 2019). Plants used in vitiligo management, such as *Ginkgo biloba*, *Olea europaea*, *Cucumis melo*, *Camellia sinensis*, *Allium sativum*, *Carpobrotus edulis* (Di Nardo et al., 2019), exhibit different mechanisms of direct and indirect antioxidant activity (Table 3; Figure 2).

6.2.2 Plants contribute to immune modulation in vitiligo management

Anti-inflammation refers to the paraphernalia of substances that reduce swelling or inflammation (Khan et al., 2019). Many bioactive compounds extracted from plants and herbs exhibit anti-inflammatory activities and are used to manage vitiligo (Mihaila et al., 2019). Recently, many herbal remedies have been prescribed for vitiligo patients (Kim et al., 2019), for example, *Ammi visnaga*, *Picrorhiza kurroa*, *Capsicum annuum*, *Curcuma longa*, *Phlebodium aureum*.

6.2.3 Plants induces Nrf2 pathways: a promising therapeutic agents to treat vitiligo

At molecular level, Nrf2 causes wide spectrum of responses that inhibits the progression of vitiligo pathogenesis including: (1) The coordinated upregulation of antioxidant and detoxification genes.

(2) It inhibits the pro-inflammatory cells (T helper 1 and T helper 17) and activates immunosuppressive regulatory cells (T reg and T helper). (3) It plays a crucial role in counteracting NF- κ B-inducing inflammatory response. (4) It reduces ER-stress (Cuadrado et al., 2018; Sarcinelli et al., 2020; Surh and Na, 2008). Furthermore, the availability of numerous natural and synthetic Nrf2 inducers isothiocyanate (sulforaphan), polyphenols (curcumin and resveratrol), flavonoids (Quercetin and kaempferol), and terpenoids (Carnosic acid) is one of the major advantage for targeting this pathway (Wang et al., 2024).

Interestingly, many herbal medicinal plants used to treat vitiligo have been implicated in inducing the Nrf2 pathway and related genes. This mechanism may partially explain their use in the management of vitiligo through the reduction of oxidative damage. Plants consistently demonstrate activation of the Nrf2 pathway, including *Ginkgo biloba*, *Olea europaea*, *Ammi visnaga*, *Picrorhiza kurroa*, *Curcuma longa*, *Allium sativum*, *Carica papaya*, *Fumaria officinalis*, *Paeonia lactiflora* and *Glycyrrhiza glabra* (Table 3). *Ginkgo biloba* extract induces Nrf2 mainly thorough the disruption of Keap1-Nrf2 interaction decreasing the content of Keap1 and releasing more Nrf2 to nucleus (Liu et al., 2007). It's worth noting that *Ginkgo biloba* extract contains bioactive flavonoids and terpenoids that act as mild electrophiles that disrupt keap1-Nrf2 interaction (Noor et al., 2022).

Olea europaea is rich with polyphenolic compounds such as oleacin, oleuropein and hydroxytyrosol that mediate keap-1 degradation and Nrf2 release (Zhou et al., 2019). Hydroxytyrosol is also reported to induce Nrf2 in PI3K dependent manner (Martín et al., 2010). Benolea® is a standardized dry olive leaf extract that is suggested as a pro-pigmenting agent for vitiligo treatment in range of concentration between 10 and 200 μ g/ml (Goenka and Simon, 2021). *Ammi visnaga* extract contains bioactive compounds such as khellin and visnagin that are able to induce Nrf2 and downregulate keap-1 (Table 3) (Abukhalil et al., 2021). The extract is also rich with phenolic compounds and flavonoids that may affect keap-1-Nrf2 association (Khalil et al., 2020). Activation of Nrf2 pathway by *Picrorhiza kurroa* is reported to be mediated through signal transduction kinases (MAPK, PKC and PI3K) (Soni and Grover, 2019). Different mechanisms were reported for Nrf2 activation by *Curcuma longa* extract including the improvement of Nrf2 translocation, keap-1 inhibition and affecting upstream signaling modulators of Nrf2 (Ashrafizadeh et al., 2020a). Although, *Allium sativa* extract is rich with direct antioxidants, studies demonstrated its potent ability to induce the endogenous antioxidant machinery of Nrf2 by enhancing its phosphorylation (by PKC and p38 MAPK) and decreasing its ubiquitination (Capasso, 2013). *Allium sativa* extracts contain allicin, diallyl disulfide and diallyl trisulfide that are able to modify directly the Cys288 of keap-1 (Kim et al., 2014). *Carica papaya* extract stimulates Nrf2 in a mechanism that depends on the interaction of the *Carica papaya* flavonoids with the Nrf2 binding pocket of keap-1, leading to release of Nrf2 and its nuclear accumulation (Kumar et al., 2024). *Fumaria officinale* contains bioactive fumaric acid derivative, isoquinoline alkaloids and high level of polyphenols (Ahmoda et al., 2025). Fumaric acid derivatives activate Nrf2 via S-alkylation of keap-1 and nuclear exit of the Nrf2 repressor (Bach1) (Ahuja et al., 2016). *Paeonia lactiflora* extract (mainly Paeoniflorin (PF)) induces Nrf2/HO-1 signaling pathway by JNK phosphorylation and may serve as a

potential therapy for vitiligo. Pf pretreatment of melanocytes with 50 μ MPF significantly reduced cell death and suppressed oxidative damage (Lu et al., 2024; Yuan et al., 2020).

Glycyrrhizin (GR) is a triterpenoid extracted from *Glycyrrhiza glabra*. GR (at 1 mM) protects melanocytes from high dose of 0.5 mM H_2O_2 by induces Nrf2/HO-1. GR generates a mild electrophilic stress that leads to modifying cysteine residues of keap-1 (Mou et al., 2019). Other studies showed that GR activates Nrf2 by stress response kinases (PI3K/AKT) (Aqeel et al., 2025). It is worth noting that the type of cells and the model used is important to determine the appropriate concentration of the extract and its outcome on the Nrf2/keap-1 signaling.

The Nrf2 inducers have been a subject of many clinical trials, dimethyl fumarate (DMF) is now in clinical use to treat the skin disorder “psoriasis” (Cuadrado et al., 2018; Robledinos-Antón et al., 2019). The DMF protects healthy and vitiligo melanocytes against monobenzene-induced toxicity via Nrf2 activation, demonstrating its therapeutic potential in vitiligo treatment (Arowojolu et al., 2017). Future clinical studies is needed to investigate the use of the herbal medicine extracts in the treatment of vitiligo, focusing on the potential role of Nrf2.

7 Conclusion

Complementary herbal therapies have gained attention as an adjunct approach in treatment of vitiligo. Herbal treatments offer potential synergistic effects when combined with standard treatments, thereby enhancing outcomes while minimizing adverse reactions.

This study suggests that many plants play promising roles in the management of vitiligo. These plants function through two primary mechanisms: immunomodulation and antioxidation. Immunomodulatory plants, such as *Ginkgo biloba*, *Ammi visnaga*, *Capsicum annuum*, *Curcuma longa*, *Carica papaya*, and *Vitex agnus-castus*, support immune regulation, potentially reducing the autoimmune response that contributes to vitiligo. In contrast, plants with antioxidant properties, including *Olea europaea*, *Cucumis melo*, *Ocimum basilicum*, *Juglans regia*, *Camellia sinensis*, *Raphanus raphanistrum*, *Phlebodium aureum*, and *Carpobrotus edulis* help neutralize OS, which is known to play a role in pigment cell damage. Moreover, many herbal plants influence OS response pathways, including the Nrf2 pathway, which protects melanocytes against oxidative damage. The Nrf2 pathway regulates the expression of various antioxidant genes, helping restore cellular balance by enhancing antioxidant defenses and reducing OS. This pathway is particularly relevant to vitiligo, as oxidative damage to melanocytes and pigment-producing cells contributes to depigmentation. Nrf2 controls the expression of some cytoprotective genes, including those encoding antioxidant enzymes such as HO-1, GST, and NQO1. Several Mediterranean herbs contain bioactive compounds that naturally activate Nrf2 and can be effective in managing vitiligo (Lu et al., 2022). For example, rosmarinic acid from *Rosmarinus officinalis* (rosemary) and carnosic acid from *Salvia officinalis* (sage) have been shown to activate Nrf2 and upregulate downstream antioxidant genes (Hu et al., 2023; Lu et al., 2022). Similarly, apigenin from *Petroselinum crispum* (parsley) and thymol from *Thymus vulgaris* (thyme) also

modulate oxidative pathways via Nrf2 activation (Ren et al., 2024; Zhang et al., 2020). By targeting Nrf2, these phytochemicals enhance the skin's endogenous defense mechanisms, reduce oxidative damage, and create a protective environment for melanocyte survival. Therefore, local Mediterranean herbs represent a promising natural source of Nrf2 activators in the development of adjunct therapies for vitiligo and may explain why incidence of vitiligo in the Mediterranean region remains less than other parts of the world.

Author contributions

AQ: Writing – review and editing, Investigation, Writing – original draft, Supervision, Data curation, Conceptualization, Project administration. MQ: Data curation, Validation, Investigation, Writing – review and editing, Writing – original draft. AI: Conceptualization, Writing – original draft, Investigation, Data curation. DK: Data curation, Conceptualization, Writing – original draft, Investigation. SS: Data curation, Investigation, Writing – original draft, Conceptualization. SF: Writing – review and editing. DH: Writing – review and editing. HS: Writing – review and editing. AK: Writing – review and editing, Writing – original draft.

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Conflict of interest

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