

# Statins Role in Vitiligo: A Mini-Review

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## Abstract

Vitiligo is a chronic acquired disease of pigmentation disorder. Melanocytes damage and hypopigmentation relate to the induction of oxidative and autoimmune disorders. Different previous studies illustrated the possible role of statins in the treatment of different types of vitiligo. Therefore, objective of this study was to elucidate the role of statins in the management of vitiligo. In general, an endeavor of this study article was to present a mini-review regarding the potential therapeutic effect of statins in the therapy of vitiligo. Results of the present study illustrated that statins inhibit the production of interferon gamma, expression of major histocompatibility complex, and T-cells activation in patients with active vitiligo. Statins have significant anti-inflammatory and immune-modulating activities in different modalities of vitiligo. Statins, have a potential effect against oxidative stress through the activation of anti-oxidant capacity and reduction of ROS in human melanocytes by upregulation of nuclear erythroid 2-related factor in the melanocytes. Statins improve melanogenesis in melanocytes through increasing tyrosinase mRNA production and augment the stimulatory effect of  $\alpha$ -melanocyte-stimulating hormone from the pituitary gland on the melanocytes. Finally, statins therapy may produce significant inhibition of inflammatory reactions through the inhibition of chemokines. In conclusion, this study highlighted the potential role of statins in the treatment of vitiligo either systemic or localized through significant suppressions of oxidative stress, autoimmunity, and inflammatory reactions. Bidirectional effects of statins on oxidative and autoimmunity/inflammatory pathway making it as a novel therapy for vitiligo.

**Keywords:** Autoimmunity, melanocytes, statins, vitiligo

## INTRODUCTION

Vitiligo is a chronic acquired disease with genetic susceptibility of pigmentation disorder, due to the destruction of skin melanocytes leading to hypopigmentation. Besides, vitiligo may involve other organs that contain melanocytes such as the inner ear, mucous membrane, and eyes, which could explain the associations between vitiligo with hearing loss and autoimmune diseases.<sup>[1]</sup> The incidence of vitiligo is 1% worldwide, and it occurs at any age, but 80% more under the age of 30, affect both sex equally.<sup>[2]</sup> It has been reported that the pathogenesis of vitiligo is linked to the three main theories, which are the followings:

### Biochemical and oxidative stress theory

Melanocytes damage and hypopigmentation relate to the induction of oxidative. The highest concentration of free radical and reduction of body anti-oxidant capacity is associated with melanocytes injury and the incidence of vitiligo. Besides, the

level of hydrogen peroxide ( $H_2O_2$ ) is increased in patients with vitiligo due to oxidative stress injury.<sup>[3]</sup> In addition, Hazneci *et al.*, the study found that nitric oxide synthase (NOS) and nicotinamide adenine dinucleotide phosphate oxidase are elevated in vitiligo.<sup>[4]</sup> Similarly, high catecholamine levels are associated with melanocytes injury due to the upregulation of monoamine oxidase A, sympathetic activation, and activation of hypothalamic-pituitary-adrenal axis.<sup>[5]</sup> The reduction of melanin production is also caused by high levels of 6-tetrahydrobiopterin (6-BHP) which inhibits phenylalanine hydroxylase, leading to the reduction of L-tyrosine and then melanin biosynthesis.<sup>[6]</sup>

### Adhesion theory (melanocytorrhagy)

Adhesion defects of melanocytes lead to migration of melanocytes through the epidermal basal layer, causing T-cells

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activation by melanocytes auto-antigens and subsequent melanocytes injury and hypopigmentation.<sup>[7]</sup> Remarkably, Ricard *et al.* illustrated that discoidin domain receptor-1, which is an adhesion molecule of melanocytes is diminished in vitiligo.<sup>[8]</sup>

### Autoimmune theory

Vitiligo is associated with different autoimmune disorders, including alopecia, Hashimoto thyroiditis, Addison disease, and polyglandular syndrome.<sup>[9]</sup> Autoantibodies against melanocytes and tyrosinase enzyme are detected in 10% of vitiligo patients. As well, VIT40, SOX transcription factor, and tyrosinase are regarded as melanocytes target antigens for different autoantibodies.<sup>[10]</sup> Besides, cytotoxic T-lymphocytes against melanocytes are increased in patients with vitiligo, highlighting the role of cell-mediated immunity in the pathogenesis of vitiligo. Moreover, regulatory T-cells are reduced in the blood that increases the risk of melanocytes damage by the cytotoxic T-lymphocytes.<sup>[11]</sup> What's more, different cytokines such as tumor necrosis factor (TNF- $\alpha$ ), interleukin 10 (IL-10), and IL-17 are elevated and regarded as biomarkers of vitiligo.<sup>[12]</sup>

### Neural theory

Certain peripheral chemical neurotransmitters such as neuropeptide Y are increased peripherally leading to the destruction of melanocytes. Furthermore, the degeneration of axons and Schwann cell has been reported to be linked with the induction of vitiligo.<sup>[13]</sup>

### Viral theory

Various types of viral infection may induce the induction of vitiligo, as the DNA of cytomegalovirus has been observed in skin biopsy in patients with vitiligo.<sup>[14]</sup> As well, hepatitis C virus and the Epstein-Barr virus might be a causative factor in the initiation of the pathogenesis of vitiligo.<sup>[15]</sup>

Therefore, it seems that the etiopathogenesis of vitiligo is likely of the convergence of several of these pathways; thus, vitiligo is regarded as a syndrome rather than a single pathologic entity.

## BASIC THERAPY OF VITILIGO

Skin repigmentation is the main goal of therapy regardless of its types; however, spontaneous repigmentation is occurring in about 1%–25% of patients.<sup>[16]</sup> Topical corticosteroids are the first-line therapy and more effective for small vitiligo lesions and should not use more than 4 months due to the risk of skin atrophy.<sup>[17]</sup> Topical calcineurin inhibitors such as tacrolimus are effective as topical corticosteroids without risk of skin atrophy.<sup>[18]</sup> Systemic corticosteroids, such as dexamethasone, prednisolone, and methylprednisolone are effective for generalized progressive vitiligo.<sup>[19]</sup> Besides, oral methotrexate is a useful therapy for vitiligo.<sup>[20]</sup> On the other hand, physical therapy such as phototherapy with ultraviolet A (UVA), narrow-band UVB with psoralen and monochromatic excimer light, is safe and more effective than other therapeutic modalities.<sup>[21]</sup> Indeed, different previous studies illustrated

the potential role of statins in the treatment of different types of vitiligo.<sup>[22]</sup> Therefore, the objective of this study was to elucidate the mechanistic role of statins and/or molecular effects of different types of statins in the management of vitiligo.

## SEARCH STRATEGY

In general, an endeavor of this study article was to present a mini-review regarding the potential therapeutic effect of statins in the therapy of vitiligo. Evidence from experimental, preclinical and clinical studies are evaluated, given the nature of the subject area; it remains clear that this literature search cannot be regarded as systemic review.

A multiplicity of search strategies took on and assumed which included electronic database searches of, Scopus, Web of Science, Medline, and PubMed using MeSH terms, keywords, and title words during the search. The terms used for these searches were as follows: (vitiligo OR pigmentation disorders) AND (statins OR cholesterol-lowering drug OR pleiotropic). (Vitiligo OR statins class OR simvastatin) AND (depigmentation OR type of vitiligo). Reference lists of identified and notorious articles were reviewed. In addition, only English articles were considered, and case reports were not concerned in the review. The key features of recognized applicable search studies were considered and the conclusions summarized in a mini-review.

## STATINS

Statins inhibit *de novo* cholesterol biosynthesis through the inhibition of hydroxy-methyl-glutaryl-coenzyme A reductase (HMG-Co A) leading to noteworthy decline in serum levels of cholesterol and low-density lipoprotein with the elevation of high-density lipoprotein.<sup>[23]</sup> Beyond cholesterol-lowering effect, statins are also effective in the management of different cardio-metabolic disorders through amelioration of endothelial functions, anti-oxidant and anti-inflammatory effects, which collectively referred to as statins pleiotropic effects.<sup>[24]</sup>

## ROLE OF STATINS IN THE TREATMENT OF VITILIGO

### Autoimmunity and vitiligo: Role of statins

Statins are conventionally used in the treatment of dyslipidemia, mainly hypercholesterolemia, which was previously evaluated in the treatment of vitiligo depending on its antioxidant, anti-inflammatory, and immune-modulating effects.<sup>[25]</sup> Repigmentation and regression of vitiligo were initially reported in man with vitiligo who was on simvastatin therapy for hypercholesterolemia.<sup>[26]</sup> The animal model study showed that statins reverse and prevent melanocytes degeneration and depigmentation through inhibiting the proliferation of CD8-T-Cells.<sup>[27]</sup>

It has been noted that statins inhibit the production of interferon-gamma (INF- $\gamma$ ), expression of major histocompatibility complex (MHC-II) and T-cells activation

in the endothelial cells.<sup>[11]</sup> The dose-dependent effect of simvastatin leads to significant inhibition of INF- $\gamma$ -dependent MHC-II expressions with subsequent inhibition of activated T-lymphocytes in patients with active vitiligo.<sup>[28]</sup> This immune-modulating effect of statins may play an important role in the management of vitiligo. The immune-modulating effect of statins was previously reported since pravastatin prevents and reduces acute transplant rejections in human subjects.<sup>[29]</sup>

Similarly, pravastatin prevents acute rejection of cardiac transplant due to the inhibition of proinflammatory mediators and expression of adhesion molecules, which are independent of its cholesterol-lowering effect.<sup>[30]</sup> It has been reported that different types of statins prohibit the expression of inflammatory and proinflammatory adhesion molecules such as lymphocyte function-associated antigen (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) on leukocytes. As well, statins block LFA-1 on the lymphocytes and inhibit its interaction with ICAM-1 on antigen-presenting cells and by this way statins prevent the activation of lymphocytes and antigen presentation.<sup>[31]</sup> Moreover, Weber *et al.* found that atorvastatin is the selective inhibitor of inducible MHC-II on the macrophages and endothelial cells as it not affect MHC-I and constitutive MCH-II.<sup>[32]</sup> In addition, statins inhibit chemokine release by endothelial cells, block chemokine receptors on T-cells, inhibition of natural killer cells, and attenuate the proliferation of stimulating leukocytes.<sup>[33]</sup> Besides, lovastatin inhibits different mediators and cytokines

such as inducible NOS, TNF- $\alpha$ , IL-6, and IL-1  $\beta$  leading to significant anti-inflammatory and immune-modulating activates in different modalities of vitiligo.<sup>[34]</sup>

The precise anti-inflammatory and immune-modulating mechanisms of statins are as the followings;

- HMG-CoA reductase dependent pathway: inhibition of HMG-CoA reductase leads to the reduction of active inflammatory metabolites known as isoprenoids<sup>[11]</sup>
- HMG-CoA reductase independent pathway
- Statins block LFA-1 so, prevent lymphocyte activations
- Statins inhibit T-cell function through the inhibition of the second messenger phosphatidylinositol-30-kinase/ Akt transduction pathway.<sup>[35]</sup>

Moreover, IL-17 serum level is increased in patients with vitiligo and statins have been found to be a potent inhibitor of IL-17 through inhibition of T-cells proliferation and induction of immunotolerance.<sup>[36]</sup>

Therefore, statins may be an effective therapy against various types of autoimmune diseases such as multiple sclerosis and vitiligo. The immune-modulating effect of statins is summarized in Figure 1.

### OXIDATIVE STRESS AND VITILIGO: ROLE OF STATINS

Oxidative stress is regarded as one of the potential pathogenic events in melanocyte loss and the development of vitiligo.

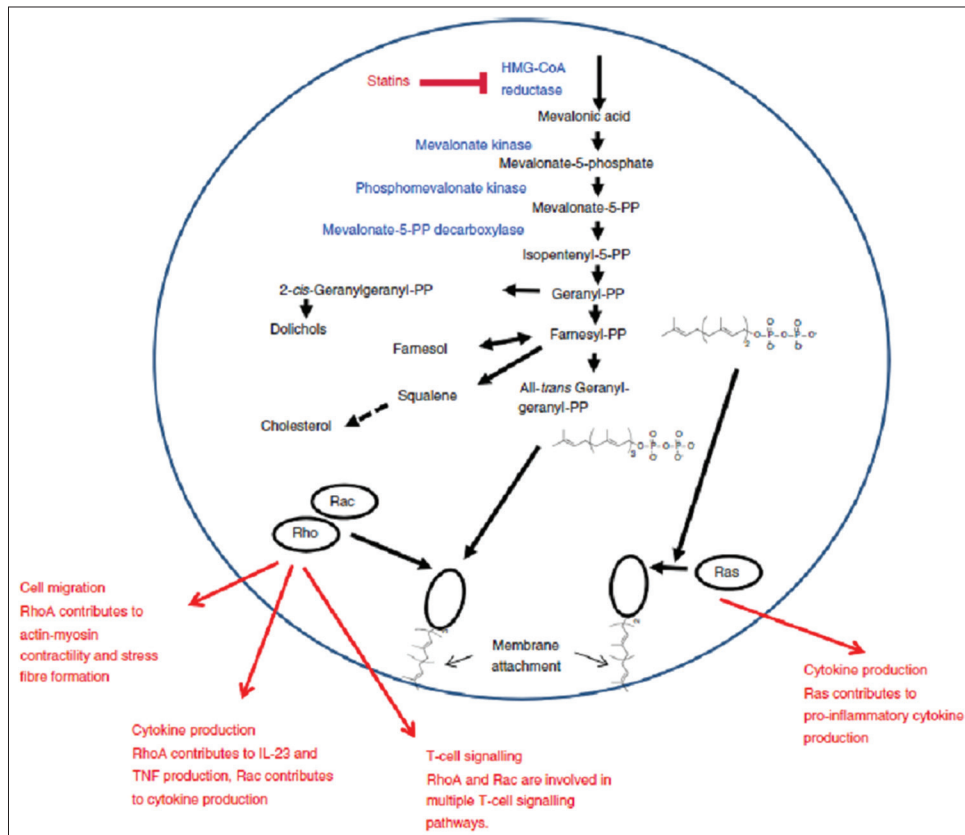


Figure 1: Immune-modulating effect of statins

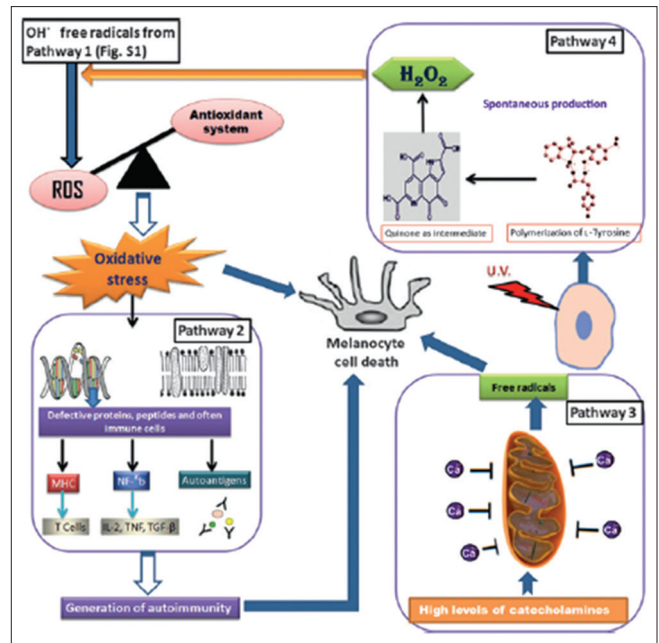
The evidences of oxidative stress in vitiligo are mitochondrial dysfunction due to highly reactive oxygen species (ROS), depletion of endogenous anti-oxidant capacity, and low epidermal tetrahydrobiopterin levels.<sup>[37]</sup>

The source of oxidative stress in vitiligo may be endogenous or exogenous. Endogenous stresses are due to melanogenesis and mitochondrial dysfunctions. Exogenous stressors are due to environmental exposure to monobenzene, cytotoxic agents, UV irradiation, and phenols as well as other factors such as severe infection, hormones, and vaccinations.<sup>[38]</sup>

High ROS leads to the inhibition of tyrosinase also; secondary substrates that are generated due to binding of  $H_2O_2$  to dihydroxyphenylalanine are also inhibiting tyrosinase.<sup>[39]</sup> Long-term accumulations of oxidative stress induced-free radicals cause epidermal cellular protein and lipid peroxidations as well as DNA damage. Besides, the inhibition of thioredoxin reductase and high extracellular  $Ca^{+2}$  contribute to the induction of epidermal oxidative stress.<sup>[40]</sup> It has been shown that systemic oxidative stress is associated with induction of vitiligo, as depletion of body anti-oxidant potential, and reduction of pseudocholinesterase are reduced by free radicals and high  $H_2O_2$ .<sup>[41]</sup> Furthermore, augmented oxidative stress in the melanocytes leads to the induction of abnormal apoptosis and the emergence of new aberrant proteins which act as auto-antigens leading to autoimmunity.<sup>[42]</sup> Moreover, ROS upregulates TNF- $\alpha$  and other proinflammatory cytokines such as TGF- $\beta$  and IL-2 which play a role in the inhibition of melanogenesis and stimulates the expression of anti-apoptotic proteins.<sup>[43]</sup> Recently, the intrinsic melanocytes defect may be the initial factor in the pathogenesis of vitiligo. Oxidative stress in the melanocytes leads to the induction of local inflammatory reactions and innate immune response which together inducing specific melanocytes immune response and the development of vitiligo in a genetically susceptible subjects, [Figure 2].<sup>[44]</sup>

On the other hand, statins, mainly simvastatin have a latent effect against oxidative stress through the activation of anti-oxidant capacity and reduction of ROS in human melanocytes. The anti-oxidative stress effect of simvastatin is mediated by upregulation of nuclear erythroid 2-related factor (Nrf2) in the melanocytes.<sup>[45]</sup> Oxidative stress factors activate Nrf2 which activates cellular anti-oxidant response element gene for the expression and synthesis of anti-oxidant enzymes. Therefore, imperfect Nrf2 activation in melanocytes increases melanocytes intolerance to the effect of oxidative stress and contributes to the melanocyte injury and development of vitiligo.<sup>[46]</sup> As a result, the direct effect of simvastatin on melanocytes may be of an additional mechanism against vitiligo.

Haendeler *et al.* found a novel anti-oxidant mechanism of statins through S-nitrosylation of thioredoxin and improvement of thioredoxin reductase activity,<sup>[47]</sup> which might explain the protective effect of statins against low level of thioredoxin reductase in vitiligo. As well, statins inhibit TNF- $\alpha$  and other proinflammatory cytokines, which are implicated



**Figure 2:** Oxidative stress and vitiligo

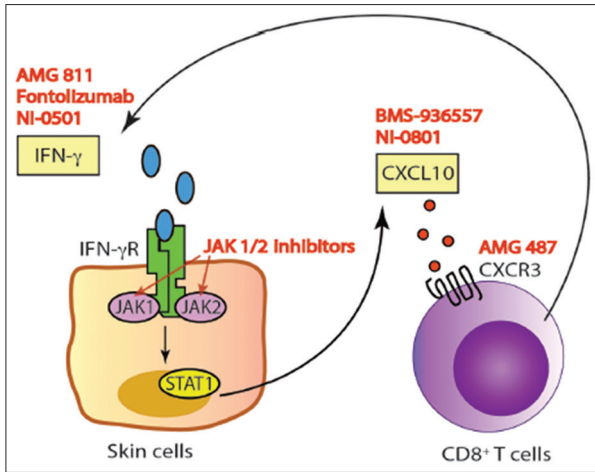
in the induction of oxidative stress and pathogenesis of vitiligo.<sup>[25]</sup> Remarkably, fluvastatin improves melanogenesis in melanocytes though increasing tyrosinase mRNA production by modulation of Akt and melanocyte proliferations. Furthermore, fluvastatin augments the stimulatory effect of  $\alpha$ -melanocyte-stimulating hormone from the pituitary gland on the melanocytes.<sup>[48]</sup> Similarly, fluvastatin increases tyrosinase activity that induced by UVB irradiation in B16F10 melanoma cell line.<sup>[49]</sup> These findings indicate the protective role of statins against UV irradiation.

It has been noticed that the effective dose of simvastatin for repigmentation of vitiligo is 80 mg/day in human, and 40 mg/kg in mice. However, high dose of statins may increase risk of adverse effects such as rhabdomyolysis, myopathy, and type 2 diabetes mellitus, limit the use of high dose of statins in the management of vitiligo.<sup>[50]</sup> Topical simvastatin may be used at a concentration of 1.0 mmol/L for vitiligo lesions, which is more effective with low adverse effects than systemic statins therapy.<sup>[51]</sup>

Indeed, Qiao *et al.* illustrated that autophagy plays a protective role in the attenuation of epidermal oxidative stress through the regulation of melanocytes proliferation. Defective autophagy increases the risk of oxidative stress induced-depigmentation and the development of vitiligo.<sup>[52]</sup> Statins, mainly pitavastatin induces autophagy in human melanoma cell line through modulation of cytochrome c; therefore, statins therapy is effective in the regulation of melanocyte growth and proliferation that prevent melanoma and the development of vitiligo.<sup>[53]</sup>

## CHEMOKINES IN VITILIGO: ROLE OF STATINS

Chemokines are small glycoproteins that are activated by INF- $\gamma$  and act on a wide variety of cell types such as



**Figure 3:** Interferon gamma/CXCL10 signaling in vitiligo

lymphocytes, fibroblasts, neutrophils, and endothelial cells. Chemokine receptors (CXCR3) and its ligand (CXCL10) are increased in vitiligo and other autoimmune diseases, leading to the induction of tissue inflammation and damage.<sup>[54]</sup> High CXCR3 and CXCL10 reflects host immune response of Th1 lymphocytes. INF- $\gamma$ -specific Th1 immune response provokes CXCL10 release and expression of CXCR3 on melanocyt-specific CD8<sup>+</sup> T-cells that lead to melanocytes injury and depigmentation [Figure 1].<sup>[55]</sup>

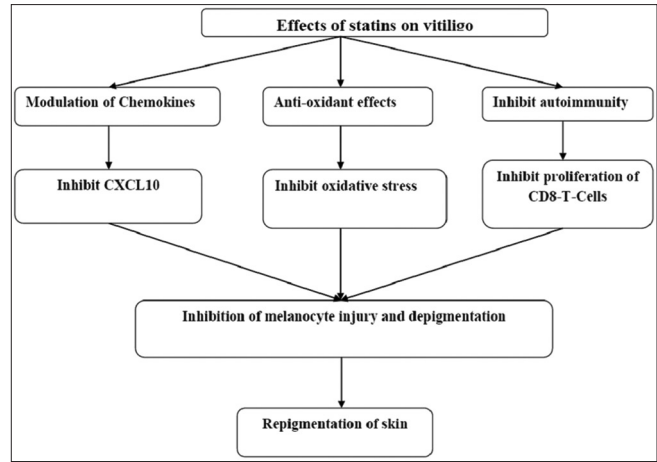
Therefore, neutralization of CXCL10 reduces depigmentation and risk of vitiligo with a significant reversal effect on the depigmentation process. Thus, CXCL10 is regarded as a novel target in the treatment of vitiligo, [Figure 3].<sup>[54]</sup>

Statins therapy may produce significant inhibition of inflammatory reactions through the inhibition of chemokines and Veillard *et al.* illustrated that statins reduce chemokine and chemokine receptors in human macrophages and endothelial cells through suppression of geranyl-geranyl pyrophosphate pathway.<sup>[56]</sup>

As well, simvastatin interferes with INF- $\gamma$ -/CXCL10 pathway which is activated in patients with vitiligo, and hence, simvastatin is regarded as a potential new treatment targeting inflammatory pathways.<sup>[57]</sup>

Similarly, signal transducer and activator of transcription (STAT) protein family, mainly STAT-1 is required INF- $\gamma$ -signaling in vitiligo.<sup>[58]</sup> Simvastatin downregulates JAK/STAT pathway in different inflammatory conditions.<sup>[59]</sup>

Furthermore, CXCR3 and its ligand CXCL10 induce the accumulation of cytotoxic autoreactive T-cells in the human epidermis leading to melanocyte degenerations and induction of vitiligo. Atorvastatin inhibits epidermal cytotoxic autoreactive T-cells that may explain the potential role of this drug in the management of vitiligo.<sup>[60]</sup> In addition, CXCR3/CXCL10 is an important pathway in the pathogenesis of vitiligo; serum level of CXCL10 is regarded as a novel biomarker in monitoring vitiligo activity and guiding treatment of progressive vitiligo.<sup>[61]</sup> Atorvastatin inhibits CXCL10 activity in different types of



**Figure 4:** Potential effects of statins on vitiligo

autoimmune diseases, which may explain the therapeutic potential effect of statins in vitiligo.<sup>[62]</sup>

**CONCLUSION**

This mini-review study highlighted the potential role of statins in the treatment of vitiligo either systemic or localized through significant suppressions of oxidative stress, autoimmunity, inflammatory reactions, and CXCR3/CXCL10 axis pathway. Bidirectional effects of statins on oxidative and autoimmunity/inflammatory pathway making it as a novel therapy for vitiligo, [Figure 4]. Therefore, statins may be used as adjuvant therapy with other basic therapy against progressive and resistance vitiligo.

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**Conflicts of interest**

There are no conflicts of interest.

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