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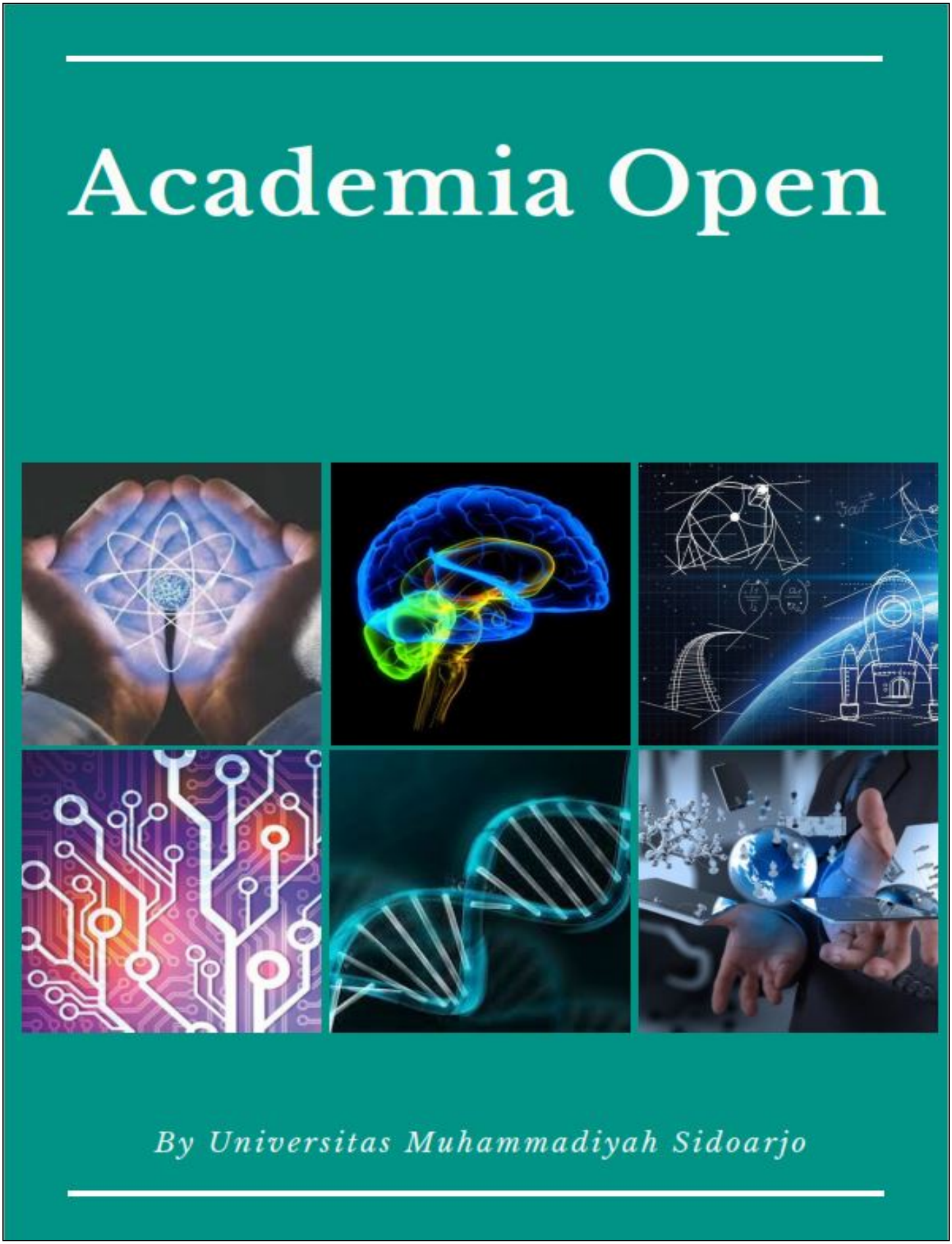

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A Comprehensive Review of Vitamin C in Autoimmune Skin Disease Management

Tinjauan Komprehensif tentang Vitamin C dalam Manajemen Penyakit Kulit Autoimun

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Abstract

General Background: Autoimmune skin diseases significantly impact patients' quality of life and, in severe cases, contribute to increased morbidity and mortality. While these diseases remain incurable, management strategies improve patient outcomes. **Specific Background:** Vitamin C (ascorbic acid), a key antioxidant, has been recognized for its role in disease management, yet its effectiveness compared to other supplements, such as vitamins D and E, remains underexplored. **Knowledge Gap:** Previous studies have not comprehensively evaluated the potential of vitamin C in autoimmune skin disease management, particularly in varying delivery methods and dosage effects. **Aims:** This review systematically examines the role of vitamin C in treating autoimmune skin diseases, synthesizing data from peer-reviewed studies, systematic reviews, and authoritative reports. **Results:** Vitamin C modulates innate and adaptive immunity, enhances collagen synthesis, supports skin wound healing, and regulates inflammatory processes. However, its instability and low bioavailability pose challenges that require targeted drug delivery strategies. **Novelty:** Unlike prior research, this review consolidates evidence on the therapeutic potential of vitamin C, addressing its limitations and proposing integrative approaches. **Implications:** Findings highlight the need for optimized delivery methods and further research into vitamin C’s role in autoimmune disorders, offering a potential alternative strategy for improving disease management.

Higlights:

1. Autoimmune skin diseases affect quality of life and lack cures.
2. Review vitamin C's role in managing autoimmune skin diseases.
3. Vitamin C aids immunity and healing but requires optimized delivery methods.

Keywords: Vitamin C, ascorbic acid, systemic lupus erythematosus, psoriasis, autoimmune skin disease, pemphigus, scleroderma, dermatomyositis, vasculitis, and vitiligo.

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Introduction

Ascorbic acid is one of the most crucial antioxidants for the human body as its role in immune system protection and reduction of allergic reactions has been well-established earlier [1]. Being a water-soluble vitamin obtained through dietary intake, vitamin C enhances the immune functions, mitigates the cellular oxidative stress and plays a substantial role in many enzymatic reactions [2]. The role played by Vitamin C in human skin is crucial as it involves in skin barrier and collagen development, antiaging, prevention of wrinkle formation, mediating the cell signalling pathways, resistance to UV-induced oxidative stress, prevention of melanogenesis, keratinocyte differentiation etc., [1]. Further, the involvement of vitamin C has been recorded in various biomechanisms such as tyrosine biotransformation, folic acid conversion to folinic acid, glucose metabolism, lipid protein synthesis, iron metabolism, infection resistance, and cellular respirations [3].

According to Kajdas et al [4], highly processed food items contain saturated fats and sugars which further complicate the autoimmune skin diseases. When there is a deficiency in the nutrients like vitamins A, C and D, omega-3 fatty acids and zinc, it tends to impair the immune function as well as skin health. Vitamin C is present in citrus fruits while *Phyllanthusemblica* contains high amounts of vitamin C, 2-3 fresh servings per day may help the vitiligo patients achieve required daily dosage of vitamin C [5]. Ravetti et al [6] mentioned that the concentration of ascorbic acid in normal skin is usually high, compared to other tissues and plasma concentration while the study also cited that the bioavailability of vitamin c for the skin is inadequate through oral administration. So, topical or locally applying vitamin c might enhance the bioavailability of vitamin c/ascorbic acid for the skin. However, the bioavailability of vitamin C or ascorbic acid gets reduced among autoimmune patients due to which various diseases occur.

At times, vitamin C deficiency causes symptoms that mimic the symptoms of autoimmune diseases such as vasculitis, pseudoscleroderma etc., Some of the commonly known autoimmune skin diseases include, Pemphigus (Pemphigus Foliaceous, Pemphigus erythematosus, Drug-induced pemphigus, IgA pemphigus, Pemphigus vegetans and Paraneoplastic pemphigus), Bullous pemphigoid, Dermatitis herpetiformis, Epidermolysis bullosa acquisita and Vitiligo [7]. Diotallevi and Offidani [8] listed a few other autoimmune skin diseases such as Psoriasis, Hidradenitis suppurativa, Vitiligo, scleroderma, Lichen sclerosus, Hyper-IgE syndrome (HIES), disseminated Granuloma Annulare (GA), Polypyrimidine Tract Binding (PTB), pyoderma caused by nivolumab and bradykinin-mediated angioedema. In addition to this, Ali et al [1] cited Porphyria Cutanea Tarda (PCT) and Atopic dermatitis that can be treated with vitamin C intervention. Majority of the autoimmune skin diseases, for instance, autoimmune bullous disease such as pemphigus and pemphigoid are categorized as polygenic diseases as it demonstrates a significant autoimmune component, while psoriasis is an autoinflammatory skin disease [7].

Diotallevi et al [9] conducted an extensive review on immune-mediated inflammatory skin diseases that detailed about the impact of nutrition upon various autoimmune skin diseases though the role played by vitamin C is negligibly quoted. Further, the studies [10], [11], [12], [13], [14] conducted upon autoimmune skin diseases mostly focused on vitamins D and E, while there is a lack of sufficient studies that establish the critical role played by vitamin C as a standalone element. Thus, the role played by vitamin C as an effective treatment regimen for autoimmune skin diseases remains incomprehensive. In this background, the current study is an attempt to provide a comprehensive review of the studies conducted earlier regarding the role played by vitamin C (ascorbic acid) in the management of autoimmune skin diseases. The purpose of this review is to detail the crucial role played by vitamin C or ascorbic acid in a few selected autoimmune skin diseases and to establish its applicability across the globe due to its unique features.

Methods

The current review article encompasses studies published as latest as February 2025 to the last five years covering double-blind peer-reviewed research articles with special reference to case-controlled studies, cross-sectional and longitudinal studies, individual case reports, region-specific studies etc., systematic reviews, meta-analyses, books, reports from statutory bodies, the World Health Organization, etc., At first, the keywords given herewith were used to retrieve the latest information from various knowledge databases including PubMed, EMBASE, and Web of Science; 'autoimmune skin diseases' AND 'Systemic Lupus Erythematosus' AND 'psoriasis' AND, 'vitamin C and autoimmune skin diseases', AND 'vitamin C and antioxidants for autoimmune skin disease treatment'. Studies published in English language were only considered for this review.

Result and Discussion

The current section provides a detailed description of the studies conducted regarding vitamin C intervention upon various autoimmune skin diseases.

1. Systemic Lupus Erythematosus (SLE)

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SLE (Systemic Lupus Erythematosus), a type of autoimmune disease, affects various body organs such as the skin, joints, kidneys, lungs, central nervous system and the haematopoietic system while the therapeutic role of vitamin C has been well established in the literature [2], [15], [16]. According to Tian et al, the incidence rate of SLE was found to be 5.14 per 100,000 person-years with 0.4 Million people getting affected on an annual basis. The survey conducted earlier among 21 regions across the globe, covering 39 countries, inferred that the UAE, Barbados and Brazil had the highest prevalence of SLE and women are highly likely to be affected compared to men [17]. The recent study published in 2024 covered the data between 2007 and 2023 in the US and the study mentioned about the increasing incidence and prevalence per 100,000 population [18]. Vitamin C scavenges the Reactive Oxygen Species (ROS), a contributory factor of uninhibited lipid peroxidation of the blood cells and its components [19]. In general, antimalarials and glucocorticoids are generally suggested for treatment [18]. However, dietary intake (maximum up to 1g per day) of vitamin C helps in preventing the oxidative stress and also mitigates the antibody concentration resulting in the mitigation of inflammation. This varies in different ethnicities, for instance, Japanese patients with SLE, the vitamin C intake of 109.99 mg/day was found to have a significant inverse association against the disease progression [15] while in an old study [16], this vitamin C intake was higher up to 500 mg along with vitamin E (800 IU). Further, it also saves the individuals from getting attacked by the disease again through reduction of oxidative stress and suppressing the production of autoantibodies. Ascorbic acid (vitamin C) possesses antioxidative characteristics and has been proved to interfere the NFκB/TNFα pathway, reducing the pro-inflammatory cytokine levels. When ascorbic acid was intravenously administered to patients undergoing Atrial Fibrillation, the sudden increase in the post-operative CRP (C-Reactive Protein) levels seemed to be mediated and minimized [19]. However, another study found that the patients administered with vitamin C had a significantly lesser length of hospital stay than the control group [20]. This study also confirmed the high effectiveness of high-dosage ascorbic acid during catheter ablation for atrial fibrillation that may also mitigate the increasing CRP up to 24 hours after the procedure.

2. Psoriasis

Having been known as a chronic, immune-mediated inflammatory disease, the etiology of Psoriasis as multiple factors among which obesity remains a major risk that may deteriorate the patient's quality of life [21]. In a recent review conducted for the studies published between 2018 and 2023, four markers were identified for the occurrence of psoriasis such as inflammation, oxidative stress, hormonal and cancer-related markers among which the first one remains the primary focus in psoriasis [22]. The role played by T cells is crucial in creating a cascading inflammatory effect in Psoriasis since the former induces the production of cytokines that eventually results in skin lesion development [8]. Vitamin C involves in the neutralization of hydrogen peroxide and hydroxyl radicals that in turn reduces the lipid peroxidation process and also enhances the antioxidant enzyme function in psoriatic arthritis. Its role in crucial in preventing the cells from the oxidative stress while it also helps in the regeneration of other antioxidants like vitamin E. Vitamin C, if provided to patients with psoriasis as a supplement, reduces the malondialdehyde (MDA) and other such oxidative stress biomarkers [23]. The impact of vitamin C in treating psoriatic patients has been well established in C57BL/6 mice model earlier. Further, Agnihotri et al [3] commented that vitamin C, with its high anti-oxidant properties, can help in the prophylaxis of various autoimmune skin diseases, especially psoriasis. The effectiveness of vitamin C among psoriatic patients was studied earlier as a single-blind randomized clinical trial among 74 psoriatic patients. The experimental group was supplemented with vitamin C while the results confirmed that this group had low MDA levels compared to the control group. Thus, vitamin C can be confirmed to have a crucial role in treating psoriatic patients, undergoing NB-UVB phototherapy [24].

3. Vitiligo

Vitiligo, a highly-complex hypopigmentation disorder, is characterized by white depigmentation patches [25], due to the loss of epidermal melanocytes [26] and is generally treated using corticosteroids, immunomodulators and phototherapy while vitamins are also used as adjuvants in the treatment regimen [9]. Being a immune-mediated disease involving the break-down of melanocytes by the IFN-γ producing cytotoxic T cells, Vitiligo is characterized by depigmentation of the skin while vitamin C supplements have been proved to enhance the re-pigmentation rate than the control groups, in association with vitamin E, alpha-lipoic acid etc., Further, topical application of vitamin C has been proved to be highly successful in melasma treatment [27]. Vitamins B12 and folic acid along with exposure to solar rays can help the vitiligo patients gain the lost pigmentation. Likewise, vitamin C's immunomodulatory and antioxidant properties have been proven to improve the quality of life among the vitiligo patients, though a few contradict these outcomes [9]. For instance, its application in vitiligo disease management has been contraindicated due to its role in disrupting the melanin synthesis pathway [25]. In spite of its non-defined pathogenesis, the causal factors identified behind Vitiligo include autoimmunity, oxidative stress, metabolic abnormalities and oxidative stress [8]. Aloe vera contains vitamin C and various other vitamins while its efficacy and safety were tested earlier among vitiligo patients [28]. The study results confirmed that after three months of treatment, re-pigmentation of the vitiligo patients was positively significant though only 9% patients achieved 90% re-pigmentation after 24 weeks of treatment. One of the study protocols published earlier [29] included 44 vitiligo patients from Iran to determine the impact of using vitamin C supplements upon the serum levels of stress oxidative factors as well as the re-pigmentation in vitiligo patients. The study outcomes may provide knowledgeable insights about the effect of vitamin C supplementation in vitiligo patients. When vitiligo patients were supplemented with nutritional antioxidants such as vitamin C, B1, L-Cysteine, lipoic acid and polyunsaturated fatty acids, the patients showed re-pigmentation under UVB 311 phototherapy [26]. A study conducted among young

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aged vitiligo patients from Madagascar responded well to a treatment regimen containing a cream with Clobetasol propionate (0.05%), oral vitamins C and B12 with the suppression of microtrauma [5].

4. Porphyria

Porphyria Cutanea Tarda (PCT) is clinically characterized by acute and chronic skin blistering, when the patient is exposed to sunlight, in its middle and later stages of the disease. Vitamin C possesses antioxidant characteristics and so, it prevents the CYP1LA2 from undergoing catalytic oxidation. Thus, ascorbic acid has a huge potential in treating the PCT [1]. Previous study established that vitamin C deficiency has a significant contribution towards the pathogenesis of PCT while its administration improves the antioxidant mechanisms of the patients. It functions in association with vitamin E and glutathione reductase [30]. Variegate porphyria (VP) is characterized by chronic inflammation, plasma oxidative damage and low protoporphyrinogen oxidase, CAT and Glutathione reductase (GR) activities. When vitamins C and E are orally supplemented for six months at 150 and 50 mg/d respectively, it mitigates the plasma oxidative damage while the erythrocyte activities of the CAT and GR get improved [31]. Patients suffering from acute porphyrias often are diagnosed with hyperhomocysteinemia, a condition caused by catabolism, vitamin deficiency (vitamin B6, B12 etc., [32].

5. Atopic dermatitis

Atopic dermatitis, a commonly-known chronic inflammatory skin disease, also known as atopic eczema with over 230 million patients recorded worldwide [33], has been established to have associated with a few autoimmune diseases such as vitiligo, Crohn's disease, alopecia areata etc., in spite of the limited evidence available to establish the association between the two [34], [35]. This condition is characterized by the release of different chemical mediators in addition to macrophages, lymphocytes, and granulated mast cells and high levels of immunoglobulin (Ig) E in the serum, which altogether results in inflammation of the cells [36]. Further, the condition is also correlated with allergies causing itching and scaling effect among 15-30% children. The intervention of Vitamin C in this disease occurs in the development of interstitial material that helps in differentiating the keratinocytes and their intercellular lipids. Further, vitamin C also stimulates the production of ceramide in keratinocytes and increases the overall epidermal barrier function [1]. NXP081, a single-stranded DNA aptamer was developed, validated in literature to overcome the issues found in vitamin C like instability and easily getting oxidized. The aptamer was tested in animal mode for Atopic Dermatitis and during oral administration, significant reduction in inflammation and improved skin conditions were recorded [36]. Studies have established the positive effect of DDH-1, a derivative of the ascorbic acid, induce anti-allergic effect in AD mouse model. This is a result of the diminishing effect of DDH-1 upon the expression of pro-inflammatory cytokines and Th2-associated chemokine [37]. L-ascorbic acid has also been proved to antioxidant and anti-inflammatory characteristic, when utilized along with γ-PGA MN for the structural stabilization of the Epigallocatechin gallate (EGCG), a promising candidate for atopic dermatitius therapy [38].

6. Pemphigus

Pemphigus occurs as a result of production of autoantibodies against the desmogleins 1 and 3 [39] while various types of pemphigus have been reported in literature such as pemphigus foliaceus (PF) [40], Pemphigus Erythematosus (PE), pemphigus vulgaris (PV) [41], paraneoplastic pemphigus etc [42]., In spite of opaque etiopathogenesis, PE can be caused by genetic predisposition of the individuals, especially Ashkenazi Jewish or Mediterranean descent [42], drugs, viral infections and other physical agents like UV-rays, heat etc., [43]. In the case study published recently, Pemphigus Erythematosus (PE) was diagnosed, a rare combination of SLE and pemphigus foliaceus and this autoimmune disorder is characterized by skin lesions, erosive eruptions, flaccid blisters etc., According to this study, PE is predominantly found in women with slow progression [43]. In literature [44], the effectiveness of vitamin C and other such antioxidants upon 30 Iranian PV patients was evaluated while the disease severity was measured using Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). The outcomes confirmed that uric acid is an efficient antioxidant whereas no serum-level changes were found in vitamin C.

7. Other autoimmune skin diseases

1. **Systemic Lupus Erythematosus (SLE)**
2. **Psoriasis**
3. **Vitiligo**
4. **Porphyria**
5. **Atopic dermatitis**
6. **Pemphigus**
7. **Other autoimmune skin diseases**

Systemic Sclerosis (SSc), an autoimmune multisystemic disease is characterized by microvascular dysregulation while skin is the largest organ that gets affected by this condition [45]. In a case study upon 17-year-old male, vitamin C deficiency was presented as a case of pseudo-scleroderma. After diagnosed with fasciitis and pseudo-scleroderma secondary to vitamin C deficiency, the patient was supplemented with ascorbic acid at a dosage of 500 mg twice a day for seven days [46]. Low serum concentration of superoxide dismutase and vitamin C is a classic characteristic of SSc patients though there is no clear information available regarding CAT, vitamin E and thiol

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[47]. Opris-Belinski et al confirmed that the patients with SSc exhibit low vitamin C serum levels in the absence of a clear underlying cause. Vitamin C deficiency in SSc patients affects not only iron absorption, but also the synthesis and degradation of ferritin and the modulation of cellular iron efflux [45].

Dermatomyositis is one of the rarest acquired immune-mediated muscle diseases [48] that not only affects the skin, but is also characterized by muscle weakness and lungs issues while its pathogenesis remains unexplained still [49]. Being a idiopathic inflammatory myopathy that has association with malignancy, patients diagnosed with this condition should be immediately diagnosed for cancer. In a case study published earlier involving a 68-year old female patient with ocular muscle weakness, the patient was intravenously administered with 3.0 g vitamin C on a daily basis while orally, the patient was given hydroxychloroquine sulfate (100 mg) twice daily [50]. Kodama and Kodama [51] found an interesting similarity between Interstitial pneumonia/Dermatomyositis complex (ID) and immunoendocrinopathy syndromes (IES) in terms of pathophysiological features. In this case study, the authors found that the drip infusion of megadose vitamin C along with other drugs was effective in treating the ID as the former helps in preventing the functional mechanisms of adrenal cortex as well as thymus against the homeostatic mechanism.

Henoch–Schönlein purpura (HSP) otherwise called as immunoglobulin A vasculitis is mostly found in children and young adults during winter and autumn periods and is predominantly an autoimmune disorder [52]. Scurvy is sometimes misdiagnosed as vasculitis, an autoimmune skin disease, as the former mimics the symptoms of vasculitis during physical examination [53]. Various studies have reported this scenario in which vitamin C deficiency is wrongly diagnosed, for instance, vasculitis [54] and IgA vasculitis [55]. Vitamin C deficiency is also reported to cause symptoms that mimic leukocytoclastic vasculitis. In the case study presented earlier, poor nutrition with extremely low ascorbic acid concentration in serum, confirmed that the patient had vitamin C deficiency rather than vasculitis [54]. The case report published earlier recorded the diagnosis of cutaneous vasculitis on hospitalization for spontaneous diffuse cutaneous lesions. When histopathological examination was conducted, the patient was diagnosed with leucocytoclastic vasculitis that occurred as a result of vitamin C deficiency [56]. A case study published earlier upon 63-year old dementia patient, who was referred for diagnosing vasculitis, was diagnosed with undetectable serum ascorbic acid level at < 0.1 mg/dL while vitamin C regimen at 1000 mg on a daily basis proved to be effective in getting rid of the rashes [57].

Oral Lichen Planus (OLP), a chronic mucocutaneous disease, caused by autoimmune disorder and due to the contradictory outcomes in different studies, the association between vitamin deficiency and Oral Lichen Planus is still under investigation. OLP can be clinically diagnosed using low vitamin C levels and higher MDA levels, according to Geetha et al [58]. In literature, the OLP patients had the least serum vitamin A, C and E levels compared to the healthy group, though the difference was insignificant [59]. In the case-control study, the relationship between OLP and oxidative stress was investigated among 15 female patients diagnosed with OLP. The results concluded that the serum vitamin C level was low in OLP group though the study did not inferred the impact of low vitamin C level in serum with that of the OLP [60]. Georgescu et al conducted a narrative review in which the authors cited that Cutaneous Lichen Planus can be treated with vitamin C supplements, thanks to the latter's antioxidant characteristic against oxidative stress [61].

Conclusion

Vitamin C has a number of key benefits for the treatment of autoimmune diseases such as its availability, water-soluble nature, while it has a few hindrances to overcome such as its easily oxidizable nature, instability and getting easily decomposed in case of exposure to pH, air, UV light and temperature. Vitamin C has the capability to regulate both innate as well as adaptive immunity while its role is crucial in a number of biological mechanisms such as immunosuppression of T-reg lymphocytes, regulation of NK cells, eosinophils, basophils, mast cells, cytokines, increased cytotoxicity of CD8+ T cells, hydroxylation of the collagen, and the regulation of NETosis processes. The disadvantages of vitamin C such as poor chemical stability and low bioavailability underplay the advantages that it brings to the appropriate functioning of the body cells. However, effective integrative therapies must be designed to overcome such drawbacks in vitamin C. In skin wound healing process that involves various stages such as hemostasis, inflammation, proliferation and remodelling, vitamin C helps in the synthesis of connective tissue, especially collagen, increased dermal fibroblast activity, mitigation of pro-inflammatory factors and the rapid removal of neutrophils from inflamed area. Varying the delivery methods such as topical, intravenous and sub-cutaneous and the dosage may bring the desired results in vitamin C application for the disease to be treated. At times, vitamin C absorption in high concentrations may bring deleterious effects such as the kidney stone formation. So, targeted drug delivery systems must be developed for effective results. Vitamin C has the potential to be an alternative therapeutic strategy that can enhance the human health through nutritional functions.

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