Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The relationship of skin disorders, COVID-19, and the therapeutic potential of ginseng: a review

Seoyoun Yang [a, 1], Su Bin Han [a, 1], Soohyun Kang [a], Junghyun Lee [a], Dongseon Kim [b], Anastasiia Kozlova [b], Minkyung Song [c, ***], See-Hyoung Park [d, **], Jongsung Lee [a, *]

[a] Molecular Dermatology Laboratory, Department of Integrative Biotechnology, College of Biotechnology and Bioengineering, Sungkyunkwan University, Suwon City, 16419, Gyunggi Do, Republic of Korea
[b] Department of Integrative Biotechnology, College of Biotechnology and Bioengineering, Sungkyunkwan University, Suwon City, 16419, Gyunggi Do, Republic of Korea
[c] T cell and Tumor Immunology Laboratory, Department of Integrative Biotechnology, College of Biotechnology and Bioengineering, Sungkyunkwan University, Suwon City, 16419, Gyunggi Do, Republic of Korea
[d] Department of Bio and Chemical Engineering, Hongik University, 30016, Sejong City, Republic of Korea

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made significant impacts on global public health, including the development of several skin diseases that have arisen primarily as a result of the pandemic. Owing to the widespread expansion of coronavirus disease 19 (COVID-19), the development of effective treatments for these skin diseases is drawing attention as an important social issue. For many centuries, ginseng and its major active ingredients, ginsenosides and saponins, have been widely regarded as herbal medicines. Further, the anti-viral action of ginseng suggests its potential effectiveness as a therapeutic agent against COVID-19. Thus, the aim of this review was to examine the association of skin lesions with COVID-19 and the effect of ginseng as a therapeutic agent to treat skin diseases induced by COVID-19 infection. We classified COVID-19-related skin disorders into three categories: caused by inflammatory, immune, and complex (both inflammatory and immune) responses and evaluated the evidence for ginseng as a treatment for each category. This review offers comprehensive evidence on the improvement of skin disorders induced by SARS-CoV-2 infection using ginseng and its active constituents.

1. Introduction

The world has been beleaguered by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since its first appearance in Wuhan, China, in December 2019, and its subsequent rapid transmission worldwide that resulted in a pandemic with high morbidity and mortality [1,3]. By April 2022, there were 510,270,667 confirmed patients and 6,233,526 deaths worldwide [2].

1.1. SARS-CoV-2

SARS-CoV-2 is a highly transmissible and pathogenic coronavirus causing an acute respiratory sickness known as "coronavirus disease 2019" (COVID-19) that poses a substantial threat to public health and safety [3].

The symptoms of COVID-19 exhibit high heterogeneity among cases and can present in a variety of ways. However, the majority of patients show few or no symptoms, with those of advanced ages and those with existing medical disorders such as high blood pressure, heart diseases, or diabetes at a higher risk of more serious side effects [4].

The COVID-19 virus is primarily spread via droplets, binding to human angiotensin-converting enzyme 2 (hACE2) as a receptor via a spike protein [5]. Transmembrane protease serine 2 (TMPRSS2) from the host cell then cleaves the spike protein, resulting in membrane fusion [6,7]. Viral infection can also occur with hACE2

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: piscesmk@skku.edu (M. Song), shpark74@hongik.ac.kr (S.-H. Park), bioneer@skku.edu (J. Lee).
[1] These authors equally contributed to this work.

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alone, without TMPRSS2 involvement, in which case the viral membrane disassociates in pH-mediated endolysosomes and secretes RNA into the cytosol. However, the efficacy of this mechanism is reported to be low compared with that of TMPRSS2-mediated infection [7]. Fig. 1 summarizes the process by which human cells are infected by SARS-CoV-2 in the presence and absence of TMPRSS2.

1.2. SARS-CoV-2 and skin disorders

The hACE2 receptor is expressed in various tissues; not only is it found in the nasal epithelial cells considered to be the primary route of infection but also in the oral cavity, respiratory tract, gastrointestinal tract, central nervous system, skin, and various other tissues. Particularly in the central nervous system, SARS-CoV-2 utilizes receptors such as neuropilin-11 and CD147 to infect host cells more easily [7]. Owing to these varied routes and mechanisms of infection, symptoms such as fever, fatigue, dry cough, muscle aches, runny or stuffy nose, sore throat, gastrointestinal problems, and anosmia are prevalent in COVID-19 patients [8].

In addition to the common symptoms, a variety of cutaneous manifestations have also been observed in a small number patients, including simple allergic reactions, purpura, erythema multiforme, and rosacea with blisters [9,10]. While such skin involvement was not recognized in the early phases of the pandemic, it has recently gained significant attention. Thus, there is a need for clarifying the possible association between COVID-19 and skin symptoms, which can both improve the understanding of its pathophysiology and help accelerate the development of more effective infection therapies.

During the pandemic, an increase in personal protective equipment (PPE) usage and hygiene measures (hand sanitization and hand washing) has been required, increasing the prevalence of related dermatological illnesses [10,11]. A variety of exanthems and cutaneous eruptions have been linked to COVID-19 infections , with new cases being reported on a regular basis, despite the fact that the virus has not yet been officially considered dermotropic [12]. Further, reports of immune, inflammatory, and complex skin disorders associated with COVID-19 infection are accumulating in the literature.

1.3. Korean Red ginseng

The root of the *Panax ginseng* Meyer plant is longstanding remedy used to cure a wide variety of ailments, as well as to boost physical strength and immunity. Specifically, Korean Red ginseng (KRG) is a prominent traditional medicine in East Asia that is widely used to treat a variety of disorders including cancer, Alzheimer's disease, and vascular diseases [13].

After ginseng undergoes heat processing, a change in the composition and biological effects of its constituent ginsenosides occurs [14]. Exclusively present in KRG are the ginsenosides Rh2, RS4, and Rg3, hydrolyzed compounds generated from saponins by heating that have been shown to limit cancer cell proliferation by inducing apoptosis [15]. Moreover, another *P. ginseng* metabolite has shown the ability to suppress the production of VEGF and TNF-a, suggesting anti-cancer action [16,17].

Numerous investigations of heat-processed KRG have revealed anti-photoaging, anti-wrinkle, and anti-melanogenic properties, drawing considerable attention in aesthetic skin care. In the realm of pathologic skin conditions, KRG water extract has been shown to

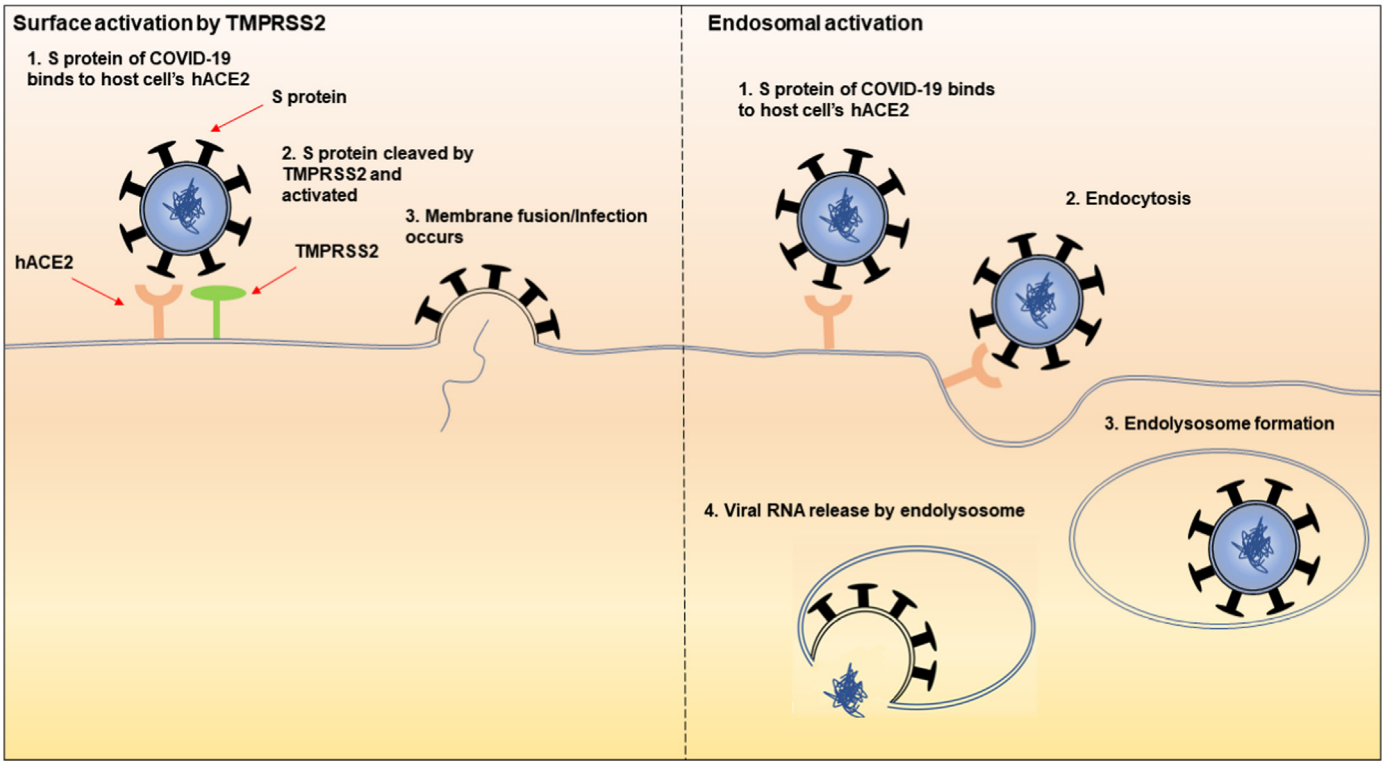

Fig. 1. COVID-19 infection with/without TMPRSS2. COVID-19 infection is initiated by the binding of the S protein to the host cell human angiotensin-converting enzyme (hACE2). When the virus binds to cells with TMPRSS2, it cleaves the S protein into S1 and S2 proteins. Activated S2 proteins mediate membrane fusion and release of viral RNA into the host cell. Without TMPRSS2, after SARS-CoV-2 binds with hACE2, the virus enters the cell by endocytosis. Inside the endosome, viral particles are degraded, and viral RNA is released into the cytosol.

dramatically improve skin conditions by reducing the production of inflammatory regulators, chemokines, and cytokines through the mitogen-activated protein kinase (MAPK) signaling pathways [18]. Oh et al reported that the ginsenoside Re can improve the barrier function by increasing the levels of filaggrin protein and caspase-14, which increases the formation of cornified cell envelopes in HaCaT cells [19].

Given this evidence and the increase in the incidence of COVID-19-related skin disorders, the purpose of this study was to evaluate the existing evidence of the effectiveness of ginseng, and in some cases specifically KRG, as a treatment using a narrative review and to classify the variety of skin disorders that have been reported as a result of the pandemic.

2. Pathogenesis of covid-19-related skin diseases and therapeutic effects of ginseng

Skin diseases can be classified according to onset factors, which include inflammatory abnormalities, immune abnormalities, and complex factors. Therefore, we classified the pathogenesis of skin diseases caused by COVID-19 into three types: those caused by inflammatory, immune, and complex (both inflammatory and immune) responses. For each category, the therapeutic potential of ginseng and its active constituents were determined.

2.1. Inflammatory response-induced skin lesions with SARS-CoV-2 infection and the related actions of ginseng/ginsenoside

Inflammatory response–induced skin lesions refer to skin lesions that occur because of the inflammatory reaction caused by SARS-CoV-2 infection. They include telogen effluvium, multisystem inflammatory syndrome in children, acral peeling lesions, red half-moon nail signs, maculopapular lesions, livedo racemose, and papulovesicular exanthem. In one study, it was seen that in areas with a large number of patients infected with SARS-CoV-2, the prevalence of multisystem inflammatory syndrome in children reached a peak after approximately 3–4 weeks. In addition, multisystem inflammatory syndrome was found to occur mostly in children and adolescents with a medical history of COVID-19. These results suggest a major contribution of COVID-19 to the occurrence of multisystem inflammatory syndrome in children. The pathogenesis of multisystem inflammatory syndrome in children has not yet been identified; however, its incidence tends to increase approximately 2–6 weeks after SARS-CoV-2 infection [20].

2.1.1. Telogen effluvium

Telogen effluvium (TE) is the most common hair loss disorder, the many triggers for which include stress, medications, febrile illness, and nutritional deficiencies [21]. TE typically occurs 2-3 months following severe infection, resulting from both general physiological stress from infection and drug administration [22].

Infection with SARS-CoV-2 specifically involves an increase in the levels of inflammatory cytokines; and it has been established that cytokine storms can damage stromal cells and cause TE [23]. One pro-inflammatory cytokine, interleukin 6 (IL-6), is a well-known TE-inducing molecule, as high levels of IL-6 act on hair follicles to induce catagen formation [24]. Interleukin 4 (IL-4) also induces keratinocyte apoptosis in the hair follicles. Thus, an increase in the levels of inflammatory cytokines induces TE [25].

When coagulation pathways are activated during immune responses to infection, pro-inflammatory cytokines are excessively produced, leading to multi-organ injury. In response to SARS-CoV-2 infection, the concentration of anticoagulant proteins decreases as the coagulation cascade is activated [26]. These factors can also cause TE by the formation of microthrombi, which block the supply of blood to hair follicles [22].

Ginseng can eliminate pro-inflammatory and anti-inflammatory cytokines such as IL-4, IL-6, and TNF-α through the positive modulation of signaling pathways including MAPK, nuclear factor-κB (NF-kB), and JAK/STAT. The regulation of interferons, which are TE-inducing molecules, by ginseng can also induce hair growth. This action can also prevent the blockage of blood supply to hair follicles due to microthrombosis. Further, the ginsenoside Rg3 promotes hair growth by increasing the expression of VEGF to enhance blood supply to hair follicles [27].

2.1.2. Multisystem inflammatory syndrome in children

Uncontrolled innate immune responses, cytokine storms, and endothelial damage are behind the more severe clinical manifestations of COVID-19. Multisystem inflammatory syndrome in children (MIS-C) induces macrophage activation and the stimulation of helper cells. This in turn produces antibodies that induce hyperimmune reactions by stimulating cytokine storms, macrophages, neutrophils, and mononuclear cells. It also leads to B-cell and plasma cell activation. A hyperimmune response is caused by this disordered immune regulation, and this is assumed to be the cause of the onset of MIS-C [28].

Ginseng has been shown to be effective in the management of both infectious and inflammatory diseases, as it attenuates immune cell cytokine production by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cell signaling and reducing inflammasome activation. Ginseng also improves MIS-C by suppressing the hyperimmune response [29].

2.1.3. Acral peeling lesions

The process by which corneodesmosomes, or cell-cell junctions, gradually peel off from keratinocyte cells present in the outermost layer of the stratum corneum in the skin is called epidermal exfoliation [30]. Corneodesmosomes consist of transmembrane proteins DSG1, DSC1, and CDSN. They are degraded by the serine proteases trypsin-like kallikrein-related peptidase 5 (KLK5) and chymotrypsin-like kallikrein-related peptidase 7 (KLK7) [31]. When serine protease inhibitor Kazal type-5 (SPINK5), a serine protease inhibitor, is secreted within the stratum corneum, KLK5 and KLK7 are inhibited [32].

During infection with SARS-CoV-2, blood flow to skin structures such as hair and nail stem cells is disrupted by systemic inflammation and microthrombosis. This inflammatory process increases the breakdown of corneodesmosomes resulting in acral peeling lesions. It is estimated that skin peeling can be improved when systemic inflammation and microthrombi are restored and blood flow returns to normal [33].

The downregulation in the expression of KLK5 and KLK7 through increasing SPINK5 levels by ginseng inhibits the degradation of DSG1 and reduces the overall epidermal exfoliation, offering promise as a treatment for acral peeling lesions [32].

2.1.4. Red half-moon nail sign

One hallmark sign of COVID-19 is a red “half-moon” nail or the appearance of transversal red bands on the fingernail. However, the pathogenesis of this sign is not well understood. As COVID-19 causes inflammatory immune responses and coagulation-promoting conditions resulting in microvascular damage, it may be surmised that damage to the capillary network of the distal subungual arcade results in the transversal red bands or red half-moon nail sign [34].

Ginsenoside Rb1 reduces microvascular leakage by inhibiting NF-κB and Src activation [35]. In addition, ginseng dilates blood vessels through the activation of endothelial nitric oxide [36]. This

offers promise for general improvement in vascular health as well as the alleviation of the red half-moon nail sign.

2.1.5. Maculopapular lesions

Maculopapular lesions are among the most common skin manifestations in patients infected with SARS-CoV-2 [37]. These rashes appear as red, flat lumps on red skin that are pruritic and of varying duration depending on the cause. These lesions are typically caused by drugs or multiple concurrent viral infections. Viral infections are the main cause of maculopapular lesion outbreaks in childhood, whereas in adulthood, adverse drug eruptions typically stimulate their development [38]. The exact causes and mechanisms behind maculopapular lesions are unknown; however, infections and both organic and inorganic substances can act as antigens, suggesting the possibility of an induced immune response. Macrophages are at the center of maculopapular rashes, responding to the stimulation of chronic cytokines. Epithelioid cells differentiated from macrophages gather to form an organization, and lymphocytes wrap around them, resulting in maculopapular rashes. In response to antigen-presenting cells, CD4+ T cells initiate an immune mechanism, while IL-2 secreted from T cells and IFN-γ and TNF-β secreted from macrophages mediate immune responses [39].

Ginsenoside, the major active component of ginseng, is a powerful therapeutic agent that inhibits the expression of pro-inflammatory cytokines [40]. In a recent study, researchers revealed that ginsenosides Rh1, Rg5, and Rk1 suppressed IFN-γ-induced iNOS gene activation by inhibiting not only the JAK/STAT and ERK signaling pathways but also downstream molecules such as STAT, IRF-1, and NF-kB. Based on these results, we predict that ginseng/ginsenosides may be a potent therapeutic agent for improving maculopapular lesions [41].

2.1.6. Livedo racemosa

Livedo racemosa is one of the most common skin symptoms in patients with COVID-19, manifesting as slow blood flow to the heart, the lack of oxygen, the inflammation of blood vessels, cutaneous thrombosis, or autoimmune diseases, and is primarily caused by the occlusion of small blood vessels. Typically observed in middle-aged women or adolescent patients, the primary symptoms of livedo racemosa include the appearance of reticulate patterns on the skin throughout the body, blue discoloration of the skin, asymmetrical dusky patches, and blood desaturation.

The pathogenesis of SARS-CoV-2-associated livedo racemosa remains unclear, but a few pathogenic hypotheses have been posited. One is the inhibition of type I interferon response, in which the binding of single-stranded RNA of the SARS-CoV-2 virus to toll-like receptors 7 and 8 promotes the production of type I interferons [42,43]. Interferons are then secreted and bound to the homodimer receptors of type I interferons. STAT1, which plays a pivotal role in signal transduction and transcriptional activation, is then phosphorylated and activated. STAT2, which initiates the generation of a host of protective proteins, such as interferon-induced transmembrane protein (IFITM) 3, is also phosphorylated, promoting its ability to reduce COVID-19 outcomes [43]. In patients with COVID-19, it has been confirmed that the type I interferon response is minimal [42]. Thus, enhancing the expression of type I interferons is a key strategy for improving livedo racemosa.

Recently, it has been reported that red ginseng extract (RGE) and its ginsenosides can activate anti-viral proteins such as IFN-α, IFN-β, and IFN-ω, which are included in type I interferons [44]. Therefore, we suggest that using RGE or standardized ginsenosides as therapeutic agents may offer effectiveness for Livedo racemosa.

2.1.7. Papulovesicular exanthem

A papulovesicular exanthem has been associated with COVID-19, the main symptoms of which include rashes on the trunk accompanied by pain, burning sensations, and pruritus [45]. Papulovesicular exanthems are divided into two categories based on their morphological patterns. The first is a polymorphic pattern characterized by the distribution of small papules and pustules of various sizes throughout the trunk of the body. The second, a localized pattern, occurs less frequently and is topically distributed on the trunk, focused on the mid-chest and back. Although papulovesicular exanthems are typically seen in patients around the age of 60 years, they sometimes occur in children [46]. A pathogenic hypothesis of COVID-19-related papulovesicular rash is associated with direct viral damage to basal keratinocytes, leading to epidermal necrosis causing acantholysis and the expansion of keratinocytes and ballooning degeneration of keratinocytes and vascular endothelium in the dermal vessels [47]. When cells are infected with SARS-CoV-2, spike glycoprotein binds to the ACE2 receptor and enters the target cells. ACE2 is known to be expressed at higher levels in keratinocytes than in other skin cells, especially in differentiated and basal keratinocytes, resulting in a high vulnerability of keratinocytes to COVID-19 and a high possibility that various skin lesions can arise owing to the dysfunction of the skin barrier [48].

According to a recent study, 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 effectively suppress the binding between the spike glycoprotein, the binding protein of SARS-CoV-2, and the ACE2 receptor. This action may play a key role in the treatment of papulovesicular exanthem by preventing entry of the virus into keratinocytes [49].

2.2. Immune response-induced skin lesions with SARS-CoV-2 infection and the potential of ginseng/ginsenoside

Infection with SARS-CoV-2 may lead to an immune imbalance by inducing an over-active immune response, resulting in an increase in the incidence of autoimmune diseases [50]. These diseases include retiform purpura, immune thrombocytopenic purpura, erythema multiforme, IgA vasculitis, and allergic contact dermatitis. Although the statistical analyses have not been shown in detail, there was a significant increase in the development of cutaneous autoimmune disorders after SARS-CoV-2 infection in patients between the ages of 18 and 65.

2.2.1. Retiform purpura

Retiform purpura has been reported in patients with severe COVID-19, presenting with acral purpura, necrosis, and ulceration. One potential cause is microthrombus synthesis following systemic complement activation as a response to the infection. Thrombosis and the hyperactivation of complements can lead to platelet microthrombus aggregation [51], and an impaired type-1 interferon response can be associated with retiform purpura, as it plays an important role in regulating the anti-viral immune response. Further, minimal type-1 interferon presence in the early stages of infection may be behind the phenomenon patients with of the cytokine storm that leads to severe COVID-19. In a review of data from 3939 patients with COVID-19, increased cytokine levels, particularly of IL-6, IL-1β, IL-10, TNF, GM-CSF, IFN-induced protein 10 (IP-10), IL-17, MCP-3, and IL-1ra, were reported [52].

Ginseng has been shown to have curing effects against thrombosis and microthrombi aggregation; specifically, ginsenosides Rg3, Rp3 and gintonin suppress platelet coagulation by targeting collagen-, ADP-, and thrombin-induced platelet aggregations [53]. Further, ginseng has been suggested to be helpful in controlling the cytokine storm in COVID-19, as ginsenosides -Rb1, -Rg3, -Rk1, and

-Rk3 can reduce the serum levels of several pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α). They also downregulate the expression of pro-inflammatory cytokines [54].

2.2.2. Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by platelet destruction [55]. The pathogenesis of COVID-19-induced ITP is unclear, but the dysregulation of T-cells and hyperactivity of the NLRP3 inflammasome have been suggested as potential causes [56]. In ITP, Th17 levels are increased, and the unbalanced Th1/Th2 ratio produces autoantibodies against platelets. The elevation of Th17 and plasma IL-17 levels have been reported in patients with COVID-19 and stimulates keratinocytes, fibroblasts, neutrophils, and endothelial cells while promoting tissue inflammation [57,58]. Additionally, inflammasome activation leads to the production of cytokines such as IL-1β and IL-18, and the overactivation of IL-18 can accelerate the proliferation and cytotoxicity of CD8+ T cells [56].

Ginseng suppresses hyperactivation of the NLRP3 inflammasome. Further, Rb1, Rg1, Rg2, Rg3, Rg5, Rd, Re, Rh1, 25-OCH3-PPD, and compound K in *P. ginseng* can inhibit NLRP3 inflammasome stimulation [59]. Jhun et al showed that RGE specifically has regulatory effects on Th17 cells and that treatment with RGE reduced the number of Th17 cells [60]. *Panax notoginseng* saponins can suppress the proliferation and differentiation of Th17 cells and downregulate IL-17 expression [61]. Further, ginsenoside Rg3, a component of red ginseng, can also interfere with Th17 cell differentiation and IL-17 expression [62].

2.2.3. Erythema multiforme

Erythema multiforme (EM) is an immune-mediated skin disease associated with viral infections accompanied by reddish papules, fever, and headache [63]. Hyperactivity of lymphocytes against SARS-CoV-2 antigens and perivascular lymphocytic infiltration have been found in COVID-19-induced EM [64]. Keratinocyte apoptosis by overreactive CD8+ T cells is associated with EM-like lesions [65].

Korean Red ginseng modulates the CD4+/CD8+ T-cell ratio [66]. Similarly, treatment with panaxadiol, a saponin component, increased the number of CD3+/CD4+ cells and reduced that of CD3+/CD8+ cells in a mice model [67]. In addition, Korean Red extract can suppress radiation-induced apoptosis in keratinocytes [68]. Ginsenoside Rg3 has anti-apoptotic effects, and *P. notoginseng* saponins upregulate the level of the anti-apoptotic protein Bcl-2 [69]. Thus, ginseng offers potential effectiveness for the treatment of EM.

2.2.4. IgA vasculitis

Immunoglobulin A (IgA) vasculitis, also known as Henoch-Schönlein purpura (HSP), is a systemic vasculitis caused by IgA accumulation in the blood vessels; thus increased levels of galactose-deficient IgA1 (Gd-IgA1) and immune complexes can cause inflammation [70]. Following SARS-CoV-2 infection of the mucosal layer, elevated IL-6 levels accelerate Gd-IgA1 synthesis. Other cytokines produced by SARS-CoV-2 such as IL-1 and TNF also stimulate IgA1-producing B cells [71].

Compound K (CK) from ginsenosides has been suggested as a possible therapeutic drug candidate for IgA nephropathy. Further, as HSP can lead to IgA nephropathy, inflammation of the kidney following IgA aggregation, CK can suppress NF-κB/NLRP3 inflammasome in IgA nephropathy mouse models and promote autophagy, offering therapeutic value for both HSP and IgA nephropathy [72].

2.2.5. Allergic contact dermatitis

Allergic contact dermatitis (ACD) is primarily related to PPE such as facial masks and hand sanitizers [73]. Irritants include polyurethane found in sponge strips on masks and formaldehyde contained in sanitizers [74]. ACD is mediated by T regulatory cells (IL-10-producing cells and CD4+/CD25+ cells), epidermal Langerhans cells, and keratinocytes. The activation of immune cells results in the release of cytokines such as IL-22, IL-18, and IL-12. These cytokines are related to Th1 and inflammatory responses [75].

Enhanced Rg3 contents from KRG can suppress the expression of IL-12 and differentiation of Th1 cells [76]. In addition, the Rb1 fraction of ginseng may help balance Th1 and Th2 immune responses [77]. Further, the gintonin-enriched fraction of KRG and Rg1 have anti-inflammatory effects and can reduce IL-18 levels [78]. Thus, KRG specifically offers therapeutic value for ACD.

2.3. Complex (both inflammatory and immune) response-induced skin lesions with SARS-CoV-2 infection and the effect of ginseng/ginsenoside

Skin lesions may occur via a complex mechanism involving both inflammatory and immune responses caused by SARS-CoV-2 infection. Such lesions include pustular psoriasis, acne, rosacea, urticaria, and hand hygiene-related hand eczema. For example, 82.4% of existing hand eczema cases occurred during the pandemic, indicating that the development of this disorder is highly related to hygiene measures aimed at preventing SARS-CoV-2 infection [79].

2.3.1. Pustular psoriasis

Pustular psoriasis is a rare immune-mediated inflammatory skin disease with fatal effects in patients with COVID-19 [80]. This condition arises primarily in adults and can be classified as generalized pustular or localized pustular psoriasis, depending on the location. Generalized pustular psoriasis is distributed throughout the body, whereas localized pustular psoriasis is found on the hands and feet [81]. The major symptoms of pustular psoriasis include inflammatory erythema, white or yellow pustules, fever, silvery scales, and thickening of the skin [82]. It has recently been reported that mutations of interleukin-36 receptor is closely associated with pustular psoriasis [83]. When IL-36α, IL-36β, and IL-36γ bind to the IL-36 receptor, recruitment of the IL-1 receptor accessory protein is induced, resulting in the activation of NF-κB and mitogen-activated protein (MAP) kinases (MAPK) [84]. NF-κB and MAPK translocate into the nuclei of keratinocytes and phosphorylate target transcription factors such as AP-1 and NF-κB genes [85]. This leads to the production and secretion of pro-inflammatory cytokines including IL-1, IL-8, CXCL1, CXCL2, CXCL8, and CXCL20, which mediate inflammatory responses. Here, interleukin-36−receptor antagonists (IL-36Ra) such as spesolimab and imsidolimab block IL-36α, IL-36β, and IL-36γ from binding to the interleukin-36−receptor, thereby attenuating NF-κB and MAPK activities [86]. SARS-CoV-2 infection causes a loss-of-function mutation in IL-36Ra, inducing excessive inflammatory responses through the hyperactivation of IL-36 signaling, resulting in pustular psoriasis [84,86,87].

Currently, few studies have shown an association between ginseng and IL-36Ra. *Panax ginseng*, ginsenosides of the new green berry cultivar K-1, and ginsenoside compound K are well known to play a role in alleviating excessive inflammatory responses by inhibiting NF-κB, leading to reduced expression of its downstream signaling molecules [88−90]. Additionally, ginseng root extract, RGE, and ginsenoside Rb3 act as potential inhibitors of the MAPK pathways [91−93]. These results suggest that ginseng and its compounds can have beneficial effects on improving COVID-19-associated pustular psoriasis.

2.3.2. Acne

Acne is a very common skin manifestation affecting adolescents and young adults [94]. *Propionibacterium acnes*, located in sebaceous areas, are the most abundant bacteria on human skin [95]. *Propionibacterium acnes* is involved in host inflammatory responses by inducing innate immune cells to secrete pro-inflammatory cytokines, such as TNF-α and members of the IL-1 family [96]. Notably, IL-1 β has been revealed to be the most potent initiator among pro-inflammatory cytokines to trigger acne lesions [97]. One study showed that *P. acnes* induces gene expression of NLRP3 in human monocytes. The NLRP3 inflammasome is a key pathogenic factor that induces the generation of IL-1 β, the main trigger for acne lesions [98]. This finding indicates that regulating the NLRP3 inflammasome effectively inhibits the secretion of IL-1 β, which triggers acne .

Ginsenosides are quite well known as a potent therapeutic substance with anti-inflammatory properties, with years of research on adjuvants in inflammatory disorder treatment [99]. They have shown potent effects on inflammasome activation, specifically on IL-1 β regulation [100]. Moreover, researchers have found that ginsenosides inhibit NLRP3. Rh1 and Rg3 were identified as the main active ginsenosides to suppress IL-1 β secretion, with Rg3 being the most potent inhibitor of NLRP3 inflammasome activation [101]. Taken together, these results suggest that ginsenosides can effectively repress acne lesions by inhibiting IL-1 β secretion.

As COVID-19 is known to spread by droplets, the use of masks as a physical barrier has become essential; however, doing so can cause cutaneous issues including acne, peeling of skin, rashes, pruritis, and pressure injuries [102]. Acne is the most prevalent of these issues owing to friction from the mask fabric [103]. Further, the N-95 mask, the most optimal barrier protection from COVID-19, increases sweating by poor air circulation which triggers clogging and congestion on the skin [104]. As the mask traps breath, it increases humidity and temperature, forming a warm and moist environment that allows bacteria to breed actively. Therefore, changes in the microenvironment of the skin due to dehydration and increased sebum promote innate immune responses and trigger inflammatory lesions [103,105].

According to one study, the oral medication isotretinoin, which is used to treat acne lesions, was identified as a treatment for COVID-19, acting by downregulating the expression ACE2 receptors, preventing SARS-CoV-2 entry into vulnerable cells [106]. Similarly, ginsenosides are known to block the receptor-binding domain (RBD)-ACE2 interaction by suppressing the RBD on the coronavirus spike glycoprotein [107]. One study showed that 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 repressed viral infection in cells that specifically express the receptors [35]. As a result, 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 show the possibility of a therapeutic effect in inhibiting the inflammatory responses caused by COVID-19 .

2.3.3. Rosacea

The impact of a dysregulatory vascular system associated with the skin-nervous system is the cause of rosacea [108]. The direct involvement of neurovascular dysregulation is related to specific cell surface receptors stimulated by several trigger factors including ethanol, spicy food, high environmental temperatures, and TRPV1 [109]. TRPV1, expressed by sensory nerves, is involved in vasoregulation and nociception, and thus neurovascular dysregulation through TRPV1 may lead to the early stage of rosacea characterized by transient flushing (“pre-rosacea”). When TRPV1 is activated in patients with rosacea, the receptor eventually becomes hyperactive, causing persistent flushing, a feeling of warmth, and often extensive neurogenic inflammation with edema and inflammatory cell infiltration [110]. According to this hypothesis, patients with rosacea show a high density of epidermal and dermal TRPV1 in nerve fibers; thus, TRPV1 may be a primary therapeutic target for rosacea.

A major symptom for patients with rosacea is pruritus that leads to scratching, which may in turn result in inflammation and severe destruction of the skin barrier [111]. Pruritogens stimulate sensory neurons to produce electrical signals in itch-mediating sensory neurons, which are then transmitted to the brain for the final itch perception [112]. Among pruritogens, histamine is an endogenous mediator of itch sensation. Histamine receptor subtype 1 [H1R] in sensory neurons is essential for transmitting signals involved in itch sensations [113]. According to one study, histamine-induced itch was considerably reduced in TRPVQ−/− mice, demonstrating its relation to H1R and TRPV1 [114].

KRG has been reported as having an anti-pruritic effect on scratching and skin diseases, specifically in animal models of atopic dermatitis, with one recent study showing KRG to have an anti-pruritic effect against histamine-induced scratching in mice. The main group of pruritus-generating sensory neurons is known as TRPV1-positive sensory neurons, which are reported to transduce the itch signal by stimulating histamine, which binds to the itch-specific H1R. Subsequently, a particular signaling cascade results into the production of endogenous TRPV1 activators. After TRPV1 activation, the itch signal is eventually transmitted to the brain [114]. Therefore, blocking of the H1R/TRPV1 pathway may be a therapeutic strategy for the treatment of rosacea through alleviation of the histamine-induced itch .

2.3.4. Urticaria

Also known as hives, urticaria presents as the rapid appearance of wheals accompanied by angioedema [115]. Several recent reports have associated urticaria with COVID-19 infection, with many theories for this connection based on the pathogenesis of urticaria involving autoinflammation and mast cell mediator release. According to recent studies, COVID-19-associated skin manifestations tend to be triggered by a systemic inflammatory response that leads to a severe acute infection. This promotes the cytokine-chemokine milieu, resulting in the aberrant activation and degranulation of mast cells which are known to be involved in the organ damage caused by SARS-COV-2. Similarly, mast cell degranulation is significantly involved in the development of urticaria [116].

Mast cells produce and release pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1 β that characterize COVID-19, and several studies have suggested that the novel coronavirus affects the activation of mast cells. First, these cells play an essential role both as key effector cells in urticaria and cytokine storms. Moreover, mast cells identify and interact with coronaviruses through a number of receptors including toll-like receptors, retinoic acid-inducible gene-I-like receptors, and IL-1 receptors. Responses to these receptors leads to the activation and degranulation of mast cells that triggers urticaria lesions. In addition, the expression of the ACE2 protein involved in urticaria allows SARS-COV-2 binding. Therefore, COVID-19 may exacerbate urticaria lesions [117].

Ginsenoside Rg3-enriched RGE has been shown to significantly suppress matrix MMP9 activity, COX-2 expression, and the production of pro-inflammatory cytokines including TNF-α, IL-1 β, and IL-6. In addition, ginsenoside Rf indicates an inhibitory effect on the inflammatory mediators downstream of p38/NF-kB activation, including the downregulation of IL-1 β, IL-6, TNF-α, NO, and reactive oxygen species production [118]. Therefore, substances extracted from ginseng are effective in reducing the levels of cytokines induced by COVID-19.

Table 1
Summary of Symptoms, Pathogenesis, and Therapeutic Effects of Ginseng for COVID-19-associated Skin Disorders (Inflammatory)

Skin disease	Telogen effluvium	Multisystem inflammatory syndrome in children	Acral peeling lesions	Red half-moon nail sign	Maculopapular lesion	Livedo racemosa	Papulovesicular exanthem
Symptoms	Hair thinning and falling out	Macules, papules, erythema, extremity swelling and desquamation, mucositis, and polymorphic rashes in the flexion area	The keratinocytes in the outermost layer of the stratum corneum are gradually peeled off.	Half-moon-shaped red bands on the nails	Red lumps grown on red skin, itchiness	Appearance of reticulate patterns throughout the body, discoloration of the skin to blue, blood desaturation and asymmetrical dusky patches	Rashes on the trunk, pain, burning sensation, and pruritus
Pathogenesis	Increased levels of cytokines such as interferon, formation of mi-crothrombosis	Activation of B cells and plasma cells Hyperimmune reaction	Degradation of corneodesmoso -mes due to expression of KLK5 and KLK7	Damage to the capillary network due to microvascular injury	Systemic initiation of immune responses by CD4+ T cells, leading to secretion of IL-2 from the T cells and secretion of IFN-γ and TNF-β from macrophages	Inhibition of type I interferon response	Spike glycoprotein of SARS-CoV-2 virus binds to the ACE2 receptor and induces epidermal necrosis involved in acantholysis and expansion of keratinocytes, ballooning degeneration of keratinocytes and vascular endothelium in the dermal vessels
Therapeutic effects of ginseng	Interferon regulation, Increases the expression of VEGF, and improves blood supply to hair follicles	Suppressing the hyperimmune response through inhibition of nuclear factor of activated B cell signaling	Downregulated expression of KLK5 and KLK7 by upregulating expression of SPINK5	Inhibits NF-κB and Src activation and improves vascular health by activating endothelial nitric oxide	Suppressed IFN-γ-induced iNOS gene activation by inhibiting JAK/STAT and ERK signaling pathways	Red ginseng extract (RGE) activates type I interferons, including IFN-α, IFN-β, and IFN-ω	20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 suppressed the binding between SARS-CoV-2 virus and ACE2 receptor

Table 2
Summary of symptoms, pathogenesis, and therapeutic effects of ginseng for COVID-19-associated skin disorders (immune)

Skin disease	Retiform purpura	Immune thrombocytopenic purpura (ITP)	Erythema multiforme (EM)	IgA vasculitis
Symptoms	Acral purpura, necrosis, and ulceration	Mucocutaneous bleeding, petechiae, bruising	Reddish papules, plaques, fever, and headache	Skin rash, purpura, cutaneous vasculitis
Pathogenesis	Microthrombi synthesis following systemic complement activation; cytokine storm	Dysregulation of T-cells hyperactivity of NLRP3 inflammasome	Keratinocyte apoptosis by overreactive CD8+ T cells	Small vessel inflammation caused by IgA accumulation
Therapeutic effects of ginseng	Ginsenosides Rg3, Rp3, and gintonin can suppress platelet coagulation Ginsenosides-Rb1, -Rg3, -Rk1, -Rk3 can reduce serum levels of IL-1β, IL-6, and TNF-α	Rb1, Rg1, Rg2, Rg3, Rg5, Rd, Re, Rh1, 25-OCH3-PPD, and CK in *Panax ginseng* can inhibit NLRP3 inflammasome stimulation	Korean red ginseng can modulate CD4+/CD8+ T cell ratio and panaxadiol, a saponin component, can reduce the number of CD3+CD8+ cells	CK can suppress NF-κB/NLRP3 inflammasome in IgA nephropathy

2.3.5. Hand hygiene-related hand eczema

Owing to frequent hand washing being highly recommended to prevent SARS-CoV-2 transmission, the number of patients affected with severe hand eczema has increased [119]. Both endogenous and exogenous factors can affect this condition, with atopic dermatitis known to be the most significant risk factor. However, exogenous factors are also of etiological importance, as handwashing with water, detergents, or alcohol-based hand rubs results in an increase in trans-epidermal water loss and alteration of barrier function, allowing for easier penetration of external irritants and allergens [120]. Water alone can eliminate free amino acids, which are natural moisturizing factors that help the skin maintain sufficient hydration. In addition, skin pH increases immediately after water contact, whereas an acidic pH is required for the critical functioning of several enzymes for the synthesis of the stratum corneum, which is required for the skin barrier and maintains lipid metabolism and desquamation [121].

Atopic dermatitis (AD) is a chronic inflammatory allergic skin disease characterized by pruritic eczema and triggered by the destruction of the skin barrier and increased levels of serum IgE and cytokines released from inflammatory cells [122].

As RGE offers anti-atopic and anti-allergic effects, it can be used to treat inflammatory skin diseases. In several recent studies, RGE from ginseng significantly lowered the levels of Th2-activated cytokines including IL-4 and IL-10 and total serum IgE and improved skin lesions [19]. Therefore, ginseng may offer effectiveness as a therapeutic agent for the treatment of eczema.

3. Conclusion

Research on COVID-19-related skin diseases has been actively conducted since the establishment of the SARS-CoV-2 global pandemic. In this study, we compiled the existing pathogenic hypotheses for skin lesions paired with the corresponding evidence for ginseng and its active compounds for showing high potential to cure these disorders. The clinical features, pathogenesis, and therapeutic effects of ginseng for COVID-19-associated skin manifestations are also summarized in Tables 1–3. The data included in

Table 3
Summary of symptoms, pathogenesis, and therapeutic effects of ginseng for COVID-19-associated skin disorders (complex)

Skin disease	Pustular psoriasis	Acne	Rosacea	Urticaria	Hand hygiene-related hand eczema
Symptoms	Inflammatory erythema, white or yellow pustules, fever, silvery scales, and thickening of the skin	Papules, pustules, excess sebum production	Persistent flushing, itchiness, scratching, burning sensation, swelling	Wheal, raised itchy bumps, pruritus, flares	Itchiness, discolored skin, dryness, crusting
Pathogenesis	Deficiency of interleukin-36 receptor antagonists	- Induces NLRP3 inflammasome which promotes generation of IL-1β - Changes of microenvironment in the skin by dehydration and increased sebum due to wearing of PPE	High density of epidermal and dermal TRPV1 in nerve fibers	Activation and degranulation of mast cells	- Increase in the trans-epidermal water loss and the penetration of external irritants and allergens by altering the skin barrier function. - Elimination of free amino acids and increased skin pH
Therapeutic effects of ginseng	- *Panax ginseng*, ginsenosides of new green berry cultivar K-1, and ginsenoside compound K inhibit NF-κB pathways. - Ginseng root extract, red ginseng extract (RGE), and ginsenoside Rb3 inhibit MAPK pathways (NF-κB and MAPK: downstream targets of IL-36)	Rh1 and Rg3 ginsenosides suppress IL-1β secretion. Additionally, Rg3 is an inhibitor of NLRP3 inflammasome activation. - 20(S)-ginsenoside Rg3 and 20(R)-ginsenoside Rg3 repress infection by blocking receptor-binding domain-ACE2 interaction.	Anti-pruritic effect on scratching or skin disease by blocking H1R/ TRPV1 pathway	- Ginsenoside Rg3-enriched RGEs suppress matrix MMP9 activity, COX-2 expression, and pro-inflammatory cytokine production including of TNF-α, IL-1β, and IL-6 - Inhibitory effect of ginsenoside Rf on the inflammatory mediators downstream of p38/NF-κB activation, including the downregulation of IL-1β, IL-6, TNF-α, NO and ROS productions	RGE from ginseng decreases the levels of Th2-activated cytokines, including IL-4 and IL-10, and total serum IgE and improves the skin lesion

Tables 1–3 have some verified information; however, most of the data are from indirect information used to describe the possible therapeutic efficacy of ginseng and its active compounds for skin diseases. Therefore, it is necessary to demonstrate the efficacy of ginseng and its active compounds for the treatment of skin diseases using systematic investigation. This may provide the opportunity to expand the applications of ginseng and its active compounds in the treatment of skin diseases.

Author contributions

SY, SBH, SK, JL, DK, AK, MS, S-HP, and JL searched and collected the literature, summarized the contents, and described the articles. SY, SBH, SK and JL organized the tables and created the pictures. MS, S-HP, and JL provided valuable suggestions during manuscript preparation and critically revised the manuscript accordingly. MS, S-HP, and JL conceptualized and wrote the manuscript. All authors have read and approved the final manuscript.

Declaration of competing interest

The authors declare no conflicts of interest associated with this study. There has been no significant financial support for this study that could have influenced its outcome.

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References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. N Engl J Med 2019;382(2020):727–33.
[2] World Health Organization. Coronavirus disease 2019 (COVID-19): situation report, vol. 88. World Health Organization; 2020.
[3] Tahvildari A, Arbabi M, Farsi Y, Jamshidi P, Hasanzadeh S, Calcagno TM, et al. Clinical features, diagnosis, and treatment of COVID-19 in hospitalized patients: a systematic review of case reports and case series. Front Med 2020;7:231.
[4] Tisminetzky M, Delude C, Hebert T, Carr C, Goldberg RJ, Gurwitz JH. Age, multiple chronic conditions, and COVID-19: a literature review. *The* Journals of Gerontology: Series A 2022;77(4):872–8.
[5] Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, Guo L, Guo R, Chen T, Hu J, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nature Communications 2020;11(1):1–12.
[6] Koch J, Uckeley ZM, Doldan P, Stanifer M, Boulant S, Lozach PY. TMPRSS2 expression dictates the entry route used by SARS-CoV-2 to infect host cells. The EMBO Journal 2021;40(16):e107821.
[7] Trougakos Ioannis P, Stamatelopoulos Kimon, Terpos Evangelos, Tsitsilonis Ourania E, Aivalioti Evmorfa, Paraskevis Dimitrios, Kastritis Efstathios, Pavlakis George N, Dimopoulos Meletios A, et al. Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. Journal of Biomedical Science 2021;28(1):1–18.
[8] Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol JEADV 2020;26. Published online March.
[9] Zheng Y, Lai W. Dermatology staff participate in fight against Covid-19 in China. J Eur Acad Dermatol Venereol JEADV 2020;34(5):e210–1. Published online March 23.
[10] Darlenski R, Tsankov N. Covid-19 pandemic and the skin - what should dermatologists know? Clin Dermatol 2020;38(6):785–7. Published online March 24.
[11] Tammaro A, Adebanjo GaR, Parisella FR, Pezzuto A, Rello J. Cutaneous manifestations in COVID- 19: the experiences of barcelona and rome. J Eur Acad Dermatol Venereol JEADV 2020;34(7):e306–7. Published online April 24.
[12] Su C-J, Lee C-H. Viral exanthem in COVID-19, a clinical enigma with biological significance. J Eur Acad Dermatol Venereol JEADV 2020;34(6):e251–2. Published online April 15.
[13] Lee SE, Park YS. Korean Red Ginseng water extract inhibits COX-2 expression by suppressing p38 in acrolein-treated human endothelial cells. J Ginseng Res 2014;38(1):34–9. https://doi.org/10.1016/j.jgr.2013.11.004. Epub 2013 Dec 8. PMID: 24558308; PMCID: PMC3915333.
[14] Wee JJ, Mee Park K, Chung AS. Biological activities of ginseng and its application to human health. In: Benzie IFF, Wachtel-Galor S, editors. Herbal medicine: biomolecular and clinical aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011 [Chapter 8]. Available from:. https://www.ncbi.nlm.nih.gov/books/NBK92776/.
[15] Liang LD, He T, Du TW, Fan YG, Chen DS, Wang Y. Ginsenoside-Rg5 induces apoptosis and DNA damage in human cervical cancer cells. Molecular Medicine Reports 2015;11(2):940–6. https://doi.org/10.3892/mmr.2014.2821.
[16] Wong AS, Che CM, Leung KW. Recent advances in ginseng as cancer therapeutics: a functional and mechanistic overview. Natural Product Reports 2015;32(2):256–72. https://doi.org/10.1039/c4np00080c.

[17] Lee DC, Lau AS. Effects of Panax ginseng on tumor necrosis factor-α-mediated inflammation: a mini-review. Mar 30 Molecules 2011;16(4):2802–16. https://doi.org/10.3390/molecules16042802. . PMID: 21455094; PMCID: PMC6260618.
[18] Ji-Ye Kee, et al. Korean Red Ginseng improves atopic dermatitis-like skin lesions by suppressing expression of proinflammatory cytokines and chemokines in vivo and in vitro.". Journal of Ginseng Research 2017;41(2):134–43.
[19] Sohn E-H, Jang S-A, Lee C-H, Jang K-H, Kang S-C, Park H-J, et al. Effects of Korean red ginseng extract for the treatment of atopic dermatitis-like skin lesions in mice. Journal of Ginseng Research 2011:479–86. Elsevier BV.
[20] Lee Joon Kee, Cho Eun Young, Lee Hyunju. Multisystem inflammatory syndromein children (MIS-C). Aug Pediatr Infect Vaccine 2021;28(2):66–81. Korean. Published online, . [Accessed 26 August 2021].
[21] Rizzetto G, Diotallevi F, Campanati A, Radi G, Bianchelli T, Molinelli E, Mazzanti S, Offidani A. Telogen effluvium related to post severe Sars-Cov-2 infection: clinical aspects and our management experience. Dermatol Ther 2021;34(1):e14547. Jan.
[22] Olds H, Liu J, Luk K, Lim HW, Ozog D, Rambhatla PV. Telogen effluvium associated with COVID-19 infection. Dermatologic Therapy 2021;34(2):e14761.
[23] Rabaan AA, Al-Ahmed SH, Muhammad J, Khan A, Sule AA, Tirupathi R, Mutair AA, Alhumaid S, Al-Omari A, Dhawan M, et al. Role of inflammatory cytokines in COVID-19 patients: a review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. Vaccines (Basel) 2021;9(5):436. Apr 29.
[24] Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34(2):327–31. March-April.
[25] Rossi A, Magri F, Sernicola A, Michelini S, Caro G, Muscianese M, Grieco T. Telogen effluvium after SARS-CoV-2 infection: a series of cases and possible pathogenetic mechanisms. Skin Appendage Disorders 2021;7(5):377–81.
[26] Darif D, Hammi I, Kihel A, El Idrissi Saik I, Guessous F, Akarid K. The pro-inflammatory cytokines in COVID-19 pathogenesis: what goes wrong? Microb Pathog 2021;153:104799. Apr.
[27] Choi BY. Hair-growth potential of ginseng and its major metabolites: a review on its molecular mechanisms. International Journal of Molecular Sciences 2018;19(9):2703.
[28] Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothetical pathogenesis, and proposed management. Children 2020;7(7):69.
[29] Ahn H, Han BC, Kim J, Kang SG, Kim PH, Jang KH, Lee GS. Nonsaponin fraction of Korean Red Ginseng attenuates cytokine production via inhibition of TLR4 expression. Journal of Ginseng Research 2019;43(2):291–9.
[30] DeHaven Charlene. Mechanisms of exfoliation. 2015.
[31] Has C. Peeling skin disorders: a paradigm for skin desquamation. Journal of Investigative Dermatology 2018;138(8):1689–91.
[32] Li Z, Jiang R, Jing C, Liu J, Xu X, Sun L, Zhao D. Protective effect of oligosaccharides isolated from Panax ginseng CA Meyer against UVB-induced skin barrier damage in BALB/c hairless mice and human keratinocytes. Journal of Ethnopharmacology 2022;283:114677.
[33] Deng J, Ngo T, Zhu TH, Halverstam C. Telogen effluvium, Beau lines, and acral peeling associated with COVID-19 infection. JAAD Case Reports 2021;13:138–40.
[34] Neri I, Guglielmo A, Virdi A, Gaspari V, Starace M, Piraccini B. The red half-moon nail sign: a novel manifestation of coronavirus infection. Journal of the European Academy of Dermatology and Venereology 2020;34(11):e663–5.
[35] Zhang Y, Sun K, Liu YY, Zhang YP, Hu BH, Chang X, Han JY. Ginsenoside Rb1 ameliorates lipopolysaccharide-induced albumin leakage from rat mesenteric venules by intervening in both trans-and paracellular pathway. American Journal of Physiology-Gastrointestinal and Liver Physiology 2014;306(4):G289–300.
[36] Lee HJ, Kim BM, Lee SH, Sohn JT, Choi JW, Cho CW, Kim HJ. Ginseng-induced changes to blood vessel dilation and the metabolome of rats. Nutrients 2020;12(8):2238.
[37] Shams S, Rathore SS, Anvekar P, Sondhi M, Kancherla N, Tousif S, Rojas GA, Ahmed NK, Munawwar M, Noman M. Maculopapular skin eruptions associated with Covid-19: a systematic review. Mar Dermatol Ther 2021;34(2):e14788. https://doi.org/10.1111/dth.14788. Epub 2021 Feb 2. PMID: 33481314; PMCID: PMC7995033.
[38] Zhao Q, Fang X, Pang Z, Zhang B, Liu H, Zhang F. COVID-19 and cutaneous manifestations: a systematic review. Nov J Eur Acad Dermatol Venereol 2020;34(11):2505–10.
[39] Kang Eun Hae. Sarcoidosis in Korea: revisited. Journal of the Korean Medical Association 2008;51(10):925–32.
[40] Kim JH, Yi YS, Kim MY, Cho JY. Role of ginsenosides, the main active components of *Panax ginseng*, in inflammatory responses and diseases. Oct J Ginseng Res 2017;41(4):435–43. https://doi.org/10.1016/j.jgr.2016.08.004. Epub 2016 Aug 18. PMID: 29021688; PMCID: PMC5628327.
[41] Jung JS, Kim DH, Kim HS. Ginsenoside Rh1 suppresses inducible nitric oxide synthase gene expression in IFN-γ-stimulated microglia via modulation of JAK/STAT and ERK signaling pathways. Biochem Biophys Res Commun 2010;397(2):323–8. Jun 25.
[42] Magro CM, Mulvey JJ, Laurence J, Sanders S, Crowson AN, Grossman M, Harp J, Nuovo G. The differing pathophysiologies that underlie COVID-19-associated perniosis and thrombotic retiform purpura: a case series. Br J Dermatol 2021;184(1):141–50. Jan.
[43] Toader MP, Branisteanu DC, Glod M, Esanu IM, Branisteanu CI, Capsa MS, Dimitriu A, Nicolescu AC, Pinzariu AC, Branisteanu DE. Mucocutaneous lesions associated with SARS-CoV-2 infection (Review). Exp Ther Med 2022;23(4):258. Apr.
[44] Im K, Kim J, Min HJ. Ginseng, the natural effectual antiviral: protective effects of Korean Red Ginseng against viral infection. Ginseng Res. 2016;40(4):309–14. Oct.
[45] Ahmed H, Yusuf N. The cutaneous manifestations associated with COVID-19: a review. Am J Dermatol Res Rev 2020;3:31.
[46] Toader MP, Branisteanu DC, Glod M, Esanu IM, Branisteanu CI, Capsa MS, Dimitriu A, Nicolescu AC, Pinzariu AC, Branisteanu DE. Mucocutaneous lesions associated with SARS-CoV-2 infection (Review). Experimental and Therapeutic Medicine 2022;23(4):258. https://doi.org/10.3892/etm.2022.11183.
[47] Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. Dermatology 2021;237(1):1–12.
[48] Xue X, Mi Z, Wang Z, Pang Z, Liu H, Zhang F. High expression of ACE2 on keratinocytes reveals skin as a potential target for SARS-CoV-2. J Invest Dermatol 2021;141(1):206–209.e1. Jan.
[49] Possibility as role of ginseng and ginsenosides on inhibiting the heart disease of COVID-19: a systematic review. Hossain MA, Kim JH. J Ginseng Res 2022;46(3):321–30. May.
[50] Khashayar Aram,Anant Patil,Mohamad Goldust,Fateme Rajabi COVID-19 and exacerbation of dermatological diseases: a review of the available literature *Dermatologic Therapy* First published: 27 August 2021.
[51] Bosch-Amate X, Giavedoni P, Podlipnik S, Andreu-Febrer C, Sanz-Beltran J, Garcia-Herrera A, Alós L, Mascaró JM. Retiform purpura as a dermatological sign of coronavirus disease 2019 (COVID-19) coagulopathy. J Eur Acad Dermatol Venereol 2020;34(10):e548–9.
[52] Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol 2020;108(1):17–41. Jul.
[53] Lee YY, Quah Y, Shin JH, Kwon HW, Lee DH, Han JE, Park JK, Kim SD, Kwak D, Park SC, et al. COVID-19 and Panax ginseng: targeting platelet aggregation, thrombosis and the coagulation pathway. J Ginseng Res 2022;46(2):175–82. Mar.
[54] Choi JH, Lee YH, Kwon TW, Ko SG, Nah SY, Cho IH. Can Panax ginseng help control cytokine storm in COVID-19? J Ginseng Res 2022;46(3):337–47. May.
[55] Idiopathic thrombocytopenic purpura-JOHNS HOPKINS medicine.
[56] Bahadoram M, Saeedi-Boroujeni A, Mahmoudian-Sani MR, Hussaini H, Hassanzadeh S. COVID-19-induced immune thrombocytopenic purpura; Immunopathogenesis and clinical implications. Infez Med 2022;30(1):41–50. Mar 1.
[57] Ji X, Zhang L, Peng J, Hou M. T cell immune abnormalities in immune thrombocytopenia. J Hematol Oncol 2014;7:72.
[58] Takahashi N, Saitoh T, Gotoh N, Nitta Y, Alkebsi L, Kasamatsu T, Minato Y, Yokohama A, Tsukamoto N, Handa H, et al. The cytokine polymorphisms affecting Th1/Th2 increase the susceptibility to, and severity of, chronic ITP. BMC Immunol 2017;18(1):26.
[59] Yi YS. Potential benefits of ginseng against COVID-19 by targeting inflammasomes. J Ginseng Res. 2022. https://doi.org/10.1016/j.jgr.2022.03.008. Apr 4. In press.
[60] Jhun J, Lee J, Byun JK, Kim EK, Woo JW, Lee JH, Kwok SK, Ju JH, Park KS, Kim HY, et al. Red ginseng extract ameliorates autoimmune arthritis via regulation of STAT3 pathway, Th17/Treg balance, and osteoclastogenesis in mice and human. Mediators Inflamm 2014;2014:351856.
[61] Wei JR, Wen X, Bible PW, Li Z, Nussenblatt RB, Wei L. Panax notoginseng saponin controls IL-17 expression in helper T cells. J Ocul Pharmacol Ther 2017;33(4):285–9. May.
[62] Park YJ, Cho M, Choi G, Na H, Chung Y. Biomolecules. A Critical Regulation of Th17 Cell Responses and Autoimmune Neuro-Inflammation by Ginsenoside Rg3 2020;10(1):122. Jan 10.
[63] Kang JH. Febrile illness with skin rashes. Infect Chemother 2015 Sep;47(3):155–66.
[64] Signore A, Lauri C, Colandrea M, Di Girolamo M, Chiodo E, Grana CM, Campagna G, Aceti A. Lymphopenia in patients affected by SARS-CoV-2 infection is caused by margination of lymphocytes in large bowel: an [18F] FDG PET/CT study. Eur J Nucl Med Mol Imaging 2022;49(10):3419–29. Aug.
[65] Bennardo L, Nisticò SP, Dastoli S, Provenzano E, Napolitano M, Silvestri M, Passante M, Patruno C. Erythema multiforme and COVID-19: what do we know? Medicina 2021;57:828.
[66] Kim IK, Lee KY, Kang J, Park JS. Immune-modulating effect of Korean red ginseng by balancing the ratio of peripheral T lymphocytes in bile duct or pancreatic cancer patients with adjuvant chemotherapy. Jeong J. *In Vivo*. 2021;35(3):1895–900. May-Jun.
[67] Zheng ZY, Yu XL, Dai TY, Yin LM, Zhao YN, Xu M, Zhuang HF, Chong BH, Gao RL. Panaxdiol saponins component promotes hematopoiesis and

modulates T lymphocyte dysregulation in aplastic anemia model mice. Chin J Integr Med 2019;25(12):902–10. Dec.
[68] keratinocytes HaCaT, Chang JW, Park KH, Hwang HS, Shin YS, Oh YT, Kim CH. Protective effects of Korean red ginseng against radiation-induced apoptosis in human. J Radiat Res 2014;55(2):245–56. Mar 1.
[69] Zhang Y, Cai W, Han G, Zhou S, Li J, Chen M, Li H. Panax notoginseng saponins prevent senescence and inhibit apoptosis by regulating the PI3K AKT mTOR pathway in osteoarthritic chondrocytes. Int J Mol Med 2020;45(4):1225–36. Apr.
[70] Sugiyama M, Wada Y, Kanazawa N, Tachibana S, Suzuki T, Matsumoto K, Iyoda M, Honda H, Shibata T. A cross-sectional analysis of clinicopathologic similarities and differences between Henoch-Schönlein purpura nephritis and IgA nephropathy. PLoS One 2020;15(4):e0232194. Apr 23.
[71] Farooq H, Aemaz Ur Rehman M, Asmar A, Asif S, Mushtaq A, Qureshi MA. The pathogenesis of COVID-19-induced IgA nephropathy and IgA vasculitis: a systematic review. J Taibah Univ Med Sci 2022;17(1):1–13. J Taibah Univ Med Sci.
[72] Wu CY, Hua KF, Hsu WH, Suzuki Y, Chu LJ, Lee YC, Takahata A, Lee SL, Wu CC, Nikolic-Paterson DJ, et al. IgA nephropathy benefits from compound K treatment by inhibiting NF-κB/NLRP3 inflammasome and enhancing autophagy and SIRT1. J Immunol 2020;205(1):202–12. Jul 1.
[73] Di Altobrando A, La Placa M, Neri I, Piraccini BM, Vincenzi C. Contact dermatitis due to masks and respirators during COVID-19 pandemic: what we should know and what we should do. Dermatol Ther 2020;33(6):e14528. Nov.
[74] Sarfraz Z, Sarfraz A, Sarfraz M, Felix M, Bernstein JA, Fonacier L, Cherrez-Ojeda I. Contact dermatitis due to personal protective equipment use and hygiene practices during the COVID-19 pandemic: a systematic review of case reports. Ann Med Surg (Lond). 2022;74:103254.
[75] Imbesi S, Minciullo PL, Isola S, Gangemi S. Allergic contact dermatitis: immune system involvement and distinctive clinical cases. Allergol Immunopathol (Madr) 2011;39(6):374–7. Nov-Dec.
[76] Cho M, Choi G, Shim I, Chung Y. Enhanced Rg3 negatively regulates Th1 cell responses. J Ginseng Res 2019;43(1):49–57. Jan.
[77] Rivera E, Ekholm Pettersson F, Inganäs M, Paulie S, Grönvik KO. The Rb1 fraction of ginseng elicits a balanced Th1 and Th2 immune response. Vaccine 2005;23(46–47):5411–9. Nov 16.
[78] Gao Y, Li J, Chu S, Zhang Z, Chen N, Li L, Zhang L. Ginsenoside Rg1 protects mice against streptozotocin-induced type 1 diabetic by modulating the NLRP3 and Keap1/Nrf2/HO-1 pathways. Eur J Pharmacol 2020;866:172801. Jan 5.
[79] Reinholz M, Kendziora B, Frey S, Oppel EM, Ruëff F, Clanner-Engelshofen BM, Heppt MV, French LE, Wollenberg A. Increased prevalence of irritant hand eczema in health care workers in a dermatological clinic due to increased hygiene measures during the SARS-CoV-2 pandemic. European Journal of Dermatology : EJD 2021;31(3):392–5. https://doi.org/10.1684/ejd.2021.4046.
[80] Shahidi Dadras M, Diab R, Ahadi M, Abdollahimajd F. Generalized pustular psoriasis following COVID-19. Dermatol Ther 2021 Jan;34(1):e14595.
[81] Fujita H, Gooderham M, Romiti R. Diagnosis of generalized pustular psoriasis. Am J Clin Dermatol 2022;23(Suppl 1):31–8. Jan.
[82] Pustular Psoriasis Shah M, Al Aboud DM, Crane JS, Kumar S. In: Stat*Pearls*; 2022. May 8.
[83] Liu ZJ, Tian YT, Shi BY, Zhou Y, Jia XS. Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2020;99(45):e23068. Nov 6.
[84] Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, Zribi J, Bal E, Cluzeau C, Chrabieh M, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. Smahi N Engl J Med 2011;365(7):620–8. Aug 18.
[85] López-Camarillo C, Ocampo EA, Casamichana ML, Pérez-Plasencia C, Alvarez-Sánchez E, Marchat LA. Protein kinases and transcription factors activation in response to UV-radiation of skin: implications for carcinogenesis. Int J Mol Sci 2012;13(1):142–72.
[86] Krueger J, Puig L, Thaçi D. Treatment options and goals for patients with generalized pustular psoriasis. Am J Clin Dermatol 2022;23(Suppl 1):51–64. Jan.
[87] Bozonnat A, Assan F, LeGoff J, Bourrat E, Bachelez H. SARS-CoV-2 infection inducing severe flare up of Deficiency of Interleukin Thirty-six (IL-36) Receptor Antagonist (DITRA) resulting from a mutation invalidating the activating cleavage site of the IL-36 receptor antagonist. J Clin Immunol 2021;41(7):1511–4. Oct.
[88] Wang YS, Zhu H, Li H, Li Y, Zhao B, Jin YH. Ginsenoside compound K inhibits nuclear factor-kappa B by targeting Annexin A2. J Ginseng Res 2019;43(3):452–9. Jul.
[89] Song SB, Tung NH, Quang TH, Ngan NT, Kim KE, Kim YH. Inhibition of TNF-α-mediated NF-κB transcriptional activity in HepG2 cells by dammarane-type saponins from Panax ginseng leaves. J Ginseng Res 2012;36(2):146–52. Apr.
[90] Xu XY, Yi ES, Kang CH, Liu Y, Lee YG, Choi HS, Jang HB, Huo Y, Baek NI, Yang DC, et al. Whitening and inhibiting NF-κB-mediated inflammation properties of the biotransformed green ginseng berry of new cultivar K1, ginsenoside Rg2 enriched, on B16 and LPS-stimulated RAW 264.7 cells. J Ginseng Res 2021;45(6):631–41. Nov.
[91] Fangyu Li, Shuyan Lu, Limei Ren, Shuai Bian, Meichen Liu, Daqing Zhao, Siming Wang, Jiawen Wang. Ginseng root extract attenuates inflammation by inhibiting the MAPK/NF-κB signaling pathway and activating autophagy and p62-Nrf2-Keap1 signaling in vitro and in vivo Song Yang. *Journal Of Ethnopharmacology* Volume 2022;283(30 January):114739.
[92] Ji-Su Shin, Jong-Myoung Kim, Won-Gun An. Anti-inflammatory effect of red ginseng through regulation of MAPK in lipopolysaccharide-stimulated RAW264.7. Journal of Physiology & Pathology in Korean Medicine 2012;26(3):293–300. Jun.
[93] Sun M, Ji Y, Li Z, Chen R, Zhou S, Liu C, Du M. Ginsenoside Rb3 inhibits pro-inflammatory cytokines via MAPK/AKT/NF-κB pathways and attenuates rat alveolar bone resorption in response to porphyromonas gingivalis LPS. Molecules. 2020;25(20):4815. Oct 20.
[94] Skroza N, Tolino E, Mambrin A, Zuber S, Balduzzi V, Marchesiello A, Bernardini N, Proietti I, Potenza C. Adult acne versus adolescent acne: a retrospective study of 1,167 patients. J Clin Aesthet Dermatol 2018;11(1):21–5. Jan.
[95] Mollerup, Sarah. Propionibacterium Acnes: Disease-causing agent or common contaminant? Detection in diverse patient samples by next-generation sequencing. Clinical Microbiology 2016;54(4):980–7.
[96] Kim Jenny, Ochoa Maria-Teresa, Krutzik Stephan R, Takeuchi Osamu, Uematsu Satoshi, Legaspi Annaliza J, Brightbill Hans D, Holland Diana, Cunliffe William J, Akira Shizuo, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002;169:1535–41.
[97] Mastrofrancesco Arianna, Kokot Agatha, Eberle Alex, Gibbons Nicholas CJ, Schallreuter Karin U, Strozyk Elwira, Picardo Mauro, Zouboulis Christos C, Luger Thomas A, et al. KdPT, a tripeptide derivative of alpha-melanocyte-stimulating hormone, suppresses IL-1 beta-mediated cytokine expression and signaling in human sebocytes. J Immunol 2010;185:1903–11.
[98] Qin, Min. Propionibacterium acnes Induces IL-1β secretion via the NLRP3 inflammasome in human monocytes.". The Journal of Investigative Dermatology 2014;134(2):381–8.
[99] Yi YS. Ameliorative effects of ginseng and ginsenosides on rheumatic diseases. J Ginseng Res 2019;43(3):335–41. Jul.
[100] Shi Y, Wang H, Zheng M, Xu W, Yang Y, Shi F. Ginsenoside Rg3 suppresses the NLRP3 inflammasome activation through inhibition of its assembly. FASEB J 2020;34(1):208–21. Jan.
[101] Korean red ginseng extracts inhibit NLRP3 and AIM2 inflammasome activation." Kim, Jeeyoung et al. Immunology Letters 2014;158:1–2. 143-50.
[102] Abdali S, Yu J. Occupational dermatoses related to personal protective equipment used during the COVID-19 pandemic. Dermatol Clin 2021;39(4):555–68. Oct.
[103] Yaqoob Sadia, et al. Association of acne with face mask in healthcare workers amidst the COVID-19 outbreak in karachi, Pakistan. Clinical, Cosmetic and Investigational Dermatology 2021;14:1427–33.
[104] Purushothaman PK, Priyangha E, Vaidhyswaran R. Effects of prolonged use of facemask on healthcare workers in tertiary care hospital during COVID-19 pandemic. Indian J Otolaryngol Head Neck Surg 2021;73(1):59–65. Mar.
[105] Damiani Giovanni, Gironi Laura C, Grada Ayman, Kridin Khalaf, Finelli Renata, Buja Alessandra, Bragazzi Nicola L, Pigatto Paolo DM, Savoia Paola. COVID-19 related masks increase severity of both acne (maskne) and rosacea (mask rosacea): multi-center, real-life, telemedical, and observational prospective study. Dermatologic Therapy 2021;34(2):e14848.
[106] Donnarumma M, Nocerino M, Lauro W, Annunziata MC, Marasca C, Fabbrocini G. Isotretinoin in acne treatment during the coronavirus disease 2019 (COVID-19): a retrospective analysis of adherence to therapy and side effects. Dermatol Ther. 2021;34(1):e14677. Jan.
[107] Hossain MA, Kim JH. Possibility as role of ginseng and ginsenosides on inhibiting the heart disease of COVID-19: a systematic review. J Ginseng Res 2022 May;46(3):321–30.
[108] Buddenkotte J, Steinhoff M. Recent advances in understanding and managing rosacea. F1000Res, vol. 7; 2018. Dec 3 F1000 Faculty Rev-1885.
[109] Del Rosso JQ. Advances in understanding and managing rosacea: part 1: connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. J Clin Aesthet Dermatol 2012;5(3):16–25. Mar.
[110] Possibility as role of ginseng and ginsenosides on inhibiting the heart disease of COVID-19: a systematic review." hossain, mohammad amjad, and jong-hoon kim. Journal of Ginseng Research 2022;46(3):321–30. 17 Jan.
[111] Song J, Xian D, Yang L, Xiong X, Lai R, Zhong J. Pruritus: progress toward pathogenesis and treatment. Biomed Res Int 2018;2018:9625936. Apr 11.
[112] Han L, Dong X. Itch mechanisms and circuits. Annu Rev Biophys 2014;43:331–55.
[113] Jeffry J, Kim S, Chen ZF. Itch signaling in the nervous system. Physiology (Bethesda) 2011;26(4):286–92. Aug.
[114] Steinhoff M, Buddenkotte J, Aubert J, Sulk M, Novak P, Schwab VD, Mess C, Cevikbas F, Rivier M, Carlavan I, et al. The journal of investigative dermatology. Clinical, Cellular, and Molecular Aspects in the Pathophysiology of rosacea Symposium Proceedings 2011;15(1):2–11.
[115] Jang Y, Lee WJ, Hong GS, Shim WS. Red ginseng extract blocks histamine-dependent itch by inhibition of H1R/TRPV1 pathway in sensory neurons. Journal of Ginseng Research 2015;39(3):257–64.

[116] Zuberbier UrticariaT. Journal of the European Academy of Dermatology and Venereology First Published 2003;87(3):196–205. 03 November.
[117] Abuelgasim Eyad, et al. Management of urticaria in COVID-19 patients: a systematic review. Dermatologic Therapy 2021;34(1):e14328.
[118] Muntean IA, Pintea I, Bocsan IC, Dobrican CT, Deleanu D. COVID-19 disease leading to chronic spontaneous urticaria exacerbation: a Romanian retrospective study. Healthcare (Basel) 2021;9(9):1144. Sep. 1.
[119] Pro-resolving effect of ginsenosides as an anti-inflammatory mechanism of *Panax ginseng*. Im, Dong-Soon. *Biomolecules* 2020;10:3–444. 13 Mar.
[120] Hand Hygiene Habits and Prevalence of Hand Eczema During the COVID-19 Pandemic, Techasatian L, Thaowandee W, Chaiyarit J, Uppala R, Sitthikarnkha P, Paibool W, Charoenwat B, Wongmast P, Laoaroon N, Suphakunpinyo C, et al. J Prim Care Community Health 2021;12: 21501327211018013. Jan-Dec.
[121] Alkhalifah Azzam. Risk factors for hand eczema in the general population of Saudi Arabia during the COVID-19 pandemic: an internet-based cross-sectional study. JAAD International Volume 2022;6:119–24. March.
[122] Klonowska J, Gleń J, Nowicki RJ, Trzeciak M. New cytokines in the pathogenesis of atopic dermatitis-new therapeutic targets. Int J Mol Sci 2018;19(10):3086. Oct 9.