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MINIREVIEWS

Red ginseng for atopic dermatitis

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Abstract

Red ginseng is known for its significant biological activities which include anti-inflammation. Red ginseng may be used for the management and prevention of atopic dermatitis based on its effect on an atopic dermatitis animal model. More therapeutic efficacies other than atopic dermatitis are also reviewed briefly.

Key words: Red ginseng; Atopic dermatitis; Allergy; Dermatitis; Inflammation

Core tip: Red ginseng has been shown to possess various biological activities, including anti-inflammatory properties. Red ginseng may be a potential therapeutic modality for the management and prevention of atopic dermatitis based on its effect on an atopic dermatitis animal model. More therapeutic efficacies other than atopic dermatitis are also reviewed briefly.

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INTRODUCTION

It has been proven that red ginseng (the steamed and dried root of *Panax ginseng* C.A. Meyer, family Araliaceae) has significant biological activities, including anti-inflammation[1]. Red ginseng is frequently consumed as an oral remedy, particularly within countries in Asia.

Ginsenosides containing an aglycone with dammarane (protopanaxadiol and protopanaxatriol) and oleanane skeletons are the known major components in raw ginseng[2]. Numerous studies on the molecular mechanisms and functioning of red ginseng and its identified ginsenosides have been done successfully.

Ginsenosides harbor a broad range of biological activities: anti-allergic features and anti-inflammatory[3-5], antitumor effects, aorta relaxation, wound healing and so on[6-10]. Ginsenoside Rg3 has been known to inhibit mast cells from releasing histamine by compound 48/80 *in vitro*[11,12]. Furthermore, ginsenoside Rb1 and Rc have also been shown to inhibit the release of both histamines and leukotrienes from pulmonary mast cells in an *in vitro* experiment with guinea pigs[11].

Recently, we showed that the oral consumption of red ginseng can suppress inflammation in atopic dermatitis (AD)-like skin lesions by inhibiting Langerhans cells (LCs), Th-1 cytokines and regulatory T (Treg) cells[13]. Moreover, oral red ginseng administration was found to markedly prevent the trinitrichlorobenzen (TNCB)-induced cutaneous inflammation in an atopic dermatitis animal model (NC/Nga mice)[1].

THERAPEUTIC AND PREVENTIVE EFFECTS OF RED GINSENG IN AN ATOPIC DERMATITIS ANIMAL MODEL

Systemic administration of red ginseng noticeably decreased the clinical severity score, the various inflammatory mediators and infiltrating cells, including CD1a+ LCs in AD mouse models. Moreover, oral administration

of red ginseng markedly prevented TNCB-induced AD-like skin lesions in NC/Nga mice.

Oral red ginseng administration significantly reduced ear thickness, along with other clinical signs. The total clinical severity score, which evaluates dryness, edema, erythema erosion and itching, was significantly lowered by red ginseng. Skin hydration was well maintained with red ginseng administration, based on the results of the trans-epidermal water loss (TEWL).

Histologically, there was a significant decrease in skin thickness as well as the degree of infiltrating inflammatory cells in AD-like cutaneous inflammation with red ginseng treatment. Red ginseng was also able to prevent lymphocyte infiltration in the dermis and exhibited beneficial effects by suppressing all LCs, Th-1 related cytokines and Treg cells in the TNCB-induced AD-like cutaneous inflammation of an atopic dermatitis animal model[13]. TNCB application caused CD1a+ dendritic cell (DCs) infiltration of the skin and this massive CD1a+ cell infiltration was greatly reduced by systemic red ginseng intake. Antigen-presenting cells (APCs) take an important role in the development of AD. These DCs play a critical role in the pathogenesis of AD, that is, recognition, phagocytosis and transmission of information from the environment to the immune system. Thymic stromal lymphopoietin (TSLP)-influenced DCs propagate the Th2 immune inflammation and the activated DCs accumulate in the epidermis and dermis of the AD cutaneous inflammation[14]. Red ginseng administration markedly suppressed the CD1a+ cell infiltration, which was induced by TNCB application.

Historically, the Th1 and Th2 balance was considered important in the pathogenesis of AD from the immunological aspect[15]. The concept was further progressed by exploring the role of the Th17 lineage and Treg cells[16]. It is crucial for the control of AD to keep the delicate balance among Th1, Th2 as well as Th17/22 and Treg cells. Moreover, the cross-talk between immune responses aberration and defect of skin barrier function with feeble cornification, abnormal terminal differentiation proteins and reduced level of intercellular lipids are found in the lesional AD skin[17]. Red ginseng was able to suppress the excessive TNF-α and TSLP expression in the AD-like cutaneous inflammation of an AD animal model. It has been suggested that an event of TNF-α production by epidermal cells initiates the development of AD[18]. Pro-inflammatory cytokines, such as TNF-α produced at the earliest stages of AD, stimulate the expression of chemokines and adhesion molecules which affect leukocyte proliferation, survival and recruitment at the lesional skin[18]. Red ginseng significantly lowered TNCB-induced TNF-α expression in cutaneous inflammation of an AD animal model which directs leukocyte recruitment. TSLP is considered a key factor in AD, with its ability to enhance the DCs shifting to Th2 immune reaction[19]. TSLP has been quoted as a "master switch for allergic inflammation" because TSLP exerted great effects on key cells of cutaneous inflammatory reactions, such as basophils, eosinophils and mast cells[20]. Systemic red ginseng and cyclosporine down-regulated the overexpression of TSLP (both mRNA and protein) in the lesional skin of an AD animal model. Therefore, red ginseng and cyclosporine are able to inhibit the initial inflammatory process in AD involving either TNF-α or TSLP. Red ginseng may mediate therapeutic effects by influencing DCs, TSLP and ultimately the Th2 response, based on these findings.

Th2 polarization causes eosinophil recruitment and increase in IgE production by B cells. Approximately 70% of AD patients show an elevation in serum IgE level. Overproduction of IgE causes both acute and chronic cutaneous inflammation in AD. Although serum IgE is not essential for the diagnosis of AD, the increased IgE level in AD classifies the AD phenotype, extrinsic type AD (with elevated IgE) and intrinsic type AD (with normal IgE). The clinical AD severity highly correlates with systemic IgE levels[21]. Itch intensity among AD patients is also closely related to IgE[22]. Red ginseng significantly modulated the total IgE level which was markedly increased following TNCB application. Thus, red ginseng has the therapeutic potential for AD *via* suppressing the antigen presentation and preventing vicious progression into the "itch-scratch cycle" at an early inflammatory stage of AD development[13].

Abnormalities of skin barriers, such as decreased skin hydration and increased TEWL, are significant indexes for the severity skin barrier defect and the intensity of itch in AD. TEWL also has a correlation with AD activity[23]. TEWL is a reliable and reproducible measure in assessing AD severity[24]. TEWL was increased in a TNCB-applied AD animal model where the elevated level of TEWL was reduced in the red ginseng and cyclosporine treated groups. By assessing TEWL, red ginseng may preserve skin hydration and modulate the disease activity in AD.

The increase of PGP 9.5 positive nerve fibers and substance P associated with AD[25] were also decreased by red ginseng[13]. It is likely that red ginseng inhibits neurogenic inflammation by decreasing the expression of PGP positive nerve fibers and substance P[13]. Oral red ginseng prevented the development of cutaneous inflammation of an AD animal model by suppressing pro-inflammatory and Th-1 related cytokines as well as LCs and Treg cells. Furthermore, red ginseng suppressed the neurogenic inflammation by reducing PGP 9.5 positive nerve fiber and substance P expression.

It has been reported that topical red ginseng and ginsenosides Rh2 and Rg3 improve cutaneous inflammation of an AD animal model. It also decreased the mRNA expression of IL-4 in the cutaneous inflammation of an AD animal model[26-28].

Intermittent use of topical steroids and/or the use of topical calcineurin inhibitors along with skin care and environment control are the only accepted methods for the prevention and maintenance of AD. For the prevention of recurrence and early treatment of AD, topical calcineurin inhibitors are allowed.

Table 1 Reported effects of red ginseng and its constituents on atopic dermatitis *in vivo*

Materials	Classification	Specification	Ref.
Korean red ginseng extract	*In vivo*	Alleviated clinical features, prevented the increase in TEWL, lowered IgE level, decreased lymphocyte infiltration, suppressed the protein expression of TSLP and TNF-α, decreased the mRNA expression of TSLP	[13]
Korean red ginseng extract	*In vivo*	Reduced the total clinical severity score, ear thickness and the level of IgE, decreased TNF-α, IFN-γ and substance P, reduced the infiltration of FOXP3+ regulatory T (Treg) cells and CD1a+ Langerhans cells	[1]

TEWL: Trans-epidermal water loss; TSLP: Thymic stromal lymphopoietin; TNF: Tumor necrosis factors; IFN: Interferon.

Table 2 Effects of red ginseng and its constituents *in vitro*, *in vivo* and clinically

Materials	Classification	Specification	Ref.
Ginsenoside Rh2	*In vivo, in vitro* In clinic	Preventing, treating diabetic disorders and improving vascular stiffness	[32,33,49]
Korean red ginseng extract	In clinic *In vivo*	Enhancing work memory, calming healthy young men and down regulating the expression of the tyrosine hydroxylase	[44,45]
Korean red ginseng extract	*In vivo*	Improving the hyperactivity and treating ischemia/reperfusion induced myocardial damage	[42,43]
Ginsenoside Rb3	*In vivo*	Protecting myocardial injury and heart function impairment	[35]
Ginsenoside Rg3	*In vivo*	Preventing the progression of renal damage and dysfunction in type 2 diabetic rats	[36]
Ginsenoside CK, Rg1	*In vitro*	Stimulating glucose uptake to treat the hypoglycemic properties	[37,50]
Korean red ginseng extract	*In vivo*	Treating human ophthalmic disease by improving the optical process	[46]
Ginsenoside Rg3,Rk1,Rg5	*In vivo*	Having beneficial effects on treating collagen induced arthritis	[48]
Korean red ginseng extract	*In vivo*	Protecting normal tissue during the radiation therapy and increasing tissue repair	[47]
Korean red ginseng	*In vitro*	Stimulating βadreno receptor and increasing various rate limiting enzyme activities	[40]
Korean red ginseng	*In vivo*	Up-regulating adipocytic peroxisome proliferator- activated receptor γ and inhibiting intestinal glucose absorption	[41]

Cyclosporine is allowed in Europe for short-term use for recalcitrant AD that cannot be controlled by topical treatment, despite FDA disapproval[29]. Both oral cyclosporine and topical calcineurin inhibitors interfere with calcineurin and suppress T cell activation[30]. Red ginseng prevented cutaneous inflammation of an AD animal model by controlling not only local but also systemic inflammation, which was proved by clinical findings, such as changes in ear thickness and TEWL, by the histological features decreasing the infiltration of inflammatory cells, and by immunological findings suppressing mRNA and protein expression of cytokines and IgE levels. Considering the red ginseng effects on cutaneous inflammation of an AD animal model, red ginseng may be an adjuvant therapeutic candidate in the prevention and treatment of early stage AD (Table 1).

MORE OF THE REPORTED CLINICAL EFFECTS OF RED GINSENG

Kim *et al*[31] reviewed 470 publications which show the efficacy of red ginseng *in vitro*, *in vivo* and clinically. His reviews covered 10 categories of clinical studies, including brain function, cerebrovascular function, antitumor, immune function and anti-inflammatory effect, bone, anti-stress, anti-fatigue and tonic effect, anti-oxidant and anti-aging effect, liver and toxicity, diabetes and obesity, sexuality and others (insomnia, eye and vision, hyperactivity and gene expression). Each category was further subdivided into specific research areas of red ginseng, such as the detoxification of anti-cancer agents, immune control, antioxidant properties and effect on allergy, obesity, blood vessels, peptic ulcers, dermatitis, cytotoxicity, brain neurons, liver disease, lipid metabolism, cancer, AIDS, stress, inflammation, sexuality, diabetes, tiredness and others.

Red ginseng can keep the ecological surroundings of the colon in metabolic equilibrium. The ginsenoside Rh2 especially can prevent and treat diabetic disorders. Red ginseng can also improve vascular stiffness in patients with coronary disease[32-34].

Ginsenoside Rg3 from red ginseng protects patients from myocardial injury and heart malfunction induced by isoproterenol and limits the aggravation of kidney dysfunction in type 2 diabetic rats by reducing oxidative stress and the formation of advanced glycation end product. Compound K and ginsenoside Rg1 increase the glucose uptake in 3T3-L1 cells, demonstrating insulin-like activity and showing potential for the treatment of metabolic syndrome and diabetes. A nutritional compound mixed with a P. ginseng extract reduces age-related mitochondrial functional degeneration and maintains physical status[35-38].

Some experiments were conducted to obtain solid scientific evidence that different ginsenosides from red ginseng have therapeutic potential for diabetes. Both protopanaxadiol type ginsenosides (Rb1, Rb2, Rc, Rg3, Rh2, compound K, PPD) and protopanaxatriol type ginsenosides (Re, Rg1, Rg2, PPT) have shown antidiabetic activities in cell and animal studies. The possible

mechanisms underlying red ginseng's hypoglycemic effects were suggested as follows: (1) modulation of insulin production and secretion; (2) modulation of glucose metabolism; (3) modulation of glucose uptake; and (4) modulation of inflammatory pathways. The effect of red ginseng on lowering blood sugar level is also due to the increased aerobic glycolysis from the stimulation of beta adrenoceptors plus the increase of a number of rate-limiting enzyme activities related to the tricarboxylic acid cycle. In a particular study conducted to investigate the anti-diabetic property and mechanism in KKAy mice, red ginseng showed hypoglycemic effects through up-regulation of adipocytic peroxisome proliferator activated receptor gamma (PPAR-γ) expression as well as by inhibiting intestinal glucose absorption in KKAy mice[39-41].

Red ginseng may have beneficial effects on ADHD, as red ginseng decreases the neonatal hypoxia-induced hyperactivity while increasing locomotor activity in lay animals. Red ginseng may also treat ischemia/reperfusion induced myocardial damage effectively due to its antioxidant effects[42,43].

Other studies show that red ginseng enhances working memory and improves calmness. This anti-stress efficacy of red ginseng is mainly driven by the suppression of the expression of the tyrosine hydroxylase and dopamine beta-hydroxylase gene[44-45].

Some scientists suggest that red ginseng can be used for treating certain human ophthalmic diseases in a study that showed significant improvement of the optical process in the eyes of a bullfrog. Other data demonstrate that red ginseng helps to increase the therapeutic effect of radiotherapy on tumor tissues and effectively treats collagen-induced arthritis[46-48]. Reported clinical effects of red ginseng are summarized in Table 2.

CONCLUSION

Red ginseng has both preventive and therapeutic efficacies for AD through immune modulation at the early stages of the disease. Oral red ginseng was shown to block the development of the cutaneous inflammation of an AD animal model by suppressing DCs, TSLP and Th2 cytokines. Early administration of red ginseng is capable of preventing the emergence of the itch-scratch cycle and maintenance therapy with red ginseng can inhibit AD progression into the chronic phase. Taken together, we suggest that red ginseng administration is a novel approach in the prevention and treatment of early stage AD.

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