

Using *Astragalus membranaceus* (Fisch.) Bge. To Treat Skin Diseases: Comparison of Traditional Uses and Research Results

Chanyong Yun, Hyungwoo Kim

Division of Pharmacology, School of Korean Medicine, Pusan National University, Yangsan, Gyeongnam, South Korea

ABSTRACT

Background: *Astragalus membranaceus* (Fisch.) Bge. (AM), a member of restoratives for invigoration qi (補氣藥), has been used to treat patients with skin diseases in the framework of traditional medicine. The major efficacies of AM related to skin diseases are tonifying defensive qi and securing the exterior (益衛固表), expelling toxins and pus (托毒排膿), and promoting tissue regeneration and wound healing (生肌斂瘡). **Materials and Methods:** We investigated the traditional usages of AM described in the textbook and encyclopedia, and we also investigated scientific research using PubMed and the National Digital Library of Korea. **Results:** In our opinion, tonifying defensive qi and securing the exterior effect of AM is related to the photoprotective, antiaging, and protecting effects on normal skin tissue. Expelling toxins and pus and promoting tissue regeneration and wound healing effects are closely related to the anti-inflammatory effects and promoting healing of wounds or ulcers on the body surface, respectively. In addition, astragaloside IV, formononetin, calycosin, cycloastragenol (TA-65), and gamma-aminobutyric acid were the major components related to therapeutic effects of AM on skin diseases. **Conclusion:** The therapeutic effects of AM on skin diseases were divided into three categories according to the theory of traditional medicine, and its effects in each category can be explained by scientific experiments.

Key words: *Astragalus membranaceus*, dermatology, herbal medicine, skin disease, traditional Chinese medicine

INTRODUCTION

In the theory of traditional medicine, skin diseases are mainly induced by the imbalance of yin (陰) and yang (陽) caused by various stimuli such as the six excesses (六淫), seven emotions (七情), and inappropriate lifestyles.^[1] This imbalance of yin and yang results in various symptoms of skin diseases including rash, suppuration, pruritus, urticaria, and exudates, which are similar to today's symptoms of dermatosis.^[2] The diagnoses of skin diseases are categorized as wind-heat (風熱), dampness-heat (濕熱), heat-toxin (熱毒), blood heat (血熱), spleen deficiency with dampness excess (脾虛濕盛), and yin deficiency (陰虛).^[2] In accordance with the diagnoses, treatments such as clearing and draining dampness-heat (清利濕熱), clearing heat and detoxifying (清熱解毒), fortifying the spleen and eliminating dampness (健脾除濕), and enriching yin and nourishing the blood (滋陰養血) are used to treat skin diseases.^[2]

Corticosteroids are mainly used as anti-inflammatory and immunomodulatory agents.^[3] Corticosteroids are very effective when applied to treat inflammatory diseases, but the dose and duration must be strictly complied with. Owing to these concerns, there has been increased interest in identifying complementary and alternative medicines (CAMs) for corticosteroids, and the use of various herbal medicines has been vigorously investigated.^[4]

Before treatment, therapists using traditional medicines in China, Japan, and Korea preferentially divide symptoms into deficiency patterns (虛證) and excess patterns (實證). Heat excess (實熱) is most common in those with excess patterns (實證), while qi deficiency (氣虛) is most common in those with deficiency patterns (虛證). The method of clearing heat (清熱) is mainly used for patients with excess patterns (實證), while tonifying qi (補氣) is primarily used for patients with deficiency patterns (虛證). There are many prescriptions for skin diseases diagnosed as being caused by deficiency patterns (虛證), with Bu-zhong-yi-qi-tang (補中益氣湯),^[5] Tuo-li-xiao-du-yin (托裏消毒飲),^[6] and Sheng-xie-run-fu-yin (生血潤膚飲)^[6] being the primary treatments. These three prescriptions all contain *Astragalus membranaceus* (AM), and AM plays a prominent role in these prescriptions.^[5,7] The frequent use of AM may be due to strengthening of the body's defense system, reinforcing the skin and generating tissue.^[8,9]

The characteristics of AM make it a good candidate for an alternative agent for corticosteroids. Among various herbal medicines proposed as complementary substances for corticosteroids, AM may be the most practical substitute.

AM is a perennial plant that belongs to the legume family. The dried root, with the exception of the fine roots and bark, is used as an herb.^[9] AM has effects that include tonifying and upraising qi (補氣升陽), tonifying defensive qi and securing the exterior (益衛固表), expelling toxins and pus (托毒排膿), promoting tissue regeneration and wound healing (生肌斂瘡), and inducing water-draining and reducing swelling (利水退腫); therefore, it has been used to treat spleen deficiency

Correspondence:

Prof. Hyungwoo Kim,
Division of Pharmacology, School of Korean Medicine, Pusan National University, Yangsan, Gyeongnam 50612, South Korea.
E-mail: kronos7@pusan.ac.kr

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diarrhea (脾虛泄瀉), qi deficiency blood collapse (氣虛血脫), and night sweating (盜汗).^[8,9]

MATERIALS AND METHODS

Literature study

We investigated the traditional usages of AM described in the textbook and encyclopedia. The two textbooks (textbook of traditional Korean Dermatology and Surgery, and Bonchohak, the textbook of Korean Herbology) are used in the regular course of Korean medicine.^[1,9] In addition, the encyclopedia of oriental herbal medicine contains many of classical literature on traditional medicine used in China, Japan, and Korea.^[8]

Data collection

We also investigated scientific research using PubMed and the National Digital Library of Korea. The criteria were restricted in skin diseases, anti-inflammation, and AM.

RESULTS

Tonifying defensive qi and securing the exterior (益衛固表)

Defensive qi (衛氣) moves outside the vessels, protects the body surface, and wards off external pathogens. In addition, securing the exterior (固表) provides a therapeutic method to treat the exterior deficiency and insecurity. This action of AM is related to its photoprotective, antioxidative,^[10] antiaging, and protecting effects on normal skin tissue.

AM has photoprotective effects, especially against ultraviolet B (UVB)-induced skin inflammation and photoaging.^[11] In human dermal fibroblasts, AM exerts photoprotective effects via regulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. Western blotting and immunocytochemistry analyses revealed that AM inhibited UVB-induced translocation of NF-κB P65 and matrix metalloproteinase-1 (MMP-1) expression and restored type I procollagen synthesis. In addition, astragaloside IV (AS-IV),^[12] one of the main active ingredients of AM, downregulates UV-induced MMP-1 expression via the suppression of mitogen-activated protein kinase (MAPK) and NF-κB activation in human dermal fibroblasts. Thus, AS-IV is a potential agent for the management of skin photoaging [Figure 1].^[13,14]

AM also protects normal skin tissue and exerts antiaging effects. For example, cycloastragenol (TA-65) extracted from the roots of AM has been found to restore DNA damage and promote elongation of shortened telomeres. Accordingly, it has been proposed that TA-65 can protect normal skin tissue via the telomerase pathway.^[15]

Expelling toxins and pus (托毒排膿)

The therapeutic method of expelling toxins (托毒) is used to treat boils and sores. This action is closely related to the anti-inflammatory effects of AM through which it suppresses atopic and contact dermatitis.^[16,17] The oral administration of AM was found to inhibit ear thickness increases and the skin lesions induced by 1-fluoro-2,4-dinitrobenzene in NC/Nga mice. Interestingly, IFN-γ production was significantly decreased by AM and interleukin (IL)-4 and serum immunoglobulin E levels were not.^[16] In addition, Kim *et al.* have reported that AM can reduce production of tumor necrosis factor (TNF)-α via suppression of NF-κB pathway in mice with 1-chloro-2,4-dinitrobenzene-induced dermatitis.^[17] Recently, Choi *et al.* have reported that AM can prevent enlargement of skin thickness and reduce scratching behavior in mice with dermatitis. In addition, AM also prevented mast cell infiltration and decreased production levels of cytokines such as interferon-γ, TNF-α,

and IL-1β via suppression of NF-κB and MAPK pathway [Figure 2].^[18]

AS-IV can regulate TNF-α and IL-6 production by suppressing the activity of NF-κB.^[19] Moreover, AS-IV downregulates the serum levels of monocyte chemoattractant protein-1, attenuating the inflammation reaction. Furthermore, AS-IV suppresses cell adhesion activity, thereby inhibiting the infiltration of neutrophils or polymorph-nuclear leukocytes.^[20,21] This phenomenon is caused by inhibiting the expression of intercellular adhesion molecule-1^[20] or vascular cell adhesion molecule-1.^[21] Formononetin is related to pro-inflammatory cytokines such as IL-6 and expression of the peroxisome proliferator-activated receptor-γ gene.^[22] Formononetin also inhibits cyclooxygenase-2 expression^[23,24] and nitric oxide production.^[25]

Promoting tissue regeneration and wound healing (生肌斂瘡)

This action of AM is a therapeutic method to promote healing of wounds or ulcers on the body surface. Several studies have investigated the effects of AM in wound healing. The wound healing effects of AM were investigated in a cutaneous open wound model.^[26] The results showed that AM significantly accelerated the cutaneous wound healing process by suppressing inflammation and stimulating basal cell growth in the wounded area.^[26] In addition, Hur *et al.* showed that AM significantly increased human umbilical vein endothelial cells (HUVECs) proliferation in a dose-dependent manner. Moreover, AM increased migration and tube-like formation in HUVECs. Furthermore, the expression of basic fibroblast growth factor (bFGF) was dose dependently increased by AM.^[27] These results imply that AM can accelerate formation of new vessels in wound sites.

It is well known that AS-IV can enhance wound healing^[28-31] and accelerate angiogenesis.^[32,33] Luo *et al.* showed that AS-IV promoted diabetic wound repair and enhanced the collagen deposition and the expression of fibronectin and collagen IIIa. AS-IV also improved the new blood vessel formation in wound tissue with increased numbers of endothelial cells and enhanced expression of vascular endothelial growth factor (VEGF).^[28-30] In addition, Li *et al.* have reported that AS-IV-mediated mouse keratinocyte proliferation and migration via regulation of the Wnt signaling pathway and downregulating β-catenin.^[31]

Recently, wound healing effects of topical AS-IV was also investigated using various delivery systems.^[34-36] In their results, AS-IV loaded hydrogel effectively activated the skin appendages regeneration and increased the transforming growth factor (TGF)-β(1) level in serum.^[34] In addition, AS-IV loaded nanoparticle-enriched hydrogel and silk fibroin/gelatin electrospun nanofibrous dressing functionalized with AS-IV also induced wound healing and antiscar effects.^[35,36]

The angiogenic effects of AS-IV were also evaluated using HUVECs and zebrafish.^[32,33] Zhang *et al.* suggested that AS-IV exerts angiogenic effects and that its angiogenic activity involves VEGF and Akt signaling pathways.^[32] In addition, Zhang *et al.* revealed that AS-IV is a novel regulator of hypoxia-inducible factor-1α and accelerate angiogenesis through the phosphoinositide 3-kinase/Akt pathway in HUVECs that are exposed to hypoxia [Figure 3].^[33]

Formononetin, a phytoestrogen from the root of AM, increases the production of growth factors such as platelet-derived growth factor, TGF-β, VEGF, and bFGF in wound sites. In addition, the extracellular signal-regulated kinase and p38 MAPK pathways are closely related to the angiogenic mechanisms of AM.^[27] In addition, formononetin also promotes angiogenesis through the estrogen receptor alpha-enhanced Rho-associated protein kinase pathway in HUVECs.^[37]

The wound healing activity of gamma-aminobutyric acid (GABA), one of its components, was also evaluated by the wound rank scoring system and

histopathological observations using a full-thickness wound rat model. Han *et al.* demonstrated that GABA primarily promoted re-epithelialization and cell proliferation at the early stage of wound healing while inhibiting inflammation response, which resulted in reduction of the time required for the overall wound healing process [Figure 4].^[26]

Calycosin, isoflavonoid isolated from AM, is also known to promote angiogenesis involving estrogen receptor and MAPK signaling pathway in zebrafish and HUVECs.^[38,39]

Skin whitening

Skin whitening is a newly elucidated dermatological effect of AM. Specifically, AM whitens skin by inhibiting melanin biosynthesis.^[40] Kim *et al.* reported that calycosin isolated from the root of AM can inhibit melanin biosynthesis via the regulation of tyrosinase activities.^[40]

DISCUSSION

AM is a major medicinal herb that is ranked 6th among herbal medicines in terms of the amount produced and consumed in Korea.^[41] AM is a

member of restoratives for invigoration qi (補氣藥), together with *Panax ginseng* (人蔘), and *Atractylodes macrocephala* (白朮). Unlike *P. ginseng* and *A. macrocephala*, AM has frequently been used to treat patients with various skin problems. Therefore, we reviewed previous dermatological studies of the traditional use of AM. In our opinion, the effects of tonifying defensive qi and securing the exterior (益衛固表) exerted by AM are related to its photoprotective, antioxidative, and antiaging effects, as well as its protective effects on normal skin tissue. The effects of expelling toxins and pus (托毒排膿) and promoting tissue regeneration and wound healing (生肌斂瘡) are closely related to its anti-inflammatory effects and promotion of healing of wounds or ulcers on the body surface, respectively.

AS-IV can protect normal skin against UV-irradiation. AS-IV and formononetin can enhance wound healing and accelerate angiogenesis. GABA has wound healing effects and calycosin accelerates angiogenesis and has skin whitening effect. In addition, cycloastragenol (TA-65) has antiaging effect. These molecules seem

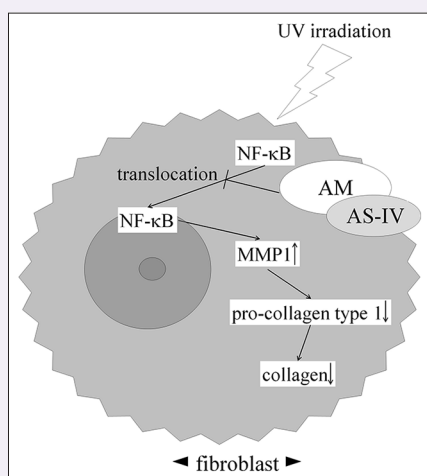


Figure 1: The photoprotective effects of AM on ultraviolet B-induced damage in fibroblasts. AM, *Astragalus membranaceus*; AS-IV, Astragaloside IV; MMP1, matrix metalloproteinase-1

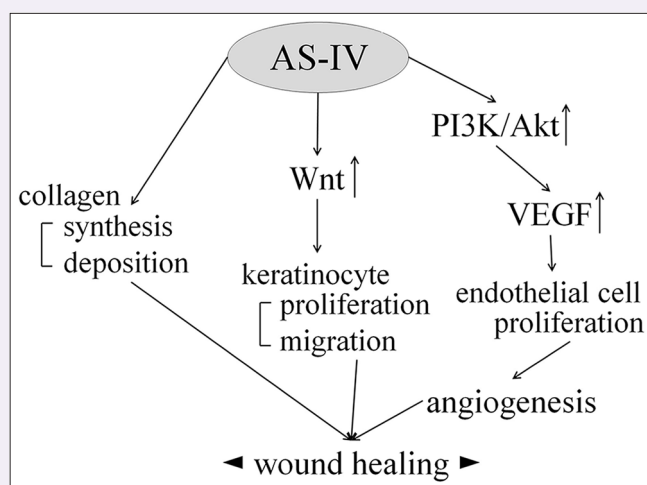


Figure 3: Wound healing effects of AS-IV. AS-IV, astragaloside IV; (PI3K)/Akt, Phosphoinositide 3-kinase/Akt pathway; VEGF, vascular endothelial growth factor

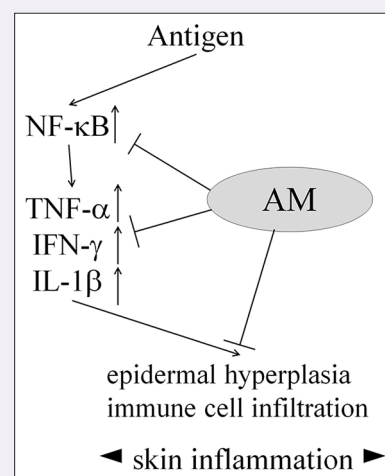


Figure 2: Anti-inflammatory effects of AM in skin inflammation. AM, *Astragalus membranaceus*

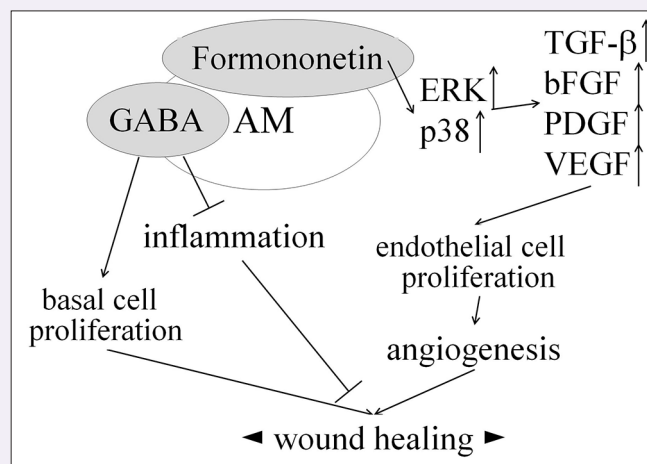


Figure 4: Wound healing effects of AM and its components, GABA and formononetin. AM, *Astragalus membranaceus*; GABA, gamma-aminobutyric acid; ERK, extracellular signal-regulated kinase; p38, p38 mitogen-activated protein kinase; (TGF)-β, transforming growth factor-β; bFGF, basic fibroblast growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor

to be major components related to therapeutic effects of AM on skin diseases [Table 1].

As we said, AM is used for patients with qi deficiency (氣虛) and can tonify defensive qi and secure the exterior. These actions of AM easily connected to promoting tissue regeneration and wound healing effects of AM. Conversely, it is difficult to explain how AM expels toxins and pus using the criteria of deficiency pattern (虛證) and excess pattern (實證). The action of expelling toxins and pus is a therapeutic method for treating excess pattern. Expelling toxins and pus is not consistent with the primary clinical usage of AM of treating qi deficiency. This discrepancy can be explained by the use of AM in conjunction with other herbal medicines to expel toxins and pus, which enables it to be used to treat excess patterns.

Interestingly, the anti-inflammatory effects of AM are well known worldwide, and the action of expelling toxins and pus seems to be explained by its anti-inflammatory effects. However, although many studies have described the anti-inflammatory effects of AM and its components, AM is used as a restorative for invigoration of qi in clinics. Even though AM is used for patients with excess patterns of skin diseases in conjunction with other herbal medicines, the therapeutic effects of AM may be occurring through tissue regeneration and wound healing via tonifying of defensive qi and securing the exterior. Therefore, if herbal therapists want to use AM to treat skin diseases, it is needed to consider the pattern of diseases according to the criteria of deficiency and excess. In general, carbuncle with transparent or mucinous exudate and ruptured but unhealed one for a long time are the most frequently shown in deficiency pattern of skin diseases. On the other hand, sore with purulent exudate and skin inflammation with fever and flare are frequently shown in excess pattern of skin inflammation.

Topical corticosteroid concerns are an important issue in patients with eczema, and its leading concerns are skin atrophy, systemic effects, and impairment of the immune system.^[42] For these reasons, there has been an increased interest in using CAM for corticosteroids. AM is one of the potent candidates for CAM to treat inflammatory skin diseases, because AM is frequently used to expel toxins and pus in clinic, and its anti-inflammatory effects have been proven by many scientists. In addition, AM can tonify defensive qi and secure the exterior and promote tissue regeneration and wound healing. These efficacies are quite different from those of corticosteroids and seem to raise its value for therapeutic agent for skin diseases.

In addition, the anti-inflammatory effects of AM cannot be explained in the category of deficiency and excess pattern. Therefore, new criteria or categories must be developed to apply scientific results such as anti-inflammatory action in clinical use to the framework of evidence-based medicine.

CONCLUSION

The therapeutic effects of AM on skin diseases were divided into three categories according to the theory of traditional medicine, and its effects

in each category can be explained by scientific experiments. As we said, AM is used for patients with qi deficiency (氣虛) and can tonify defensive qi and secure the exterior. Therefore, if herbal therapists want to use AM to treat skin diseases, it is needed to consider the pattern of diseases according to the criteria of deficiency and excess.

Summary

We investigated the traditional usages of AM and scientific research. In our opinion, tonifying defensive qi and securing the exterior effect of AM is related to the photoprotective, antiaging, and protecting effects on normal skin tissue. Expelling toxins and pus and promoting tissue regeneration and wound healing effects are closely related to the anti-inflammatory effects and promoting healing of wounds or ulcers on the body surface, respectively. In addition, AS-IV, formononetin, calycosin, cycloastragenol (TA-65), and GABA were the major components related to therapeutic effects of AM on skin diseases.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Major constituents of *Astragalus membranaceus* related to skin diseases

Scientific name	Action	Reference
Astragaloside IV	Anti-inflammatory Photoprotective Wound healing	[12,19-21] [12-14] [12,28-36]
Calycosin	Wound healing Skin whitening	[38,39] [40]
Formononetin	Anti-inflammatory Wound healing	[22-25] [27,37]
Cycloastragenol (TA-65)	Skin-protect	[15]
GABA	Wound healing	[26]

GABA=Gamma-aminobutyric acid

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