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Herbal medicines that benefit epidermal permeability barrier function

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A B S T R A C T
Epidermal permeability barrier function plays a critical role in regulating cutaneous functions. Hence, researchers have been searching for effective and affordable regimens to enhance epidermal permeability barrier function. In addition to topical stratum corneum lipids, peroxisome proliferator-activated receptor, and liver X receptor ligands, herbal medicines have been proven to benefit epidermal permeability barrier function in both normal and diseased skin, including atopic dermatitis, glucocorticoid-induced skin damage, and UVB-damaged skin. The potential mechanisms by which herbal medicines improve the permeability barrier include stimulation of epidermal differentiation, lipid production, antimicrobial peptide expression, and antioxidation. Therefore, utilization of herbal medicines could be a valuable alternative approach to enhance epidermal permeability barrier function in order to prevent and/or treat skin disorders associated with permeability barrier abnormalities.

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Introduction
Epidermal permeability barrier function influences multiple cutaneous functions, including epidermal proliferation, differentiation, lipid production, cytokine expression, as well as innate immunity.\(^7\) Moreover, studies have revealed that epidermal permeability barrier function plays a critical role in the development of contact dermatitis\(^6\) and atopic dermatitis (AD).\(^1\) Furthermore, a link between permeability barrier status and cutaneous antimicrobial defense and oxidative stress\(^1\) has been established. Enhancement of permeability barrier does not only improve atopic dermatitis, but also delays the relapse of AD in humans.\(^2\) Therefore, researchers have been searching for products that can enhance the permeability barrier. Although both stratum corneum (SC) lipids, ligands of peroxisome proliferator-activated receptors (PPARs), and liver X receptor (LXR) can improve the permeability barrier,\(^6,7\) clinical use of either SC lipids or PPAR/LXR ligands often requires special preparation. For example, a proper molar ratio of SC lipids is required for maximum benefits,\(^6\) and both lipids and certain PPAR/LXR ligands, such as T0901317 and farnesol, only dissolve in solvents. Thus, they are not readily available worldwide. However, studies have shown that herbal medicines benefit the epidermal permeability barrier. Here, we review the beneficial effects of herbal medicines on the permeability barrier and their mechanisms.

Effects on barrier function

Normal skin

Although the beneficial effects of herbs on skin have been known for years, their effects on epidermal permeability barrier have not been well appreciated until recently. Several studies showed that topical herbal medicines accelerated barrier recovery although they did not affect basal permeability barrier. For instance, topical applications of extracts of a herbal mixture twice daily for 7 days significantly accelerated barrier recovery at both 2 hours and 4 hours after barrier disruption in a normal murine skin without
changing either baseline transepidermal water loss rates (TEWL), skin surface pH, or SC hydration. Similarly, topical applications of 2% hesperidin, a main constituent of citrus, twice daily for 6 days not only increased barrier recovery without altering basal TEWL, skin surface pH, and SC hydration in a normal murine model. Whereas topical applications of 0.1% apigenin, an ingredient from chrysanthemum, twice daily for 9 days induced a significant acceleration in barrier recovery only 4 hours after barrier disruption, and a reduction in SC hydration in normal murine skin. Moreover, topical application of herbal extracts to barrier damaged skin also accelerated barrier recovery. These results indicate that the influences of topical herbal medicines on permeability homeostasis vary with the ingredient.

In addition to murine models, clinical studies have also demonstrated beneficial effects of herbal medicines on epidermal permeability barrier in normal humans. Rasu and Akhtar reported that topical applications of 3% basil extract to the cheek once daily for 2 weeks lowered TEWL and increased SC hydration. More significant improvements in both TEWL and SC hydration were observed 12 weeks after topical applications of basil extract. Likewise, topical applications of Lithospermum erythrorhizon extract at concentrations ranging from 1% to 5% for 7 days significantly lowered TEWL and increased SC hydration. Again, a further improvement in both TEWL and SC hydration were observed 28 days after applications. In comparison to vehicle alone, cream containing 10% Laminaria japonica markedly decreased TEWL and increased SC hydration 8 hours after application. Moreover, topical 4% Foeniculum vulgare extract also improved both TEWL and SC hydration in normal humans. Some herbal medicines not only affect barrier function and SC hydration, but also influence melanin and sebum content. For example, in addition to the decrease in TEWL, a remarkable reduction in melanin index was seen after topical applications of a cream containing 5% Terminalia chebula extract for 1 week while skin surface sebum content and SC hydration were increased. A more profound improvement was observed 6 weeks after applications. Furthermore, topical applications of 0.25% extract of Terminalia arjuna extract for 8 weeks reduced TEWL in aged humans. Finally, improvement of barrier function by oral herbal extracts has also been demonstrated in both young and aged humans. Herbal medicines that benefit barrier function are listed in Table 1.

**Diseased skin**

Studies have shown that herbal medicines are effective in treating and preventing some skin disorders accompanied by an abnormal permeability barrier. Herbal medicines can also improve permeability barrier function in some dermatoses, such as AD, acne, and glucocorticoid-damaged skin.

(1) Atopic dermatitis

Both humans and murines with AD exhibit a higher TEWL. Herbal medicines not only improve AD, but also prevent the development of AD. In a 2,4-dinitrochlorobenzene (DNCB)-induced murine AD model, topical applications of Bambusa caulis in liquamen prevented the expected increase in TEWL during the development of AD. Similarly, topical applications of 0.1% apigenin lowered both TEWL and skin surface pH, and elevated SC hydration in an ozaxolone-induced murine AD like model. A number of studies have demonstrated that oral administration of herbal extracts could also prevent the increase in TEWL, and the development of AD symptoms in murine AD models.

Clinically, there were two separate studies showing that topical applications of borage oil, a constituent of herbal medicines such as Borago officinalis, for 2 weeks or 4 weeks significantly improved clinical symptoms and TEWL in AD children. Moreover, it was reported that loratadine in combination with herbal bathing one to two times daily for 4 weeks lowered TEWL readings from 38.12 ± 5.56 to 13.45 ± 2.91 in AD patients in addition to an overall 65% reduction in AD severity scores. By contrast, loratadine in combination with topical petrolatum only lowered TEWL readings from 37.72 ± 5.23 to 22.12 ± 3.91 and had a 56% reduction in AD severity scores. Another study showed that oral herbal medicines once daily for 4 weeks also significantly reduced TEWL (from 36.54 ± 4.04 to 17.15 ± 3.77) in AD patients in comparison to loratadine alone (from 36.01 ± 3.49 to 26.59 ± 3.09). These studies reveal that either topical herbal medicines or oral herbal medicines improve epidermal barrier function in both murine AD models and AD in humans.

(2) Glucocorticoid-treated skin

Glucocorticoids (GC) are among the most common medications used for various disorders. Our prior studies have demonstrated that either topical or systemic applications of GC compromise epidermal permeability barrier. In a murine model, either psychological stress, which elevates GC levels in serum or saliva, or systemic administrations of GC significantly increased basal TEWL levels. In addition to stratum corneum lipids, PPAR and LXR activators, herbal medicines are also effective in overcoming GC-induced epidermal barrier abnormalities. Following each psychological stress, inhalation of rose essential oil for 2 hours prevented the expected increase in TEWL in psychological stressed rat and humans. In humans, topical applications of GC raise TEWL. Qi et al. reported that topical skin care products containing Prinsepia utilis and purslane in combination with zinc oxide ointment for 1 month significantly reduced TEWL in patients with glucocorticoid dependent dermatitis as compared with zinc oxide ointment alone. Moreover, other clinical studies showed that systemic administrations of herbal medicines markedly lowered TEWL and improved dermatitis scores in patients with glucocorticoid dependent dermatitis. These results indicate that herbal medicines can effectively overcome epidermal barrier abnormalities induced by either topical or systemic glucocorticoids.

(3) Others

Following UVB irradiation, defective permeability barrier function is commonly seen in both human and murine skin. Studies indicate that either topical or oral herbal extracts can prevent UVB irradiation-induced increase in TEWL. For example, rats irradiated with UVB three times per week for 8 weeks caused a significant elevation of TEWL. Rats pre-fed with (−)-epigallocatechin-3-gallate (EGCG) prevented the increase in both TEWL and epidermal thickness in addition to the inhibition of the development of clinical scores. Human studies revealed that topical 0.1% oleuropein emulsion 30 minutes prior to UVB irradiation induced a 22% reduction in erythema, and 35% reduction in TEWL.

Skin with acne vulgaris exhibits a higher level of TEWL. Two separate clinical studies demonstrated that either topical or oral herbal extracts improved barrier function in acne patients. For example, topical applications of a formulation containing extracts of Prinsepia utilis and purslane to acne sites twice daily for 30 days caused a 43% reduction in TEWL while formulations without herbal extract only induced a 10% reduction in TEWL. Du et al. reported that oral Callicarpa nudiflora tablets in combination with a blue-red light induced further improvements in both clinical processes.
Table 1 List of herbal medicines that benefit epidermal permeability barrier.

<table>
<thead>
<tr>
<th>Herbal extracts</th>
<th>Species/models</th>
<th>Treatment</th>
<th>Number of subjects</th>
<th>Permeability barrier</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radix Paeoniae rubra, Cat Nut, Phellodendron, Rhizoma Alismatis, Angelica sinensis, &amp; Glabrous Greenbrier</td>
<td>Normal mice</td>
<td>Topically applied to intact skin for 7 d</td>
<td>5</td>
<td>(-)</td>
<td>8</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>Normal mice</td>
<td>Topically applied to intact skin for 6 d</td>
<td>10</td>
<td>(-)</td>
<td>9</td>
</tr>
<tr>
<td>Apigenin</td>
<td>Normal mice</td>
<td>Topically applied to intact skin for 9 d</td>
<td>12</td>
<td>(-)</td>
<td>10</td>
</tr>
<tr>
<td>Ursolic acid &amp; oleanolic acid</td>
<td>Normal mice</td>
<td>Topically applied to tape-stripped skin once</td>
<td>30</td>
<td>N/D</td>
<td>11</td>
</tr>
<tr>
<td>Eucalyptus</td>
<td>Normal humans</td>
<td>Topically applied to acetone/diethyl ether-treated skin for 4 d</td>
<td>18</td>
<td>N/D</td>
<td>13 a</td>
</tr>
<tr>
<td>Basil leaves &amp; flowers</td>
<td>Normal humans</td>
<td>Topically applied to intact skin for 84 d</td>
<td>11</td>
<td>↓</td>
<td>14</td>
</tr>
<tr>
<td>Terminalia chebula</td>
<td>Normal humans</td>
<td>Topically applied to intact skin for 56 d</td>
<td>11</td>
<td>↓</td>
<td>15</td>
</tr>
<tr>
<td>Terminalia arjuna</td>
<td>Normal humans</td>
<td>Topically applied to intact skin for 56 d</td>
<td>15</td>
<td>↓</td>
<td>18</td>
</tr>
<tr>
<td>Borage oil</td>
<td>Normal humans</td>
<td>Orally given for 84 d</td>
<td>15</td>
<td>N/D</td>
<td>19 b</td>
</tr>
<tr>
<td>Bambusae caulis in Liquamen</td>
<td>Mouse dermatitis-induced by topical DNCB</td>
<td>Topically applied for 35 d</td>
<td>Not indicated</td>
<td>↓</td>
<td>20</td>
</tr>
<tr>
<td>Apigenin</td>
<td>Mouse dermatitis-induced by topical oxazolone</td>
<td>Topically applied for 7 d</td>
<td>24</td>
<td>↓</td>
<td>21 b</td>
</tr>
<tr>
<td>Red ginseng</td>
<td>Mouse dermatitis-induced by topical oxazolone</td>
<td>Topically applied for 5 d prior to TNCB application</td>
<td>5</td>
<td>↓</td>
<td>25</td>
</tr>
<tr>
<td>Lithospermum erythrorhizon</td>
<td>Mouse dermatitis-induced by topical oxazolone</td>
<td>Orally given for 13 d</td>
<td>4-8</td>
<td>↓</td>
<td>26</td>
</tr>
<tr>
<td>Persimmon leaves</td>
<td>Dermatitis in NC/Nga mice</td>
<td>Orally given for 28 d</td>
<td>5</td>
<td>↓</td>
<td>27</td>
</tr>
<tr>
<td>Atractylodes lancea rhizome, Hoelen, Cnidium rhizome, Japanese Angelica root, Bupleurum root, Glycyrrhiza root, &amp; Uncaria thorn</td>
<td>Dermatitis in NC/Nga mice</td>
<td>Orally given for 42 d</td>
<td>5</td>
<td>↓</td>
<td>28</td>
</tr>
<tr>
<td>Actinidia arguta</td>
<td>Dermatitis in magnesium deficient rats</td>
<td>Orally given for 16 d</td>
<td>2-7</td>
<td>↓</td>
<td>29</td>
</tr>
<tr>
<td>Beta vulgaris</td>
<td>Dermatitis in low fat diet mice</td>
<td>Orally given for 56 d</td>
<td>8</td>
<td>↓</td>
<td>30</td>
</tr>
<tr>
<td>Borage oil</td>
<td>Atopic dermatitis humans</td>
<td>Wearing borage oil-coated undershirt for 28 d</td>
<td>26</td>
<td>↓</td>
<td>31</td>
</tr>
<tr>
<td>Squama manis, cortex moutan, cortex albizia, cortex łyci, periostracum cicadae, periostracum serpentis, pericarpium citri reticulatae, oriental variegated coralbean bark, cortex dictamni, &amp; cortex phellodendri</td>
<td>Atopic dermatitis humans</td>
<td>Topically applied for 28 d</td>
<td>32</td>
<td>↓</td>
<td>32</td>
</tr>
<tr>
<td>Radix Astragali, Radix Polygony multiflori, fructus tribuli, rhizoma atractyloids macrocephalae, radix angeliaceae sinensis, radix saposhnikoviae, &amp; scolopendra</td>
<td>Atopic dermatitis humans</td>
<td>Not indicated</td>
<td>30</td>
<td>↓</td>
<td>33</td>
</tr>
<tr>
<td>Rose essential oil</td>
<td>PS rats</td>
<td>Rats were stressed 8 h/d for 14 d. Rose essential oil for 13 d</td>
<td>6</td>
<td>↓</td>
<td>34</td>
</tr>
<tr>
<td>Prinsepia utilis &amp; purslane</td>
<td>GC-treated humans</td>
<td>Topically applied for 30 d</td>
<td>30</td>
<td>↓</td>
<td>35</td>
</tr>
<tr>
<td>Flos chrysanthemi, Flos sophorae, flos carthami, flos rosae rugosae, radix rehmanniæ, flos Celosia cristata, radix glycyrrhizae, &amp; Herba Artemisiae annuae</td>
<td>GC-treated humans</td>
<td>Orally given for 30 d</td>
<td>38</td>
<td>↓</td>
<td>36</td>
</tr>
<tr>
<td>Radix scutellariae, rhizoma coptidis, Herba Taraxaci, flos campsis, Flos Loniceræ, cortex moutan, radix arnbiae radix lithospermi, rhizoma imperatae, rhizoma anemarrhenææ, radix ophiopogonis, radix rehmanniæ, &amp; Flos Celosia cristata</td>
<td>GC-treated humans</td>
<td>Orally given for 28 s</td>
<td>68</td>
<td>↓</td>
<td>37</td>
</tr>
</tbody>
</table>
efficacy and TEWL in patients with acne as compared with blue-red light alone.

**Mechanisms**

Although studies have demonstrated that herbal medicines improve barrier function, the exact mechanisms remain unclear. Some evidence suggests the effects of herbal extracts on barrier function could be via multiple mechanisms, including the upregulation of keratinocyte differentiation, proliferation, lipid production and/or transportation, innate immunity, as well as antioxidation.

**Epidermal differentiation and proliferation**

Expression of epidermal differentiation-related proteins, such as filaggrin, loricin, and involucrin, are required for permeability barrier formation. The regulatory roles of some herbal medicines on barrier function are via the upregulation of the expression of epidermal differentiation-related proteins. It is reported that oleanolic acid upregulated expression of filaggrin, involucrin, loricin, and stimulated cornified envelope formation in keratinocyte cultures via enhancing expression and activation of peroxisome proliferator-activated receptor γ (PPARγ). The latter is known as a critical regulator for keratinocyte differentiation and proliferation. Likewise, hesperidin increased epidermal filaggrin and loricrin expression, and keratinocyte proliferation in a murine model while topical apigenin only unregulated epidermal filaggrin and its mRNA expression. Moreover, studies indicate that hesperidin increased PPARγ and its mRNA expression in NALM-6 cells and human preadipocytes. Our prior study showed that activation of PPARγ upregulated epidermal differentiation, resulting in improvement of barrier function. Furthermore, another barrier enhancer, EGCG, stimulates keratinocyte differentiation via the upregulation of activator protein 1 expression. These studies suggest that at least some herbal medicines induce improvement of barrier function through the stimulation of epidermal differentiation and proliferation.

**Lipid production and transportation**

Epidermal lipid production is crucial for permeability barrier homeostasis. Our prior studies showed that topical applications of herbal extract increased epidermal lipid content and the expression of mRNA for lipid synthetic enzymes. Topical applications of either 1% ursolic acid or 1% oleic acid for 3 days significantly increased epidermal ceramide content. Ishikawa et al reported that both macrocarpal A and extract of *Eucalyptus globulus* increased ceramide production and expression of mRNA for ceramide synthetic enzyme. Additionally, formation of the epidermal permeability barrier function requires not only the synthesis of lipids, but also the formation and secretion of lamellar bodies as a means to deliver lipids to the SC. Studies show that some herbal medicines improve barrier function via the stimulation of lamellar body formation and secretion. For example, either topical apigenin or hesperidin accelerated lamellar body formation and secretion. It is known that formation of a lamellar body requires ATP-binding cassette transporter 12 (ABCA12), a transmembrane glycosylceramide transporter. Topical applications of certain herbal extracts elevated epidermal ABCA12 mRNA expression. Thus, stimulation of epidermal lipid production and transportation could account for another potential mechanism whereby herbal extracts improve epidermal permeability barrier function.
Antioxidant

Nowadays the association of oxidative stress and skin barrier function is greatly appreciated. Several in vivo studies have demonstrated the beneficial effects of antioxidants on skin barrier function in both normal and diseased skin. Some herbal extracts that improve barrier function exhibit potent antioxidant property. In vitro studies showed that ginseng extract decreased reactive oxygen species, and increased both glutathione content and superoxide dismutase activity in keratinocytes. Although some studies showed that EGCG could cause oxidative damages to cells, numerous studies have demonstrated that it inhibited H$_2$O$_2$ production and lipid peroxidation in UVB or UVA irradiated keratinocytes. Moreover, EGCG inhibited the expression of inducible nitric oxide synthase mRNA, nitric oxide production, as well as IL-6 secretion in keratinocytes via inhibition of UVB-induced activation and translocation of NF-kappaB. The antioxidant properties of other barrier enhancing herbal extracts are also well demonstrated. For example, rats fed with hesperidin for 4 weeks displayed lower levels of serum thiobarbituric acid-reactive substances, product of lipid peroxidation, and higher levels of serum antioxidant capacity. Similarly, oral hesperidin or ginseng or their combination significantly reduced serum malondialdehyde and nitrite levels, and increased total superoxide dismutase activity in chickens. Likewise, orally given hesperidin lowered serum malondialdehyde and nitrite levels, and increased the activity of serum antioxidant enzymes, including catalase and superoxide dismutase in pentylenetetrazole-treated mice. Hence, the antioxidant properties of herbal extracts can be attributed to the improvement of barrier function.

**Innate immunity**

Prior studies showed that epidermal antimicrobial peptides are also required for epidermal permeability barrier function. At least two epidermal antimicrobial peptides, CAMP (LL-37) and mBD3 (hBD2), are packaged and secreted by lamellar body and regulated in parallel with changes in permeability barrier function. Our previous studies revealed that extract of a herbal mixture increased both epidermal CAMP and mBD3 expression in addition to improving barrier function in vivo. In addition, the same extract upregulated the expression levels of mBD3 mRNA in vivo, and induced a dose-dependent increase in LL-37 and hBD2 mRNA expression in cultured human keratinocytes. Moreover, as stated above, topical apigenin improved barrier function in both normal and diseased skin. We have demonstrated that topical applications of apigenin twice daily for 9 days markedly increased epidermal CAMP and mBD3 expression in mice. Therefore, the upregulation of antimicrobial peptide expression could be an additional potential mechanism for herbal extract-induced improvement of barrier function. The potential mechanisms whereby herbal medicines benefit epidermal permeability barrier function are summarized in Table 2.

**Conclusion**

Epidermal permeability barrier function has a significant impact on cutaneous functions. Improvement of skin barrier function is becoming a valuable approach to prevent and treat some skin disorders. Evidence indicates that herbal medicines benefit barrier function in both normal and diseased skin with fewer adverse effects and lower cost. Thus, herbal medicines could be used as an optional alternative for preventing and treating certain dermatoses accompanied by epidermal permeability barrier abnormalities.

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**References**


**Table 2** Mechanisms by which herbal medicines benefit epidermal permeability barrier.

<table>
<thead>
<tr>
<th>Herbal extracts</th>
<th>Keratinocyte differentiation</th>
<th>Lipid production</th>
<th>Lamellar body formation</th>
<th>Antimicrobial peptides</th>
<th>Others</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radix Partheniae rubra, cat nut, <em>Phellodendron, Rhizoma Alismatis, Angelica sinensis, &amp; Glabrous greenbrier</em></td>
<td>N/D</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>8</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>9,52</td>
</tr>
<tr>
<td>Apigenin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>10,26</td>
</tr>
<tr>
<td>Ursolic acid &amp; oleanolic acid</td>
<td>↑</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>↑</td>
<td>11</td>
</tr>
<tr>
<td>Terminalia arjuna</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>↑</td>
<td>12</td>
</tr>
<tr>
<td>Red ginseng</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>↑</td>
<td>19</td>
</tr>
<tr>
<td>Rose essential oil</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>N/D</td>
<td>↓</td>
<td>27.51</td>
</tr>
</tbody>
</table>

PPAR – peroxisome proliferator activated receptor.

* Aged human.


