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RESEARCH HIGHLIGHT

Anti-aging effect of magnesium lithospermate β from *Salvia miltiorrhiza* Bunge on skin

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Magnesium lithospermate B (MLB, also called salvianolic acid B), one of the hydrophilic phenolic compounds of Salvia miltiorrhiza Bunge has been reported to possess numerous health benefits, but a role for MLB in the prevention of skin aging has not been fully explored. In a recent publication, we reported that the skin anti-aging action of MLB depends on its ability to suppress collagen degradation via its anti-oxidant activity, and subsequently, to increase the expressions of type I and III collagen genes through PPARβ/δ activation. For this research highlight, we describe the salient findings from our recent study on the anti-wrinkle effect of MLB and the molecular mechanism underlying its skin anti-aging action.

Keywords: skin aging; collagen; Magnesium lithospermate B; PPARβ/δ; wrinkles

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Danshen is the dried root of *Salvia miltiorrhiza* Bunge (Fig. 1) and one of popular medicinal herbs that have been used for hundreds of years in China [1]. Danshen was used to improve blood stasis and blood circulation and is highly effective in the treatment of hyperlipidemia, cardiovascular disease, and cerebrovascular disease [2]. Danshen is classified mainly into two groups based on its structural characteristics and chemical properties. One group is hydrophilic phenolic compounds including the active constituents; magnesium lithospermate B (MLB, also called salvianolic acid B), caffeic acid, rosmarinic acid, salvianolate, and lithospermic acid. The other group is lipophilic triterpenoidal compounds such as tanshinone I, tanshinone IIA, and other tanshinone derivatives [3]. Accumulated data show the diverse pharmacological activities of these compounds, such as their anti-oxidant, anti-cancer, and anti-inflammation actions [1, 2, 4].

As one of Danshen's main hydrophilic phenolic compounds, MLB has strong pharmacological activities; the chemical structure of MLB is shown in Fig. 1. MLB is reported to possess multiple bioactivities that contribute to beneficial effects in various diseases such as coronary artery disease, ischemia stroke, chronic renal disease, and liver

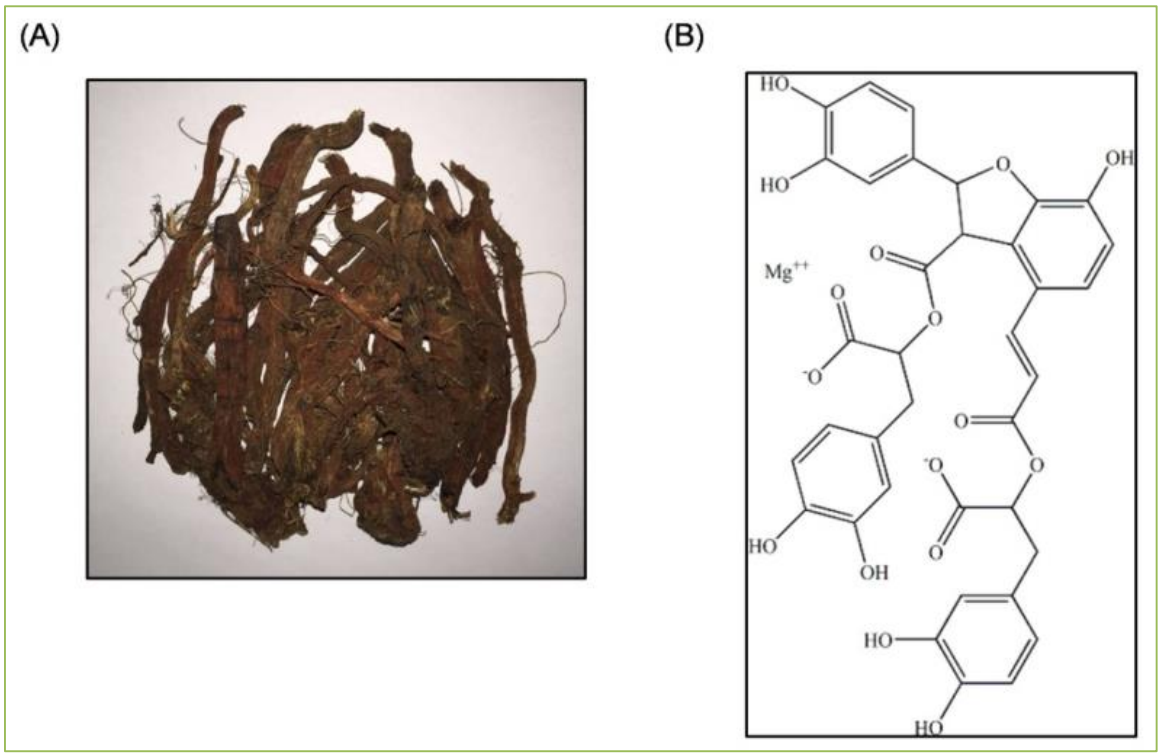

Figure 1. The *Salvia miltiorrhiza* Bunge (A) and the chemical structure of MLB.

disease [5-9]. MLB prevents intracellular or intravascular oxidative stress as well as the expression of endothelial-leukocyte adhesion molecules in cardiovascular endothelial cells [5]. Also, MLB ameliorates diabetic renal injury via its anti-oxidant ability [6] and attenuates the inflammatory response in ischemia/reperfusion-mediated hepatocellular damage and hepatocellular apoptosis [7]. In addition, a recent study revealed that MLB treatment prevents brain injury induced by ischemic stroke by inhibiting apoptosis and inflammation through the activation of sirtuin 1 signaling [8]. Although studies propose the pharmacological functions of MLB for various diseases, the anti-aging potential of MLB for skin remains unexplored until now.

As the proportion of the world's aging population continues to increase, concerns about skin aging are growing. The skin is the largest organ in our body and clearly reflects the consequences of aging. Aging of the skin is influenced by two separate processes, intrinsic and extrinsic aging processes. Intrinsic skin aging occurs as the general aging process and is determined by genetic factors, hormonal status and metabolic reactions, such as oxidative stress; whereas, extrinsic aging is accelerated by ultraviolet (UV)-radiation, smoking, excess alcohol consumption, and air pollution. Skin aging appears with features of wrinkle formation, skin discoloration, breakdown of collagen and elastin, dehydration, and slowdown of cell turnover, that are triggered by diverse biochemical reactions occurring within the skin [9].

Reactive oxygen species (ROS) play an important role in skin aging and are regarded as the main cause of both intrinsic and extrinsic aging. They stimulate the synthesis of matrix metalloproteinases (MMPs), the proteolytic enzymes responsible for the degradation of extracellular matrix (ECM). In general, the primary role of MMP is to recycle skin matrix through degradation of the structural proteins, collagen and elastin, but it also induces the imbalance of matrix synthesis and breakdown/recycling; damaged matrix then accumulates, thereby leading to skin aging such as wrinkle formation [10].

Moreover, ROS generation induces damage of ECM structures through the oxidation of lipid, DNA, and proteins. These oxidative products lead to loss of function on cell surface receptors (G-protein-coupled receptors, interleukin-1 receptor; IL-1R, tumor necrosis factors-α receptor; (TNF-αR) through the imbalance of protein tyrosine kinase and protein tyrosine phosphatase, and subsequently, ligands such as epidermal growth factor, TNFα, IL-1 on the membrane of fibroblast and keratinocytes bind receptor freely, leading to activation of intracellular signal transduction pathways. Alterations in mitogen-activated protein kinases (MAPKs, JNK, ERK, and p38) pathway especially have been shown to promote intrinsic aging as well as UV-induced damage. Activated MAPKs promote transcription factor, activator protein 1 (AP-1) and nuclear factor-κB (NF-κB), regulating the transcription of

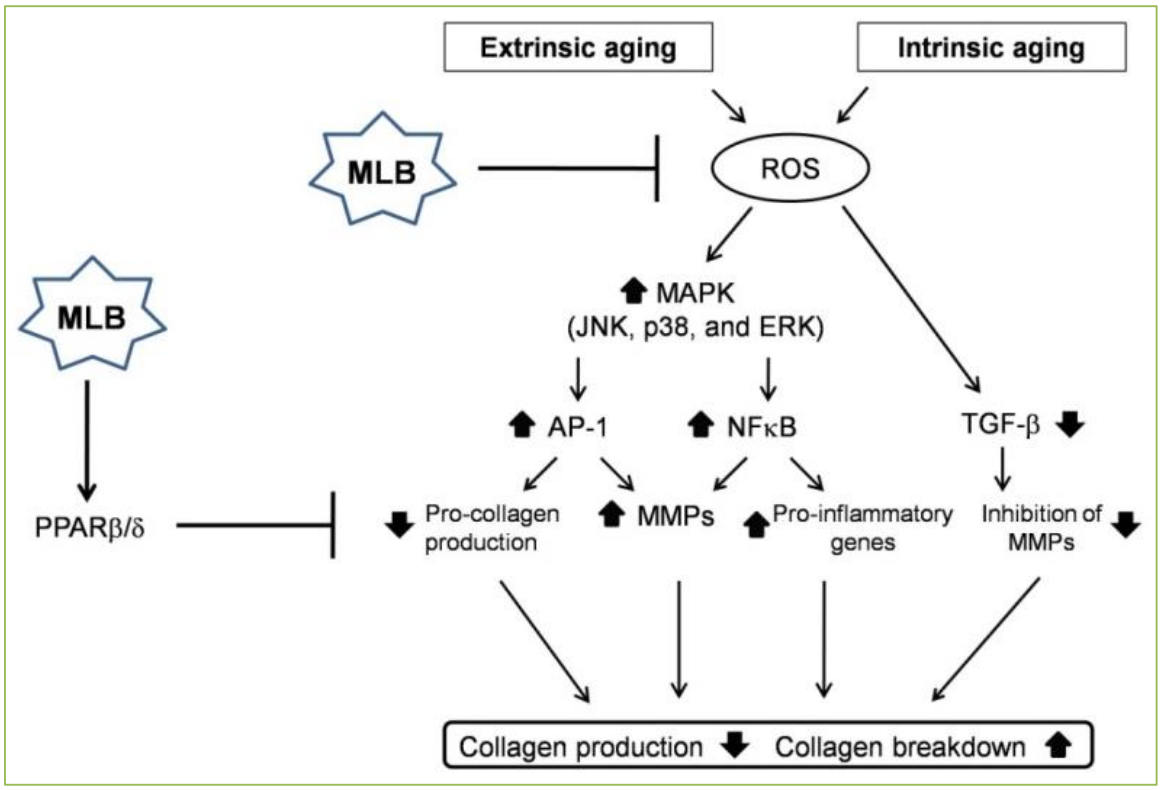

Figure 2. Schematic diagram showing the anti-aging effect of MLB on skin.

MMPs. Activated AP-1 and NF-κB in fibroblasts stimulate the infiltration and releasing neutrophil collagenase (MMP8) of inflammatory cells, such as neutrophils by inducing the transcription of proinflammatory cytokines, IL-1, IL-6, and TNF-α, which lead to further matrix degradation. Also, subsequent AP-1-induced down-regulation of the transforming growth factor-β (TGF-β) type II receptor decreases the binding of the cytokine TGF-β related to the expression of type I and III collagen [11, 12].

In recent dermatology research, peroxisome proliferator-activated receptors (PPARs) have emerged as attractive targets in skin health and diseases. PPARs (PPARα, PPARβ/δ, and PPARγ) are transcription factors activated by various molecules such as fatty acids and fatty acid metabolites, and they play essential roles in the regulation of metabolism, inflammation, tumorigenesis, differentiation, and development in different cell types [13]. One of the PPAR isoforms, PPARβ/δ expresses abundantly in the skin and has beneficial actions in skin physiology and skin pathologies. PPARβ/δ, which presents throughout all epidermal layers, enhances barrier function via keratinocyte proliferation and differentiation. Also, PPARβ/δ inhibits both tumor promoter-inducing skin hyperplasia and melanoma cell proliferation [14]. In addition, PPARβ/δ activation controls wound healing processes through the induction of collagen and fibronectin in a TGF-β-dependent or independent signaling in injured skin [15]. In contrast, deletion of PPARβ/δ leads to an aggravation of the inflammatory state [16].

Recently, our group showed the anti-wrinkle effects of MLB on aged rat skin and UVB-exposed cells [17, 18]. In these research articles, we focused on the molecular mechanism of MLB in its anti-wrinkle action on skin aging models. In particular, MLB exhibited inhibition in the expressions of cyclooxygenase-2 and inducible nitric oxide synthase, pro-inflammatory genes and MMPs via activation of NF-κB and AP-1 in these skin aging models. Furthermore, the ROS scavenging activity of MLB decreased phosphorylation of MAPKs (JNK, ERK, and p38), NF-κB and AP-1-inducing kinases. It was further demonstrated that PPAR β/δ activation was a possible target of MLB by increased expression of collagen genes in fibroblasts [17]. These findings represent an important achievement into the understanding of how MLB has anti-wrinkle effects in aged rat skin and UVB-irradiated cells (Fig. 2).

Today, cosmetic formulations from natural resources derived from polyphenols, flavonoids, and carotenoids are commonly used in anti-aging products on the worldwide market. Since synthetic skincare cosmetics are known for their severity of adverse effects, the naturally derived compounds are usually hypo-allergenic in nature and

therefore more commonly accepted [19]. Moreover, most natural compounds contain anti-oxidant activity, and their effects improve photo-radiation damage and epidermal anti-oxidant capacity [20]. MLB studied by our group not only prevented collagen degradation, but also induced type I and III collagen expression through its anti-oxidant activity in skin aging models. Thus, based on our data, we propose that MLB has anti-wrinkle effects on aging skin by its ability to modulate a balance between degradation and synthesis.

Here, we summarize a novel role for MLB that shows its potential skin anti-aging properties that protect against UV radiation and intrinsic aging. MLB is reported to possess numerous health benefits, but a role for MLB in the prevention against skin aging is highlighted for the first time in a research article. Therefore, the present review may be helpful to future studies that further investigate the safety and efficacy of MLB as a novel therapeutic and cosmetic agent in anti-aging skin products.

Conflicting interests

The authors have declared that no conflict of interests exist.

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