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The Role of Herbal Medicine for Hypertrophic Scars Management

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ABSTRACT

The process of wound healing is intricate, involving highly coordinated and synchronized mechanisms. Deviations from normal physiological responses can result in hypertrophic scarring. In recent years, there has been a global resurgence of interest in herbal remedies. Many plant-derived compounds and extracts have demonstrated the capacity to inhibit hypertrophic scar formation. The primary mode of action involves inhibiting proliferation and/or triggering apoptosis in scar fibroblasts by modulating various pathways, including PI3K/AKT, VEGF, and TGF-*β*/SMAD. Advancing our comprehension of hypertrophic scar pathophysiology, conducting follow-up research, and pursuing future investigations will help overcome current challenges and lead to the development of promising therapeutic approaches.

Herbal medicine, Hypertrophic scars, Wound healing

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INTRODUCTION

The process of wound healing is intricate, involving a delicate equilibrium of regulatory pathways, including the coagulation cascade, immune response, and fibrosis. Deviations from the normal physiological healing process can result in complications such as ulcers, hypertrophic scars, and keloids.[1-4] Research indicates that 33-91% of burn victims and 40-70% of surgical patients develop secondary hypertrophic scars. Annually, approximately 100 million individuals in developing nations acquire post-surgical scars.[5]

The treatment of hypertrophic scars remains an area of ongoing research. Recent years have witnessed a global resurgence of interest in herbal medicine. Most published clinical trials have concentrated on examining the pharmacokinetics and metabolism of medicinal plants. However, experimental studies on herbal treatments for hypertrophic scars in humans are still uncommon. Recent literature has highlighted various potential benefits of herbal remedies in addressing hypertrophic scars.[6] Consequently, this text explores the potential role of herbal medicine in treating hypertrophic scars.

HERBAL MEDICINE FOR HYPERTROPHIC SCAR MANAGEMENT

Many plant extracts have antihypertrophic scar activity due to their phytochemical constituents. Additionally, many of them have not been tested for cytotoxicity against normal cells, which seriously precludes in vivo investigation.[6,7] Many are used in combination with other therapeutic regimens, i.e. in cream formulations or added to mixtures, to try and improve wound healing conditions.[8]

CENTELLA ASIATICA

Gotu kola, scientifically known as *Centella asiatica*, is a member of the Apiaceae family. This herb is often prescribed for various skin conditions, including hypertrophic scars.[9,10] Its wound-healing properties

include enhancing skin microcirculation, stimulating connective tissue formation, and limiting excessive connective tissue growth. Additionally, *Centella* helps regulate fibroblast activity and collagen production. A clinical study revealed that 82% of participants experienced reduced inflammatory symptoms after receiving daily doses of 60-150 mg of *Centella asiatica*. The plant contains several key active components, with triterpenoid saponins (asiaticoside, centelloside, madecassoside, and asiatic acid) being the most significant.[11,12]

Madecassoside has been shown to promote apoptosis in hypertrophic scar fibroblasts through the mitochondrial pathway. It also demonstrates the ability to curb SVK-14 keratinocyte proliferation in psoriasis and suppress LPS-induced TNF-α production in cardiomyocytes by inhibiting ERK, p38, and NF-κB activity. Another important component, asiaticoside, is known to decrease the protein and mRNA expression of TGF-βRI and TGF-βRII while increasing that of Smad7. The reduced expression of TGF-βRI leads to decreased phosphorylation of R-Smads (Smad2/3). Given the close connection between TGF-β signaling and collagen production, inhibiting this signaling pathway can suppress fibroblast proliferation and collagen synthesis, thereby preventing the development of hypertrophic scars or keloids.[13-16]

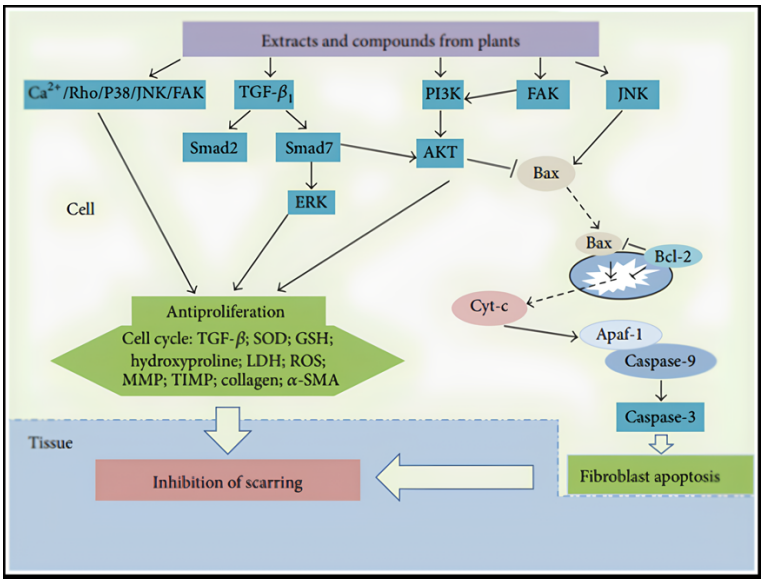

Figure 1. Mechanism of anti-hypertrophic scar activity of herbal plant extracts and components.[6]

ALLIUM SATIVUM

Allium sativum, commonly known as garlic, contains several key components: an enzyme called alliinase, a sulfur-containing compound named alliin, and allicin, which is enzymatically produced from alliin. Additionally, garlic comprises arginine, oligosaccharides, flavonoids, and selenium. Research has shown that garlic extract in preserved form can enhance immune functions, including lymphocyte proliferation, cytokine release, natural killer cell activity, and phagocytosis.[17]

Preserved garlic extract exhibits antioxidant properties through various mechanisms. It scavenges reactive oxygen species, enhances cellular antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, and boosts cellular glutathione levels. Furthermore, garlic extract offers protection to DNA against free radicals and ultraviolet light-induced damage. It also inhibits several factors involved in the development of hypertrophic scars and keloids, including NF-κB, nitric oxide (NO), MMP-2, IL-6, and ACE.[17,18]

CURCUMA LONGA

Curcumin, also known as diferuloylmethane [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], is the primary natural polyphenol found in the Zingiberaceae family.19,20 Research on mice has shown that curcumin can enhance wound healing by increasing contractions and reducing healing time. After 12 days

of curcumin treatment (200 µl at 40 mg/kg body weight), wounds exhibited higher levels of fibronectin and collagen expression, along with improved collagen maturation and cross-linking, resulting in increased wound tensile strength.[21]

In vitro studies by Scharstuhl et al. revealed that *curcumin* treatment (>25 µM for 48 h) triggered fibroblast apoptosis and hindered FPCL contraction in human dermal fibroblasts through ROS-mediated mechanisms. The researchers suggested that high concentrations of curcumin could potentially be used as a therapeutic approach to minimize or prevent hypertrophic scars by regulating heme oxygenase (HO) molecule activity or administering HO effector molecules.[21]

ALLIUM CEPA L.

Red onion extract contains compounds with anti-inflammatory and anti-infective properties, specifically quercetin and kaempferol. Additionally, it functions as a mast cell stabilizer and inhibits cell proliferation.[3] It can impede fibroblast growth by blocking the TGF-β/SMAD signaling pathway. The extract's ability to induce MMP-1 aids in breaking down newly formed collagen, which significantly enhances scar height and softness. This extract can be used in conjunction with other treatments, such as intralesional triamcinolone or surgical scar revision.[22-26] Despite its molecular benefits on scars, the clinical effectiveness of onion extract in scar prevention and treatment remains uncertain (based on level I and II studies).[27]

A randomized, open, controlled study compared the use of intralesional triamcinolone combined with onion extract gel to intralesional triamcinolone alone for treating hypertrophic scars and keloids. The combination of triamcinolone and onion extract proved more effective in reducing pain, itching, and elevation than triamcinolone by itself, although no significant differences were observed in erythema or induration. In a separate study by Hosnuter et al., which compared onion extract, silicone gel sheets, and a combination of both, the combined therapy showed significant improvements in scar color and height compared to onion extract alone.[3]

CAMELLIA SINENSIS

Camellia sinensis, commonly known as green tea, contains catechins, which are phenolic compounds with antioxidant, anti-inflammatory, and antimicrobial qualities. Research has demonstrated the beneficial effects of green tea polyphenols, particularly catechins and epigallocatechin-3-gallate (EGCG), in promoting keratinocyte growth and differentiation, as well as exhibiting antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic properties.[5,8,20]

One investigation revealed that EGCG significantly inhibited mast cell-induced type I collagen expression by blocking the PI-3K/AkT signaling pathway. Another study showed that EGCG considerably suppressed collagen production and proliferation by inhibiting the STAT3 signaling pathway. In an ex vivo culture model using punch biopsies, EGCG was found to significantly impede growth and cause keloid shrinkage.[8,20] Park et al. observed that EGCG suppressed keloid growth and collagen production in a mouse model. Syed et al. demonstrated that EGCG inhibited keloid tissue growth and induced shrinkage of human keloid tissue in a human keloid OC model. Furthermore, both zonal priming and direct application of EGCG showed benefits for scar therapy in double-blind trials, indicating its potential to improve hypertrophic scars and warranting further investigation.[5]

HIBISCUS SABDARIFFA

Hibiscus sabdariffa L., commonly known as roselle, has gained increasing popularity among the public in Indonesia. Phytochemical analysis of roselle flower petal extract revealed the presence of tannins, flavonoids, steroids/triterpenoids, and glycosides. These chemical compounds possess anti-inflammatory properties that can inhibit the inflammatory process involved in hypertrophic scar and keloid formation. Research conducted by Putra et al., (2020) demonstrated that roselle flower petal extract enhances apoptosis in human keloid fibroblast cells at various concentrations, with the effect proportional to the concentration used. This finding suggests that the extract can impede the proliferation of human keloid fibroblast cells in vitro.[28]

SOPHORA JAPONICA

Sophora japonica L, also referred to as *Japanese acacia*, is a shrub species that belongs to the Faboideae subfamily within the Fabaceae family, which is known as the pea family.[29] The primary quinolizidine alkaloid extracted from Sophora japonica roots is Oxymatrine (OMT). Studies have demonstrated that OMT possesses anti-inflammatory, antiviral, and anti-hepatic fibrosis properties, as well as the ability to suppress immune responses. In CCl4-induced liver fibrosis in Sprague–Dawley SD rats, OMT has been shown to enhance SMAD7 expression while reducing SMAD3 expression, thereby modulating fibrogenic signal transduction of the TGF-β/SMAD pathway. In addition, OMT may inhibit the development of hypertrophic scars and keloids. A study conducted by Fan et al. determined that OMT hinders collagen synthesis, potentially through its interaction with the TGF-β/SMAD signaling pathway. These results indicate that OMT could be a promising candidate for the prevention of hypertrophic scars, keloids, and other fibrotic conditions.[30-32]

GLYCINE MAX

Soybean (*Glycine max* L. Merr.) is a crucial and cost-effective protein source among oilseeds. Genistein, a phytoestrogen extracted from soybeans, has the ability to inhibit NIH 3T3 cell proliferation and collagen production induced by serum, PDGF, and TGF-β1.[33-35] Genistein effectively inhibits HSFB proliferation, suppresses mitosis, and promotes apoptosis. Its mechanisms of action include: (1) TPK inhibition, caspase-3 increase, and α-SMA and Bcl-2 protein reduction, (2) Bax protein elevation, (3) type I/III precollagen mRNA expression inhibition, collagen I/III mRNA downregulation, PCNA expression reduction, and c-Raf, MEK1/2, ERK1/2, and p38 phosphorylation inhibition, (4) induction of apoptotic cell morphology changes, (5) prevention of fibroblast to myofibroblast transdifferentiation, (6) G0-G1 phase decrease and G2-M phase increase, (7) C-JUN mRNA expression increase and FOS-B mRNA expression decrease in skin keratinocytes, and (8) C-JUN and C-FOS mRNA expression inhibition in human fibroblasts. In keloid fibroblasts, C-JUN and C-FOS mRNA expression decreases at 37 M but increases at 370 M.[36,37]

CONCLUSION

Various extracts and compounds derived from herbal plants have the ability to impede hypertrophic scar formation. The primary mechanism involves inhibiting proliferation and/or triggering apoptosis in scar fibroblasts by modulating several pathways, including PI3K/AKT, VEGF, and TGF-β/SMAD. Advancing our knowledge of hypertrophic scar pathophysiology and conducting further research will help overcome existing challenges and lead to the development of promising treatments. Collaboration among a multidisciplinary team is essential for progress in this field.

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CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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