

## Review Article

# Effects of Herbal Medicines on Wound Repair *via* the Modulation of the Transforming Growth Factor Beta (TGF $\beta$ ) and Basic Fibroblast Growth Factor (bFGF): A Mini-Review

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Received: 06.06.2023; Accepted: 27.11.2023

## Abstract

The transforming-growth factor  $\beta 1$  (*TGF $\beta 1$* ) and basic fibroblast growth factor (*bFGF*) are two factors with significant roles in the wound healing process. There are two therapeutic approaches to wound repair consisting of beauty wise and strength wise. This study was conducted to review the roles of herbal medicines in the wound repair process focusing on the roles of TGF $\beta 1$  and bFGF according to approaches. Scientific databases, including Google Scholar, PubMed, Web of Science, and Scopus were searched to find review articles about using herbal medicines in wound repair. Further evidence confirmed the efficiency of aloe vera in comparison with other medicinal plants. That is, it could up-regulate both TGF $\beta 1$  and bFGF. Wound repair is a very complex process that requires interdisciplinary management. Targeting different parts of this complex mechanism may have different clinical results. Medicinal plants are not exceptions, and the use of these plants may have different outcomes. The management strategy of wounds depends on several fac.

**Keywords:** Wound healing, Transforming growth factor beta1, Medicinal plants

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**Please cite this article as:** Hormozi M, Beigi Boroujeni M. Effects of Herbal Medicines on Wound Repair *via* the Modulation of the Transforming Growth Factor Beta (TGF $\beta$ ) and Basic Fibroblast Growth Factor (bFGF): A Mini-Review. *Herb. Med. J.* 2023;in press.

## Introduction

Scar formation is a natural process that occurs during wound repair. The transforming-growth factor  $\beta 1$  (*TGF $\beta 1$* ) and basic fibroblast growth factor (*bFGF*) are two factors with key roles in the wound healing process. Fibroblasts are matrix producing cells, and the up-regulation of *TGF $\beta 1$*  and *bFGF* results in further proliferation of fibroblasts during wound repair. It has been observed that *TGF $\beta 1$*  is up-regulated in fibroblastic diseases. Moreover, the antisense of *TGF $\beta 1$*  could prevent scar formation. This

growth factor increases collagen, elastin and fibronectin synthesis (1). Wound healing involves the processes of hemostasis (1-60 minutes), inflammation (1-48 hours), proliferation (1-10 weeks) and remodeling (1-24 months). Formation of scar tissue was attributed to collagen synthesis, and the remodeling occurred during proliferation and remodeling steps (2). Collagen synthesis is a process that depends on vitamin C (3). *TGF $\beta 1$*  expression decreases due to vitamin malnutrition. Hence, vitamin C is necessary for wound healing (4).

TGF $\beta$  superfamily consists of a large group of cell-

regulatory proteins that contribute to tissue development during the embryonic period and also in a mature human. This superfamily consists of some families, including the TGF $\beta$  family. Members of this family are TGF $\beta$ 1, TGF $\beta$ 2 and TGF $\beta$ 3 isoforms. TGF $\beta$ 1 is the isoform most commonly found in human tissues. TGF $\beta$  isoforms, particularly particular TGF $\beta$ 1, are effective in wound healing and fracture healing processes (5, 6). FGF is a family of growth factors and signaling proteins. FGF2, also known as bFGF, is an angiogenic protein playing a role in endothelial cell migration and acute dermal inflammation (7). bFGF is central to the wound healing process because it is effective in the migration and proliferation of fibroblasts (8). Herbal medicines are commonly used by people due to cultural reasons for their beneficial effects such as analgesic, antimicrobial, and anti-inflammatory effects (9). According to the epidemiological significance of wounds, many herbal medicines are used in this regard (2). About 2% of the US population have chronic non-healing wounds with billions of dollar medical costs (2, 10). Hence, there are tendencies to make herbal formulae and compounds. Researchers believe that interdisciplinary approaches and novel technologies should be used in this regard (2).

Although many studies have been conducted on the role of herbal medicines in wound repair, no consensus of either opinion or interpretation for the justification of the controversial findings regarding the related mechanisms has been achieved. For instance, yarrow down-regulated TGF $\beta$ 1 in a study (11), while in another study aloe vera up-regulated TGF $\beta$ 1 (12). A challenge not mentioned in the literature is that there are two therapeutic approaches to wound repair, i.e. beauty and strength approaches. In the beauty approach, fibroblast proliferation should be suppressed while in the other approach, scar formation is necessary for the strength of repaired wounds. It seems that the first therapeutic approach is better for superficial wounds, while the second one is suggested to be used for deep and internal lesions. This challenge may justify the controversial findings of previous studies.

Given the controversy of the approaches mentioned above and also distinct mechanisms of different herbal medicines in the wound repair process, this mini-

review study was conducted to summarize the roles of herbal medicines in the wound repair process focusing on the role of TGF $\beta$ 1 and bFGF. Finding the response of this research question may help clinical researchers investigate these approaches in clinical medicine.

#### Evidence Acquisition

A mini-review was conducted on the relevant original studies with a narrative approach. Scientific databases, including Google Scholar, PubMed, Web of Science, and Scopus were searched to find documents about using herbal medicines in wound repair. The general syntax was (herbal OR plant) AND ("wound repair" OR "wound healing"). Then, the most important plants were selected from the articles. Subsequently, the articles were searched to find out whether there were studies about their effects through TGF $\beta$ 1 and bFGF. *In vitro* studies had priority to the authors, and these studies were subjected for quality assessment using Quality Assessment Tool for *In Vitro* Studies (QUIN) (Table 1) (13).

#### Effective Herbal Medicines

*Yarrows (Achillea Millefolium/Santolina)*

Yarrows, with the scientific name *Achillea Millefolium/Santolina*, is used in integrative medicine because of its different chemical compounds (14, 15). It is a flowering plant characterized by a penetrating smell with a bitter taste in all its parts. The species *Millefolium* has white flowers, while the species *Santolina* has yellow flowers. Yarrow is a kind of weed in farms and grows wildly in different places like beside roads. Its flowering time is about May–July (16). An *in vitro* study on embryonic fibroblast cells in mice showed that *Achillea biebersteinii* Afan (as another species of yarrow with yellow flowers) extract could down-regulate the TGF $\beta$ 1 and up-regulate the bFGF expression (11). However, a study investigating the role of yarrow oil in a mice model of ulcerative colitis showed a significant up-regulation for TGF $\beta$  (17). Another study on rabbit indicated that the alcoholic extract could of yarrows could contribute to the healing process of experimental burn wounds and also reduce topical microorganisms with its anti-microbial effects (18).

*Aloe vera (Asphodelaceae)*

Aloe, with scientific name *Asphodelaceae*, is a genus of plants having more than 500 species (11). It has been indicated that the *in vitro* administration of the aloe vera extract on mice embryonic fibroblast cells up-regulates

**Table 1:** Summary of the *in vitro* studies and quality assessment based on QUIN.

	Hormozi, 2019	Hormozi, 2017	Hsiao, 2012	Qu, 2022	Enciso Gutiérrez, 2010
Intervention	Achillea biebersteinii Afan	aloe vera	Angelica Sinensis	Angelica sinensis	Achiote, asmachilca, golden gooseberry, cauda equina
Outcome	TGFβ1 and bFGF	TGFβ1 and bFGF	TGFβ	microRNA-373-3p, TGF-β/Smad4 signaling	Cell stimulation rate
Cell line	Mice embryonic fibroblast	Mice embryonic fibroblast	Human embryonic skin fibroblast	Human glioma (U251)	Mice embryonic fibroblast
QUIN criteria					
Clearly stated aims/objectives	Yes	Yes	Yes	Yes	Yes
Detailed explanation of sample size calculation	No	No	No	No	No
Detailed explanation of sampling technique	Yes	Yes	Yes	Yes	Yes
Details of comparison group	Yes	Yes	Yes	Yes	Yes
Detailed explanation of methodology	Yes	Yes	Yes	Yes	Yes
Operator details	No	No	No	No	No
Randomization	No	No	No	No	No
Methods of measurement of outcome	Yes	Yes	Yes	Yes	Yes
Outcome assessor details	Partial	Partial	No	No	No
Building	No	No	No	No	No
Statistical analysis	Yes	Yes	Yes	Yes	No
Presentation of results	Yes	Yes	Yes	Yes	Yes

both *TGFβ1* and *bFGF* (12). Another study reported similar results with regard to the expression of *TGFβ1* and *bFGF* in radiation exposed rats. Moreover, angiogenesis, inflammatory cell infiltration, fibroblast proliferation, and collagen deposition were increased (19). Another study reported the increase in the *TGFβ* gene expression and fibroblast count (20). Other mechanisms of aloe vera on wound healing have been described previously (21). In addition to wound healing, a study showed that TGFβ1 immunohistochemistry expression increased by aloe vera gel in a mice model of laceration (22). Similar results were observed in a rat model of radiation dermatitis (23).

#### *Dong quai (Angelica Sinensis)*

Dong quai, with the scientific name *Angelica Sinensis*, is a plant whose root is used in Chinese medicine (24). This plant is alternatively called ginseng. However,

there are many other medicinal plants also called ginseng. A cell culture study showed that *Angelica Sinensis* can increase the protein expression of TGFβ and also collagen synthesis (25). However, suppression of the TGFβ/Smad pathway has been observed in other studies (26, 27). No information was available for bFGF.

#### *Other Medicinal Plants*

Although many studies have been conducted on the role of medicinal plants in wound healing, there are few studies investigating TGFβ and bFGF. For instance, one of other medicinal plants is horsetail (equisetum), which is known as living fossil. A study on human showed that episiotomy-resulted wounds could be healed by horse tail ointment. However, there are no genetic evaluations in this study (28). Enciso Gutiérrez *et al.* founded that horsetail plant could increase fibroblast proliferation (29).

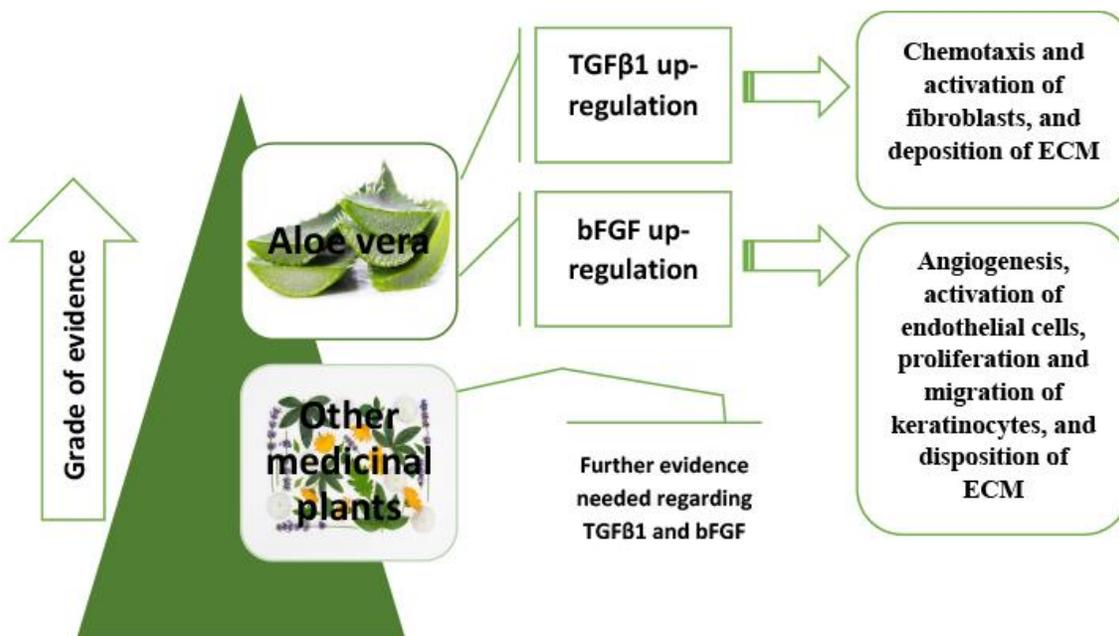
## Discussion

The present mini-review was conducted to summarize the medicinal plants improving wound repair through the modulation of TGFβ1 and bFGF. There has been a controversy about whether the suppression of fibroblasts is better for the prevention of scar formation (beauty approach) or increased fibroblast activation is better for more strength (strength approach). Our literature review showed different mechanisms of different medicinal plants indicating their distinct uses. Moreover, wound repair has four steps. Each of these steps may need a different therapeutic strategy. In general, there were more evidence supports for aloe vera in comparison with other medicinal plants. In this regard, a larger number of studies was found, and the studies showed similar results (figure 1). Thus, the findings about aloe vera was more scientific and reliable.

According to our literature review, yarrow decreases TGFβ1 and increases bFGF, while aloe vera increases both of them. The cause of such controversies may be related to the distinctions with regard to chemical compounds of different medicinal plants. It seems that yarrow may be better for superficial wounds (based on

the beauty approach), while aloe vera may be better for deep wounds (based on the strength approach) as yarrow decreases TGFβ1. From the other point of view, aloe vera may be better for steps one to three of wound healing (hemostasis, inflammation and proliferation), while yarrow may be better for the final step (remodeling) to prevent scar formation. However, there is no clinical evidence and it needs clinical studies in the future.

TGFβ1 and bFGF may have different roles in wound repair. A review article conducted by Low et al. (2021) listed the effects of TGFβ as chemotaxis and activation of fibroblasts, and deposition of extracellular matrix (ECM). They listed the sources of TGFβ as fibroblast, macrophage and platelet. For FGF, they listed its functions as angiogenesis, activation of endothelial cells, proliferation and migration of keratinocytes, and disposition of ECM. Moreover, they listed the sources of FGF as endothelial cell, fibroblast and macrophage (30). Song et al. (2008) showed that adrenalin could inhibit the proliferation of fibroblasts through the down-regulation of TGFβ1 and up-regulation of bFGF. Hence, they believed that the roles of TGFβ1 and bFGF in wound repair were not the same. If their hypothesis is correct, it seems that the balance between these two



**Figure 1.** Effects of herbal medicines on wound repair *via* the modulation of TGFβ and bFGF.

factors is effective on the regulation of fibroblast proliferation and wound repair (1). Another source of the controversies is the cause of wound. For instance, in surgical wounds, strength is very important to prevent herniation (31, 32). Hence, our management strategy also depends on the cause of wound. Li et al. (2023) showed that bFGF gel could induce angiogenesis during wound healing in a rat model (33). The results of their research were consistent with those of many other studies (19, 30) regarding the role of angiogenesis in the mechanism of the effect of bFGF on wound repair.

Apart from TGF $\beta$ 1 and bFGF, the vascular endothelial growth factor (VEGF) is an angiogenic factor and a chemoattractant attracting immune cells to the wound site (34). As reported by Li et al. (2023), bFGF could in turn increase the expression of VEGF (33). Some growth factors such as epidermal growth factor (EGF), bFGF, VEGF and TGF-1 act as the primary regulators of cell signaling in the wound repair process in humans. These growth factors play roles in angiogenesis (35). In general, growth factors play key roles in cell migration and differentiation during wound repair (1). As described by Nafiu et al. (2015), papaya extract could improve wound repair through increasing fibroblasts recruitment via early transient expressions of VEGFA and TGF $\beta$ 1 at the wound area (36). It seems that their aim was the strong wise approach.

From the limitations of this study, it should be pointed out that it is difficult to approve the efficacy of herbal medicines due to many methodological limitations. Today, researchers growingly rely on modern scientific methods and evidence-based medicine. Finding the mechanisms of actions is necessary to improve the rationale of creating hypotheses for herbal medicine studies (15). In order to overcome this major limitation, we tried to review many pieces of evidence from primary studies. However, clinical studies should be conducted to verify the results as scientific rules.

## Conclusion

Wound repair is a very complex process that requires interdisciplinary management. Using medicinal plants can be a part of this interdisciplinary approach. Targeting different parts of this complex mechanism

may have different clinical results. Medicinal plants are not exceptions. The use of these plants may have different outcomes. The most important medicinal plants regarding the existing evidence were Aloe vera, yarrow, and ginseng. Clinical studies should be conducted to determine the efficacy and safety of such medicinal plants.

## Acknowledgements

None.

## Funding

None.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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