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REVIEW ARTICLE **OPEN ACCESS**

Investigating the Influence of Natural Compounds on the Healing Process of Wounds

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Abstract:
Advancements in modern medicine have not fully resolved the complexities associated with wound healing, particularly for chronic wounds, such as diabetic ulcers and burn injuries. Effective wound management necessitates not only the regeneration of damaged tissue but also minimizing scar formation. In this context, natural compounds derived from plants have emerged as promising candidates for enhancing wound healing. Ethnobotanical research has demonstrated that various herbal extracts possess properties that could significantly improve wound healing outcomes. This review explores the potential of these natural compounds, focusing on their mechanisms of action, efficacy in clinical and preclinical studies, and the challenges that still need to be addressed. By synthesizing findings from traditional medicinal practices and contemporary scientific research, this review aims to provide a comprehensive understanding of how natural compounds can contribute to more effective wound healing strategies.
In this review, widely used and studied plants are discussed, along with their ability to induce wound healing through all the phase and their mechanism of action.

Keywords: Wound healing, Angiogenesis, Plant Extracts, Medicine, Chronic wounds, Ethnobotanical.

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1. INTRODUCTION

Cutaneous wound healing involves four key phases: hemostasis, inflammation, proliferation, and remodeling. This process integrates various cells and chemical signals, influencing fibroplasia, epithelialization, and angiogenesis. Angiogenesis, the formation of new blood vessels, is crucial for delivering oxygen and nutrients needed for tissue repair and occurs during the proliferative phase. Type and the degree of injury determine its healing period. Some wounds are long-lasting, such as chronic wounds, which need special management and therapeutic attention to hasten the healing process [1]. Chronic wounds affect nearly 6.5 million people in the U.S., and thereby, high-cost and effective therapeutic demands necessitate this field [2].

Wound healing aims to repair damaged tissues. Oral mucosa heals faster and with less scarring than skin. Fibroblasts from oral mucosa and skin differ in tissue remodeling, ECM molecule secretion, cellular migration, and adhesion, growth factor responses, and ECM receptor expression [3]. After the exposure of tissue to the trauma, blood flow from the opening is initiated along with the infiltration of lymph and release of chemicals like growth factors and chemokines. During the inflammatory period, immune cells like lymphocytes and macrophages imbue at the site of injury to phagocytize debris and initiate the proliferation of new tissues. The process of proliferation is mediated by the regrowth of epithelial cells *via* fibroblasts and keratinocytes, the formation of the collagen matrix, the growth of fibrous tissue, and the angiogenesis and shrinkage of the wound. Lastly, the degradation of the old

collagen matrix and formation of the new one is processed, providing the desired mechanical strength, closing the wound, and waning of blood vessels, hence reducing the reddishness of the site.

Angiogenesis plays a significant role in the restoration of blood supply in the injured area by the development of new blood vessels or the repair of injured ones by the proliferation of endothelial cells and pericytes. However, in carcinogenic conditions, inhibition of angiogenesis is the target to minimize blood supply to the tumor cells [4]. Angiogenesis is instigated by the decrease in oxygen and nutrients, leading to the growth of blood vessels from the already existing ones. These vessels reach out at the site of injury and form a closed network of vessels. Equilibrium in this process is achieved by several angiogenic and anti-angiogenic agents [1].

The main idea behind the entire healing process is to hasten the growth of the injured area in a way that brings minimum pain and scarring [5]. This is supported by a series of chemicals like growth factors, such as fibroblastic growth factor (FGF), transforming growth factor (TGF), endothelial growth factor (EGF), platelet-derived growth factors (PDGF), and keratinocyte growth factor-1(KGF-1) [6], particularly seen in angiogenic phase. Additionally, matrix metalloproteinase, cyclooxygenase, reactive oxygen species, and some other cytokines are lowered for the progression of angiogenesis [1].

Several natural compounds, derived from plants and animals, have shown effective potencies in wound healing. Chitosan, alginate, fibrin, and elastin, extracted from plants, are also used to prepare scaffolds that are used to treat wounds [7]. They aid proliferation, reduce inflammation, and stimulate angiogenesis. This review summarizes the efficacy of these natural compounds to mediate wound healing, particularly in the sub-phase of angiogenesis.

Commonly used plant extracts in wound healing.

1.1. Aloe Vera

Aloe Vera has been known for its medicinal effects in several aspects, such as dermatological, renal, gastric, oral, orthopedic, cardiac, psychiatric, and gonadal problems, exhibiting anti-inflammatory, anti-tumorigenic, anti-microbial, anti-allergic, wound-healing and immuno-regulatory effects [8]. These properties are due to the rich composition of its gel, comprising of flavonoids, isoprenoids, lectin proteins, tricyclic ketones, hydroxy-cinnamates, 5-methylchromone, mannose, acemannan (mucopolysacchride), anthraquinones [9, 10] and other biological agents. Additionally, animal models have revealed that hydro-alcoholic extracts from aloe vera induce low-to-no toxicity [11].

Aloesin, from aloe vera, a tyrosinase inhibitor, is seen to have several biologically beneficial characteristics. Wahedi and Jeong [9] demonstrated that aloesin stimulates different phases of wound healing processes, such as induction of angiogenesis, anti-inflammatory response (increased in transforming growth factor-β (TGF-β) and IL-6), formation of granular tissue, increased rate of wound closure and collagen deposition and upregulation of Smad and MAPKs (mitogen-activated protein kinase) pathways. Wound treatment with aloe vera is also characterized by well-organized skin regeneration, decreased inflammation, enhanced vascularization, and minimal scarring [12]. Similarly, the role of aloe vera in the diminution of host *versus* graft disease due to allogenic transplant has also shown advantageous outcomes. It is seen that spleen cell donors, when administered with oral aloe vera gel, imposed a decrease in lymphocyte-mediated angiogenic activity in recipient animals, thereby showing the potency to suppress the disease [13]. Treatment of burn wounds with aloe vera gel also decreases inflammatory response and aids collagen development and vascularization [14]. The combination of emodin from aloe vera and resveratrol also enhances the secretion of IL-1β from macrophages, monocytes, chemoattractant protein-1 (MCP-1), and VEGF when applied to burn wounds [15]. A mixture of honey, milk, and aloe vera is also effective in this regard [16]

The wound healing effect of aloe vera gel is mediated by enhanced expression and production of several important cytokines and growth factors that are critical for this particular effect, such as TGF-β, basic fibroblast growth factor, vascular endothelial growth factor (VEGF) and KGF-1 [3, 17]. At the cellular level, it improves the proliferation, viability, and migration of fibroblast and keratinocytes by increasing the expression of cell-adhering molecules like integrin and E-cadherin [5, 18]. Topical application of aloe vera on large wounds has also concluded similar results [19]. Recent research has also demonstrated the potencies of aloe vera in the treatment of diabetic wounds [20, 21]. Ulcer wounds are also treated using potassium permanganate and aloe gel [22].

Aloe vera is also used for the generation of scaffolds since it has better biocompatibility and supports cell growth, adhesion, and angiogenesis. Polydioxanone with aloe vera supports the growth and adhesion of endothelial cells and fibroblasts, aiding the regeneration of injured skeletal tissue [23]. Components of aloe vera are also studied to possess ECM (extracellular matrix)-like properties. Polycaprolactone with aloe vera, generated by an electrospinning technique to generate a nanofibrous membrane that can mimic ECM, has also demonstrated tissue regeneration potencies. These matrices are biodegradable, hydrophilic, and mechanically strong, and they support cell proliferation.

Additionally, poly(lactic-co-glycolic acid) (PLGA) with aloe vera scaffolds aid in wound healing potencies, stimulating reepithelization and cell proliferation due to glucomannan in the gel. Hydrogel films, prepared with aloe vera gel, are also beneficial in this regard. They allow cell attachment and proliferation, hence supporting the engineering of several different types of tissues [10]. PLGA membranes loaded with epidermal growth factor (EGF) and aloe vera extract are also applicable to chronic wound healing [24]. In a recent study, alginate and aloe vera films were successfully used to treat surgical wounds. They

inherited mechanical strength and were capable of regulating inflammatory response and collagen formation [25]. 3D porous wound dressing using aloe vera and gelatin enhances wound healing by inhibiting inflammatory response and reducing scarring. It aids cell proliferation and has anti-microbial properties [26].

Naseri-Nosar and Farzamfar [27] produced polyvinyl alcohol and chitosan film using wet electrospinning linked with aloe vera and loaded with erythropoietin nanoparticles to treat wounds. This non-toxic dressing inherited water-up-taking power and mechanical strength and allowed wound healing, mediating vascularization and epithelialization. Nanosuspension of silver sulfadiazine in aloe vera gel has also shown improved wound healing in comparison to burnt creams that are already available in stores [28]. Tragacanth and aloe vera emulsion promote the proliferation of fibroblasts and have antimicrobial characteristics, thereby assisting wound healing [29].

Clinical studies have shown that aloe vera is also effective in cesarean surgery wound healing [30]. Similar findings have also reported that aloe vera, in combination with olive oil, can treat chronic wounds [31]. Burn wounds, when treated with aloe vera in clinical patients, hasten the healing process and are a cost-effective option compared to silver sulfadiazine ointments [32]. Skin graft donors' wounds are also healed using aloe vera gel; however, it failed to provide analgesic effects [33]. Polyester wound dressing composed of Aleo vera and Centella asiatica has also shown clinical effectiveness with no sign of adverse effects [34].

Wounds treated with Aloe vera heal promptly due to its hypertonicity and acidic pH, which accelerate the healing process. Aloe vera boosts glycolytic enzyme activities, providing energy for cellular restoration. It is economical, readily available, safe, and potent for wound treatment [35].

Aloe vera therapy expedites wound healing. Modern wound dressings maintain moisture, accelerating tissue growth around the wound edges. Adequate protein nutrition significantly aids wound healing, as protein is crucial for growth, maintenance, and tissue repair [36].

1.2. Propolis

Propolis is extracted from the plant by bees to protect their hives from microbial invasion. Therefore, this substance inherits anti-microbial characteristics. It is also a potent anti-inflammatory, anti-oxidant, and anti-carcinogenic compound. Propolis is rich in multiple-compound composition, which includes resin, wax, alcohol, phenolic compounds, ketones, amino acids, vitamins, and other small elements [35]. Recent reviews have suggested that it is an efficient therapeutic option for wound treatment [36].

Rubber latex, along with propolis, results in membranous wound dressing with anti-bacterial and mechanical properties, allowing a proliferation of fibroblast [37]. Likewise, bacterial cellulose with red propolis has also been found to heal diabetic wounds by regulating inflammatory response *via* inflammatory cytokines (increase in the levels initially and decrease with the time of treatment) and leukocyte recruitment [38]. Cellulose film composed of polyvinyl alcohol, vitamin C, and propolis also hastens wound healing [39]. It is also effective for treating cutaneous wounds [40].

Wound treatment with a mixture of propolis and honey enhances cell proliferation, angiogenesis, and collagenization [41]. Hozzein and Badr [42] studied diabetic found healing in animals using propolis. They concluded that propolis topical application on the sight of a wound decreases inflammatory cytokines, such as TNF-α, IL-1, and MMP, and stimulates TGF-β production by upregulating smad pathways and collagen formation. Oral administration of this compound is also characterized by anti-inflammatory outcomes, mediated by nuclear factor (NF-κB) pathway [43]. Nano membrane using polyurethane and propolis is effective for wound healing along with its nanofibers [44]. Studies have suggested its effectiveness in treating ulcer wounds topically by upregulating the expression of FGF, VEGF, growth of fibroblasts, and decreased expression of MMP-9 [45, 46]. Additionally, a mixture of propolis extracted from different sources hastens the wound-healing process and the application of single-sourced propolis alone [47]. Chitosan and propolis biofilms for wound dressing have recently been shown to be beneficial in this regard, by stimulating angiogenesis, collagenization, cell proliferation and re-epithelization [48].

Recent clinical studies have shown that topical propolis cream shows healing in diabetic ulcer feet [49]. This compound is immune tolerant in human subjects [50].

Propolis is well tolerated and non-toxic, making it an excellent candidate for burn management by enhancing skin cell proliferation and growth. Studies confirm its efficacy through the analysis of collagen types in the wound matrix, indicating that it supports re-epithelialization. Propolis ointments are promising for accelerating the healing process in future trials. Wound dressings, made from natural polymers like proteins and polysaccharides, absorb exudates, maintain moisture, and prevent infection. This review explores biodegradable materials, including various propolis formulations, for wound care [51-53].

1.3. *Blumea Balsamifera*

Blumea balsamifera (BB), also known as Ngai camphor, is widely used in Chinese medicine for dermatological conditions. Extracts from leaves, roots, and branches have shown great pharmacological significance in the treatment of snake bites, as well as anti-coagulant, anti-oxidant, and anti-carcinogenic properties [51]. Flavonoids are one of the richest compounds of BB leaves. A recent study has shown that a high dose of flavonoids from BB speeds up the epithelialization and wound-contraction phase. Also, it increases the filtration of macrophages at the site of the wound in the first 5 days after the injury. Similar effects were seen in the expression of TGF-β and VEGF. However, after injury,

there was a linear increase in collagen formation [52].

Oil from BB plants also has wound-healing capacities, as seen by the stimulation of fibroplasia, angiogenesis, and collagen regeneration [53].

Fan and Pang [54] also demonstrated the efficiency of BB leaf oil for the treatment of second-degree burns. Animal models-based study revealed that BB oil provided better wound healing as compared to the controls. Further, inflammatory markers, such as IL-1 and TNF-α, were significantly decreased after the application of the oil. It also enhanced the expression of FGF, TGF-β, and VEGF, followed by complete wound closure.

1.4. *Achyranthes Aspera (AA)*

Devil's Horsewhip or Prickly Chaff flower (*Achyranthes aspera*), commonly found in Asian and African regions, is used for the treatment of ringworms, gut, bone, urinary tract, and gynecological-related disorders. It is well-known for its antimicrobial and antifungal properties. Phenolic compounds from its leaf extract have wound healing and anti-inflammatory abilities. Aa-EE targets NF-κB to deliver its anti-inflammatory effects by inhibiting Src and Syk. Consequently, our research suggests that this extract could be developed into a new natural treatment for inflammation [55, 56]. Silver nanoparticles of AA have also been reported to possess similar properties [57]. Seeds of AA can be used to treat burn wounds, owing to their ability to restore skin structure [58]. Topical application on burn wounds mediates anti-oxidation at the site, proliferation of cells, collagenization, and formation of skin [59]. Its aqueous extract is also therapeutically effective for edema [60]. The anti-inflammatory and antioxidant properties of AA phenolic extracts have been justified in a recent study, as they have the ability to reduce ischemic reperfusion injury [61]. The nanocomposite of silver, chitosan, and AA leaf extract has antibacterial and wound-healing characteristics [62].

1.5. *Astragalus Membranaceus (AM)*

Astragalus is among the most well-known Chinese plants, and it is commonly used as the formula in many Chinese medicines and utilized to treat aging, cancer, and gut-related disorders. Its composition is rich in flavonoids, sugars, and glucosides [63]. Polysaccharide APS2-1, extracted from the roots of AM, has wound healing potencies by stimulating the cell cycle, proliferation of fibroblast, and angiogenesis. It also regulates the production of growth factors, such as FGF, TGF, and EGF [64, 65]. The anti-inflammatory properties of this compound are also effective for the treatment of foot ulcers [66] by down-regulating cyclooxygenase-2, NF-κB, and MAPK (mitogen-activated protein kinase) pathways, prostaglandin and IL-1 [67]. The glycoprotein-based fraction of this plant also upregulates angiogenesis by increasing the expression of VEGF receptors and kinase insert domain receptors [68].

Yang and Wang [69] engineered a PLGA scaffold loaded with the polysaccharide from the root of astragalus using an electrospinning technique. The tissue-engineered membranes had faster tissue healing capacities, allowing the complete restoration of dermal structures, collagenization, and proliferation of fibroblasts. It enhances the expression of VEFG and Von Willebrand factor endothelial cell growth, thereby promoting vascularization [70]. It is immune tolerant and can not lead to incontrollable changes in body hemostasis [71].

1.6. Panax Ginseng

Several biological functions are mediated by the herbal use of Panax ginseng (Korean/ Chinese ginseng), and wound healing is one of them. It is composed of polysaccharides, proteins, alcohol, and ginsenosides [72].

At a concentration of 10ng/ml, extract from this plant is seen to promote the proliferation of fibroblast and collagen formation [73]. A similar concentration of ginseng mediates increased expression of VEGF and TGF and is an inhibitor of MMP, thereby supporting vascularization [74]. Rd, one of the therapeutic ginsenosides in ginseng, aids the growth of keratinocytes and fibroblast and collagen formation by decreasing MMP concentration and upregulating protein kinase A and cAMP pathways [75]. Furthermore, topical application of Rb stimulates S1P (sphingosine-1-phosphate)- mediated TGF-β upregulation, thereby stimulating ERK (extracellular signal-regulated kinases) and NF-κB pathways [76].

20(S)-protopanaxadiol from ginsenoside also has healing effects, particularly in the case of diabetic wounds, by promoting the production of VEGF and Hypoxia-inducible factor 1-alpha and angiogenic pathways, such as PI3k (Phosphoinositide 3-kinases) and ERK [77, 78].

1.7. Asiatic Pennywort

Centella asiatica (a.k.a Asiatic pennywort or gotu kola) is a leafy vegetable that is composed of flavonoids, oil, triterpenes, and tetraterpenoids and is known for its wound-healing abilities [79]. Electrospun nanofibers of gelatin and gotu kola are biodegradable and are beneficial in dermal, burn, and incision wound healing by supporting re-epithelialization and keratinization [80, 81]. Madecassoside is an effective ingredient for burn wounds in pennywort [82]. Centiderm ointment containing asiatica is shown to be highly effective in complete wound closure and skin growth, compared to silver sulfadiazine [83]. Hydrocolloid wound dressing containing gotu kola and a topical spray of pennywort are also potential wound healers [84, 85].

Camacho-Alonso and Torralba-Ruiz [86] used a matrix derived from the porcine urinary bladder and used extract from this plant for topical application in wounded animal models. They found that this dressing was effective in healing skin and cell growth.

2. OTHER PLANT EXTRACTS

2.1. *Cordia Verbenacea*

Cordia verbenaea (CV) extracts are widely used in Brazil for phytomedicine. It has pain-relieving, anti-inflammatory, and anti-microbial characteristics. Topical

application of its extracts on the wound stimulates regeneration and organization of epithelium and collagenization and increases expression of VEGF, followed by a decrease in MMP levels [87].

2.2. Eugeina Plants

Recent studies have also shown that oil from *Eugenia dysenterica* leaves promotes angiogenesis, cell proliferation, and anti-inflammatory responses at the site of injury, and it is not cytotoxic [88].

Furthermore, lectin extracted from *Eugenia malaccensis* seeds has anti-bacterial characteristics and promotes the proliferation of fibroblast, re-epithelia- lization, angiogenesis, and granular tissue formation followed by complete healing of the cutaneous wounds [89].

2.3. Sea Buckthorn

Hydrogel composed of polyvinyl alcohol and pectin, loaded with *Hippophae rhamnoides* (sea buckthorn) phenolic and flavonoid-rich extract, has anti-inflammatory and wound healing potentials [90]. Its seed oil is effective for treating graft wounds since it aids fast re-epithelialization [91]. It enhances collagen regeneration and angiogenesis by upregulating VEGF [92]. A mixture of sea buckthorn with olive oil dressing also aids in the granulation of skin growth, as compared to silver sulfadiazine ointment [93].

Other studied natural compounds for wound healing include phenolic extracts from Parrotia persica [94], ethanol from sea cucumber [95], *cinnamomum zeylanicum* (true cinnamon) and *cinnamomum cassia* (Chinese cinnamon) [96-103], *Uncaria rhynchophylla*, Korean stewartia, Brazilian Red Hots, and green chireta. However, studies related to these plants do not provide clear evidence of their mechanism of action [1] (Table **1**).

Table 1. Summarizes the therapeutic effects of plant extracts in wound healing.

Plant	Extract/formula	Therapeutic Effects
Aleo Vera (AV)	Aloesin	Angiogenic, anti-inflammatory, granulation, collagenization, faster wound closure [9, 12]
	Emodin + AV + resverstrol	Angiogenesis, modulation of inflammation in burn wounds [15, 16]
	Milk + honey + Av	Treatment of burn wounds [16]
	Potassium permanganate + aloe vera	Treating ulcer-like wounds, drying of wound, decrease in reddishness, and wound closing [22]
	Polydioxanone + aloe vera scaffolds	Cell adhesion and proliferation [23]
	Polycaprolactone + AV	ECM-like structure for tissue regeneration [10]
	Alginate film + AV	Treating surgical wounds, angiogenesis, collagen regeneration, regulation of inflammation, good mechanical strength [7]
	PLGA + glucomannan from AV	Re-epithelialization, cell proliferation for the treatment of chronic wounds [10]
	PVA + chitosan + AV with erythropoietin nanoparticles	Non-toxic, vascularization, and epithelialization [27]
	Nanosuspension of AV gel and sulfadiazine	Quicker and more efficient wound closure [28]
	Tragacanth + AV gel	Proliferation of fibroblast, anti-bacterial properties [29]
	Polyester + AV + Centella Asiatica	Non-cytotoxic wound healing [34]
Propolis	Rubber latex + propolis	Anti-bacterial, good mechanical strength and cell proliferation [38]
	Bacterial cellulose + red propolis	Diabetic wound healing, regulation of inflammation [39]
	Cellulose + PVA + vitamin C + propolis	Faster and better wound healing, cell proliferation, collagenization [35]
	Propolis + honey	Cell proliferation, angiogenesis, collagen regeneration [36]
	Propolis (topical and oral)	Diabetic wound, anti-inflammation, stimulation of angiogenesis, and collagenization [38]
	polyurethane + propolis	Wound healing, regulation of growth factors and cytokines [39]
	Chitosan + propolis	Angiogenesis, collagenization, re-epithelialization, and cell proliferation [48]
Blumea Balsamifera (BB)	Flavonoids	Re-epithelialization, modulation of inflammation, induction of angiogenesis [52]
	Oil extract	Treatment for second-degree burn, angiogenesis, fibroplasia, anti-inflammatory, and collagen regeneration [88]
Achyranthes aspera (AA)	Phenolic extract	Anti-inflammation [67]
	Silver nanoparticle + AA	Anti-inflammation [63]
	seeds of AA	Burn wound treatment, restoration of skin architecture [59]
	menthol leaf extract of AA	Anti-oxidant, collagenization, cell proliferation, skin regrowth [64]
	Silver + chitosan + AA leaf extract	Antibacterial and wound healing [65]
Astragalus membranaceus (AM)	Polysaccharide extract from the roots	Progression of cell cycle, angiogenesis, production of growth factors [67, 68]
	glycoprotein fraction	VEGF mediated angiogenesis [71]
	PLGA + polysaccharide from roots	Restoration of the injured site, collagenization, vascularization, immune tolerant [24]

(Table 1) contd.....

Plant	Extract/formula	Therapeutic Effects
Panax Ginseng	Ginseng	Increases expression of growth factors that mediate angiogenesis in wound healing [75]
	Rd (ginsenoside)	Fibroplasia, keratinization, collagenization [75, 76]
	20(S) protopanaxadiol (ginenoside)	Diabetic wound healing, increased expression of VEGF mediating angiogenesis and activating of other such pathways [77-81]
Asiatic pennywort (AP)	nanofibers of gelatin + AP	Growth of epithelial cells and keratinocytes [79]
	Madecassoside	Healing burn wounds [83]
	Centiderm (ointment)	Skin growth and wound closure [86]
	porcine bladder matrix + AP	Cell proliferation and wound closure [89]
Cordia Verbenacea	Acheflan (containing oil from the plant)	Epithelialization increases the expression of VEGF and collagen regeneration [91]
Eugeina plants	leaves of *E. dysenterica*	Angiogenesis, cell proliferation, anti-inflammation, and non-cytotoxic [91, 92]

CONCLUSION

Wound healing is a complex process regulated by various biochemical events. Medicinal plants are extensively studied for their ability to enhance these events efficiently. Polyherbal extracts, combining multiple plant sources, can further boost this effect. Research shows that many herbal extracts are non-cytotoxic and immune-tolerant. Angiogenesis, a key phase in wound healing, must be properly regulated for effective tissue repair. Herbal extracts can stimulate angiogenesis in wound healing but may also exhibit anti-angiogenic effects in tumor cells, potentially aiding cancer treatment. This dual effect is likely due to the diverse compounds in these plants. Nonetheless, further evidence-based studies are needed to identify specific therapeutic targets for each compound.

AUTHORS' CONTRIBUTIONS

Dr. M.H.: Conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. P.B.: Designed the data collection instruments, collected data, carried out the initial analyses, reviewed and revised the manuscript, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

LIST OF ABBREVIATIONS

FGF = Fibroblastic Growth Factor

TGF = Transforming Growth Factor

EGF = Endothelial Growth Factor

PDGF = Platelet-derived Growth Factors

VEGF = Vascular Endothelial Growth Factor

PLGA = Poly(lactic-co-glycolic Acid)

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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