

Role of NGF and its receptors in wound healing (Review)

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Abstract. Wound healing is an important and complicated process that includes four highly integrated and overlapping phases, haemostasis, inflammation, proliferation and tissue remodelling. Nerve growth factor (NGF) was the first member of a family of neurotrophic factors to be discovered, and is an essential neurotrophic factor for the development and maintenance of the central and peripheral nervous systems. Several studies have proposed that NGF and its receptors, tropomyosin-related kinase receptor 1 and NGF receptor, are involved in the wound healing process, and are important components of the healing of several wounds both *in vivo* and *in vitro*. Topical application of NGF significantly promotes the healing of different types of wounds, including diabetic foot ulcers, pressure ulcers and corneal wounds. The present review summarizes the status of NGF and its receptors in current literature, and discusses data obtained in the last few years on the healing action of NGF in cutaneous, corneal and oral wounds.

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1. Introduction

Wound healing is a complex pathophysiological process involving different types of cells, cytokines and the

extracellular matrix (1). Wound healing mainly consists of four highly integrated and overlapping phases, haemostasis, inflammation, proliferation and tissue remodelling (1,2). Several endogenous and exogenous factors, such as growth factors, cytokines and chemokines, play important regulatory roles in each phase of wound healing (2-4). Increasing evidence suggest that neurotrophins, particularly nerve growth factor (NGF) and its receptors, play critical roles in the regulation of wound healing (5-8). In addition to its crucial role in the nervous system, NGF also exerts a wide range of effects in wound healing. For example, NGF promotes fibroblast and keratinocyte proliferation, extracellular matrix component expression and secretion, angiogenesis and myofibroblast differentiation (9-11). The topical application of NGF is considered a potential treatment strategy for promoting wound healing under pathological conditions, without obvious side effects (12-14). In addition, the Food and Drug Administration (FDA) has approved NGF eye drops for the treatment of rare neurotrophic keratitis (15). The present review discusses the role of NGF and its potential molecular mechanisms in wound healing in laboratory animal and clinical research.

2. Biology of NGF and its receptors

Biology of NGF. NGF is one of the most common neurotrophic factors that was first discovered by Rita Levi-Montalcini in the early 1950s (16,17). NGF belongs to the neurotrophin (NT) family, which also includes brain-derived neurotrophic factor (BDNF), NT-3 and NT-4/5 (18). The gene encoding NGF is located on the proximal short arms of the first pair of chromosomes, 1p13.2. NGF is a high molecular weight complex that contains three subunits, α , β and γ (19,20). The different subunits are bound together by non-covalent bonds, and there are also two Zn^{2+} ions that enhance the stability of the complex (21). Only the β -NGF subunit of NGF exhibits neurite-stimulating activity (21). This subunit is a dimer that is composed of two identical peptide chains that interact through non-covalent bonding, and each monomeric amino acid sequence contains 118 amino acid residues and three pairs of intramolecular disulfide bonds (22). The γ subunit is a highly specific active protease, whereas the α subunit appears to have no significant activity (23).

NGF is synthesized in the endoplasmic reticulum in its prosomal form (proNGF) and is subsequently folded and transferred to the Golgi apparatus via the persistent secretory pathway or the regulated secretory pathway (24). proNGF

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is subsequently cleaved by the calcium-dependent serine protease, furin convertase, to expose the biologically active carboxyl terminus, thereby forming the β -NGF protein (24). In addition, some proNGF is directly released from cells, and mature β -NGF proteins are formed under the action of extracellular proteases (23,25,26). NGF is predominantly secreted by nerve cells (23); however, some studies have reported that NGF can also be synthesized and secreted by non-neuronal cells, such as immune inflammatory cells, epithelial cells, keratinocytes, smooth muscle cells and fibroblasts (27-29).

NGF and proNGF are essential neurotrophic factors for the development and maintenance of the central and peripheral nervous systems (30,31). In addition, NGF and proNGF play critical roles in the degeneration and repair events of neurological disorders, with different underlying aetiologies (32-34). An imbalance of NGF/proNGF is associated with early inflammation and neurodegeneration (35). Increasing evidence suggest that in addition to their neurotrophic functions, proNGF and NGF participate in several biological processes, including the immune response, inflammatory response, pulmonary hypertension, wound healing and cancer metastasis (23,33,36-42). Studies on NGF and its receptors have identified novel therapeutic approaches for malignant tumors, diabetes, chronic wounds and cardiovascular diseases (13,40).

Biology of NGF receptors. NGF exerts its biological functions through the activation of the high-affinity tropomyosin-related kinase receptor 1 (NTRK1) and the low-affinity nerve growth factor receptor (NGFR), which collaborate in mediating signaling (43-45) (Fig. 1).

NTRK1 receptor. NTRK1, also known as Trk-A, TRKA, MTC, TRK, TRK1 and p140-TrkA, is a 140-kDa transmembrane glycoprotein that belong to the receptor tyrosine kinase family and is encoded by a gene located on chromosome 1p23.1 (21,46). NTRK1 consists of three domains, an extracellular receptor domain, a single transmembrane helix and an intracellular tyrosine kinase domain (47). The NTRK1 extracellular sequence, which exhibits intrinsic tyrosine kinase activity, is composed of five distinct domains (D1-D5) (48). D1 and D3 contain cysteine-rich repetitive motifs, D2 contains three leucine-rich repeat domains, D4 and D5 are immunoglobulin-like domains, and D5 is responsible for NGF binding (48,49). In the nervous system, NTRK1 is primarily expressed in cholinergic neurons that are implicated in spatial learning and memory, such as the central cortical pyramid, basal forebrain, striatum, compartment and lateral geniculate body, as well as in peripheral sensory neurons and sympathetic nerves (50). However, NTRK1 is also extensively expressed in non-neuronal tissues, including immune cells, tumor cells and stem cells, suggesting pleiotropic functions outside the nervous system (51,52).

NGF binds to the D5 extracellular domain of NTRK1, resulting in dimerization of NTRK1 and activation of its intracellular kinase (48). A total of six tyrosine residues in the intracellular tyrosine kinase domain, namely, Tyr670, Tyr674, Tyr675, Tyr490, Tyr751 and Tyr785, are phosphorylated (53). Autophosphorylation of Tyr490, Tyr751 and Tyr785 results in activation of the three main downstream signal transduction pathways, the mitogen-activated protein kinase/extracellular

signal-regulated protein kinase (MAPK/ERK) signaling pathway, the phosphatidylinositol-3-kinase/serine protein kinase (PI3K/Akt) signaling pathway and the phospholipase C- γ (PLC- γ) signaling pathway (53,54). Most NGF-mediated biological activities, including the proliferation, survival and differentiation of neuronal cells, are due to the ligand-dependent NTRK1 activation of several signal transduction cascades (32,33). NGF-NTRK1 activation has been reported to have several clinically relevant biological effects on non-neuronal cells, including promoting the survival, proliferation, metastasis and invasion of tumor cells (55-57).

NGFR receptor. NGFR, also known as p75^{NTR}, CD271, tumor necrosis factor receptor (TNFR)SF16 and Gp80-LNGFR, is a 75-kDa highly conserved transmembrane glycoprotein that belongs to the TNFR superfamily and is encoded by a gene located on chromosome 17q21.33 (58,59). NGFR consists of three domains, an extracellular receptor domain, a unique transmembrane helix and an intracellular tyrosine kinase domain (60). The extracellular sequence of NGFR contains four cysteine-rich (CR) sequence regions (CR1-CR4) that are responsible for binding to neurotrophic factors, with a nanomolar affinity, and binding to proneurotrophins (60-62). The intracellular domain of NGFR contains a potential TNFR-associated factor (TRAF)-binding region and Fas antigen (also called the death domain), which regulates apoptotic signals (60-62). In addition to the central and peripheral nervous systems, NGFR is also extensively distributed in several tissue systems throughout the body, such as epithelial, mesenchymal, lymphoid haematopoietic and tumor tissues (63).

The common neurotrophin receptor, NGFR, binds to NGF and all other neurotrophins, including BDNF, NT-3 and NT-4/5, with similar affinity and an extremely fast dissociation rate (44,64). The binding of NGF to NGFR is a specific electrostatic interaction between polar amino acid residues, and two specific sites play important roles in this interaction, site I is composed of the CR1-CR2 junction and the CR2 domain, while site II is composed of the CR3-CR4 junction (65,66). NGFR activation involves different molecular mechanisms in different types of cells and tissue environments, and active NGFR participates in regulating fundamental biological processes, such as cell survival, proliferation, attachment, migration, differentiation and apoptosis, via the nuclear transcription factor-kappa B, Jun N-terminal kinase (JNK), and ceramide signaling pathways (67-70). Although NGFR is a low-affinity NGFR, it may also participate in NGF high-affinity binding by interacting with the NTRK1 receptor to induce the growth and survival of neurites (54,69,71). Activation of NGFR by proNGF induces the activation of apoptotic signaling pathways, involving the co-receptor, sortilin (72-74). In addition, NGFR is involved in the regulation of several physiological functions, and cooperates with Nogo-R, LINGO-1, A β , viral glycoprotein and tetanus toxin (75).

3. Healing effects of NGF on different wounds

Cutaneous wound healing. When damage causes a loss of skin integrity, the body immediately initiates the skin repair process to restore its integrity and maintain its function (1). Cutaneous

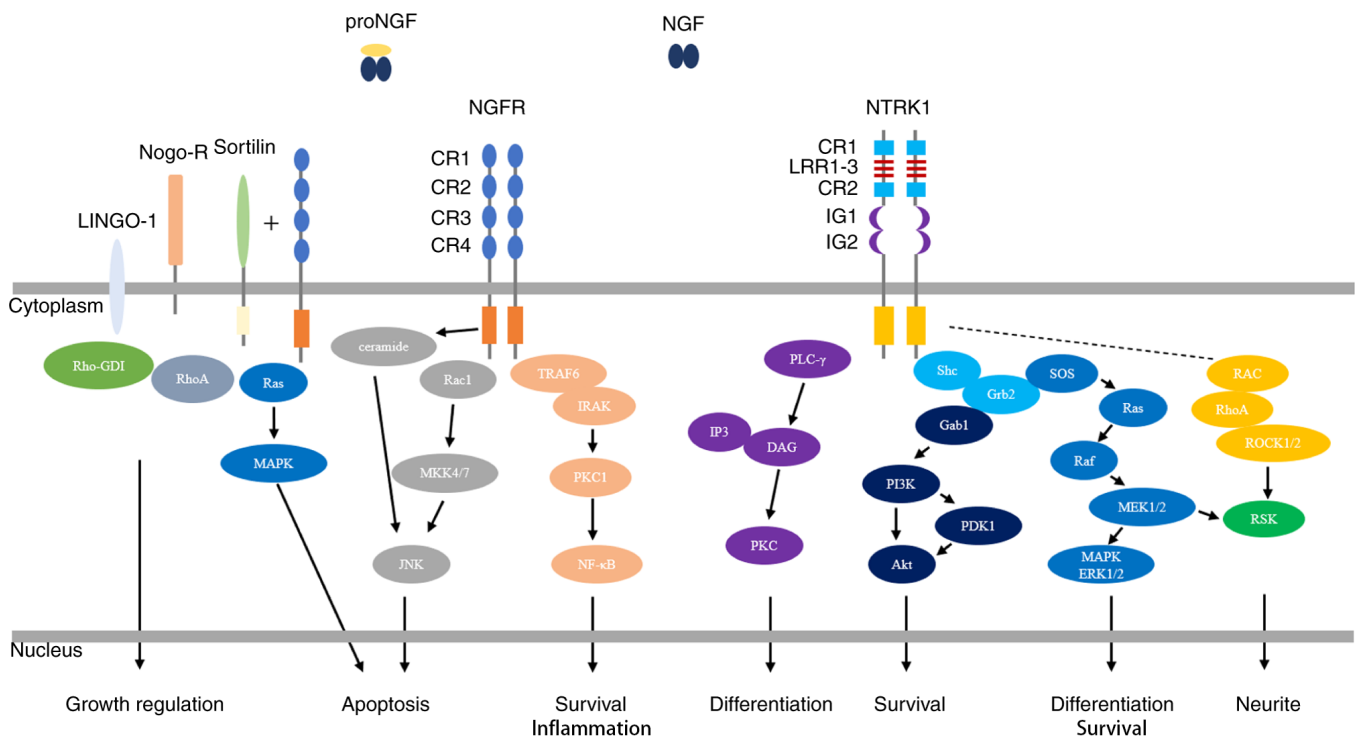


Figure 1. NGF-mediated regulation of the NGFR and NTRK1 signaling pathways. NGF binds to the extracellular domain of NTRK1 with high affinity, resulting in dimerization of NTRK1 and activation of its intracellular kinase. NTRK1 signaling is best characterized by activation of the three main downstream signal transduction pathways, the MAPK/ERK, PI3K/Akt and PLC- γ signaling pathways, which results in the differentiation and survival of neurites. NGF binds to NGFR with low affinity. NGFR activation involves different molecular mechanisms in different types of cells and tissue environments, and exerts effects via the NF- κ B, JNK and ceramide signaling pathways, resulting in apoptosis, survival and inflammation. Interactions of NGFR with sortilin allow the high-affinity binding of proNGF. Subsequent activation of the Ras/MAPK pathway results in apoptosis. Interactions of NGFR with Nogo-R and LINGO-1 play roles in the regulation of growth. Activation of RhoA by the displacement of Rho-GDI inhibits neurite outgrowth from postnatal sensory neurons and cerebellar neurons. NGF, nerve growth factor; NTRK1, tropomyosin-related kinase receptor 1; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated protein kinase; PI3K/Akt, phosphatidylinositol-3-kinase/serine protein kinase; PLC- γ , phospholipase C- γ ; NF- κ B, nuclear transcription factor-kappa B; JNK, Jun N-terminal kinase; CR, cysteine-rich; Nogo-R, Nogo receptor; LINGO-1, leucine-rich repeat and immunoglobulin-like domain-containing protein-1.

wound healing is a complex pathophysiological process involving different types of cells (immune cells, keratinocytes, fibroblasts and vascular endothelial cells), cytokines (fibroblast growth factor, platelet-derived growth factor, transforming growth factor, epidermal growth factor, vascular endothelial growth factor and NGF) and signaling pathways (38,76). The normal wound healing process is divided into four overlapping phases, haemostasis, inflammation, proliferation and tissue remodelling (2). Any disruptions in these processes can lead to wound healing disorders, such as chronic nonhealing ulcers or keloids (77).

Under physiological conditions, NGF is sustainably expressed in skin tissue by different types of cells, including keratinocytes, fibroblasts and mast cells, which is essential for maintaining skin homeostasis (78-81) (Table I). NTRK1 and NGFR are extensively expressed on the surfaces of different types of cells in the skin, including keratinocytes, melanocytes, fibroblasts and mast cells (82-86). Matsuda *et al* (87) reported that full-thickness skin wounds made in normal mice significantly increase NGF expression levels in the sera and wounded skin tissues of the mice. In addition, NGF mRNA and NGF have been detected in newly formed epithelial cells at wound edges and fibroblasts, which is consistent with the granulation tissue produced in the wound spaces (87). Previous studies have demonstrated that NGF is stored in the submandibular glands of mice, and sialoadenectomy prior to wounding

inhibits serum NGF levels and delays the skin wound healing process (87,88). Taken together, these findings suggest that NGF may play an important role in wound healing.

Topical application of NGF to wounds significantly promotes the healing of different types of wounds, including diabetic foot ulcers, pressure ulcers and nonhealing surgical wounds (87,89,90). Preliminary experimental animal studies have reported that NGF expression significantly decreases in diabetic wounds and wound tissues following radiation treatment compared with normal skin wounds (91,92). Generini *et al* (12) treated three diabetic patients with leg or foot ulcers that were unresponsive to conventional therapies with topical application of NGF, and the results demonstrated that NGF promoted healing after 5 \pm 14 weeks of treatment. Even chronic ulcers with damage extending below the hypodermis and muscle layers healed in a few weeks following treatment with NGF, and the size of the ulcers significantly decreased for the first time after 8 weeks of NGF administration (32). Topical NGF also exerts a healing effect on human pressure ulcers (93,94). A randomized clinical trial of 36 patients demonstrated that topical application of murine NGF significantly accelerated the healing of pressure ulcers compared with traditional treatment (94). Cutaneous ulcers secondary to vasculitis in patients with rheumatoid arthritis (RA) are extremely difficult to heal (95). A total of four patients with RA-associated skin ulcers were treated with

Table I. Sources and role of nerve growth factor in wound healing.

Type of wound	Cellular sources	Main function	Refs.
Cutaneous	Keratinocytes, fibroblasts, mast cells	Inflammation response Re-epithelialization Keratinocyte proliferation Epidermal stem cell proliferation, differentiation and migration Angiogenesis Fibroplasia Wound contraction Myofibroblast differentiation Collagen maturation and remodeling Peripheral nerve regeneration	(11,75-78,93-95 97-100)
Corneal	Corneal epithelial cells	Inflammation response Re-epithelialization Corneal epithelial cell proliferation, survival and migration Fibroplasia Myofibroblast differentiation Peripheral nerve regeneration Corneal sensitivity Tear function	(102,104,106, 109-111)
Oral	Keratinocytes, fibroblasts, leukocytes, salivary ductal cells	Inflammation response Re-epithelialization Oral epithelial cell proliferation Fibroplasia Myofibroblast differentiation Collagen maturation and remodeling	(114-116,118-122)

topical NGF, and the symptoms of pain and inflammation were significantly relieved after 2-3 weeks (96). The ulcers progressively improved and were completely healed after 8 weeks (96). Notably, intraperitoneal and topical applications of NGF increase the survival rate and may increase wound healing and promote survival in irradiated animals (92).

The molecular mechanisms underlying NGF-induced cutaneous wound healing are not yet fully understood. However, studies have reported that NGF participates in several biological activities during the healing process via complex molecular mechanisms (Table I). In the skin, NGF is predominantly synthesized and released by keratinocytes (97). Different types of cells express NGF receptors, including keratinocytes, melanocytes, fibroblasts and mast cells (98). Skin injury can increase the secretion of neurotrophic factors by peripheral nerve endings (97). Among these factors, substance P and neurokinin A directly induce NGF mRNA expression and NGF secretion in keratinocytes (99,100). Conversely, NGF can increase the secretion of neurotrophic factors, including calcitonin gene-related peptide, by peripheral nerve endings, thereby regulating the immune inflammatory response associated with the wound healing process (101,102). NGF significantly stimulates the proliferation of normal human keratinocytes in a dose-dependent manner (79). NGF plays a functional role in reparative neovascularization via

a VEGF-Akt-NO-mediated mechanism (103). NGF accelerates wound healing by promoting wound re-epithelialization, which partly relies on accelerated dermal fibroblast migration via activation of the PI3K/Akt-Rac1-JNK and ERK signaling pathways (7). In wound granulation tissue, NGF can also induce myofibroblast differentiation and collagen synthesis via the NGFR-F-actin-MRTF-A signaling pathway, and induce wound contraction and extracellular matrix remodeling (9,97). In addition, NGFR promotes the healing of skin burn wounds by improving the potential of epidermal stem cells to differentiate, proliferate and migrate (104).

Corneal wound healing. The cornea is the transparent outer layer of the eye that serves as a protective barrier (105). Damage to the corneal epithelium caused by scratches or surgery is common (106). Corneal wound healing is an exceedingly complex process involving the coordination of cellular activities stimulated and regulated by several growth factors that reach the wound through tears and limbic vessels (107). Delays in corneal wound healing results in keratinization of the corneal epithelium and corneal opacity (108).

NGF is extensively expressed in normal human and rat corneal tissues and is predominantly produced by corneal epithelial cells (109) (Table I). In addition, NTRK1 and NGFR are widely expressed in corneal epithelial cells, endothelial

cells, stromal cells, limbal stem cells and conjunctival epithelial cells (110). Ocular surface damage and inflammation can increase NGF levels (109,111). A transient increase in corneal NGF levels is observed following corneal epithelial injury *in vivo* (109). Inhibition of endogenous NGF activity by neutralizing anti-NGF antibodies delays the corneal epithelial healing rate, whereas administration of exogenous NGF accelerates healing (109). Lambiase *et al* (111) reported that plasma NGF levels are significantly higher in patients with vernal keratoconjunctivitis compared with controls, which is associated with higher inflammatory cell numbers in the conjunctival tissue of vernal keratoconjunctivitis. Given the positive effect of NGF in promoting corneal healing, the FDA has approved NGF eye drops for the treatment of rare neurotrophic keratitis (15). Cellini *et al* (112) observed complete wound healing in patients treated with NGF eye drops, and the stromal incision was not visible when assessed via optical coherence tomography on day 21.

The epithelium needs to be reconstructed during corneal healing, and this process mainly relies on the proliferation and migration of adjacent corneal epithelial cells (105,106). During corneal wound healing, NGF plays a major role in promoting cell survival and migration by binding to the NTRK1 receptor, which is mediated by both the upregulation of matrix metalloproteinase-9 and the cleavage of $\beta 4$ integrin (47,113,114). In addition, NGF promotes the healing of corneal stroma and endothelial cells (109,110). The role of NGF in corneal angiogenesis remains controversial; however, NGF can facilitate innervations of perivascular nerves to regulate blood flow in neovessels (10,115,116). In addition, it has been demonstrated that topical application of exogenous NGF can promote corneal healing by increasing corneal sensitivity and improving tear function in patients with neurotrophic keratitis (117).

Oral wound healing. Oral injuries are very common and usually caused by trauma, surgery, periodontal treatment and radiation therapy (118). Improper treatment can cause severe complications, which can affect breathing, language articulation, chewing and swallowing (119). Oral wound healing is rapid and results in little scar formation compared with cutaneous wound healing (120). Recent studies have suggested that the reduced scar formation in oral mucosa is associated with fibroblast phenotypes, oral bacteria, saliva and the moist environment of the oral cavity (118,121).

NGF is extensively expressed and synthesized by oral keratinocytes, fibroblasts, infiltrating inflammatory leukocytes and salivary ductal cells, and can be secreted into saliva (122-124) (Table I). The main form of NGF in saliva is proNGF, which can be further converted by enzymes released at the site of activity (123). In addition, NGF receptors are also expressed in oral tissues. NTRK1 is predominantly expressed in mucosal basal cells, salivary duct epithelial cells and gingival epithelial cells, while NGFR is only expressed in mucosal basal cell layers and salivary duct epithelium (123,124).

Recent studies have reported that NGF and proNGF are involved in oral wound healing (Table I). When the oral mucosa is wounded, NGF and proNGF in the saliva can reach NGF receptors on keratinocytes and fibroblasts that were previously hidden by oral epithelial layers (125). Plasmin generated by

keratinocytes at wound sites can cleave pro-NGF to form mature NGF (126). Mature NGF can access NTRK1 on the basal keratinocytes of the wound edges, thereby enhancing the proliferation and migration of keratinocytes (124). NGF can upregulate the expression levels of E-cadherin and zona occludens-1 in mucosal epithelial cells, suggesting that NGF may contribute to re-establishing mucosal epithelial barrier function (127). Infiltrating inflammatory cells in the epithelium and the connective tissue of the oral mucosa express NGF and NGF receptors (128,129). Proinflammatory cytokines released after tissue damage promote NGF synthesis, while NGF enhances superoxide production via neutrophils (128). Fibroblasts and myofibroblasts that appear during wound healing synthesize and secrete NGF and express NGF receptors (130). NGF induces the differentiation of fibroblasts into myofibroblasts, which are responsible for both tissue contraction and extracellular matrix component secretion (131). Thus, NGFR mediates the apoptosis of myofibroblasts in the late stages of healing, and decreases collagen deposition and scar formation (122,123,125).

4. Conclusions

Wound healing is a complex process involving different types of cells, tissues, cytokines, chemokines and growth factors in each phase. Understanding its physiology will provide more mechanism-based therapeutic alternatives for the treatment of different types of wounds. Previous studies have demonstrated the vital roles of NGF in the regulation of wound healing. The present study summarized the biology of NGF and its receptors (NTRK1 and NGFR), and recent studies have revealed the involvement of NGF and its receptors in different types of wound healing. NGF and its receptors exert several biological effects on the process of wound healing, including participation in epithelial cell and fibroblast migration, inflammatory immune response regulation, angiogenesis, myofibroblast differentiation and tissue remodelling. Notably, topical application of exogenous NGF exerts a significant healing effect on cutaneous, corneal and oral wounds, without obvious side effects. This healing action is also applicable to some wounds that fail to respond to conventional treatment. However, further studies are required to determine the underlying molecular mechanisms by which NGF and its receptors participate in wound healing processes. In addition, more randomized controlled trials are required to assess whether topical application of high concentrations of NGF can be used to treat different types of wounds.

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Authors' contributions

SH conceived the present review and designed its framework. ZL and HW performed the literature review and drafted the initial manuscript. ZL and HW edited the manuscript. Data sharing is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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