

# Synergistic Wound Healing: Unraveling the Multi-Target Effects of Traditional Chinese Medicine and Its Biomaterials on Chronic Wound Pathways

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**Abstract:** Chronic wounds, including diabetic ulcers (DUs), radiation-induced ulcers, and burns, present significant clinical challenges due to their distinct pathological mechanisms, necessitating tailored therapeutic strategies. Diabetic ulcers, characterized by impaired angiogenesis, persistent inflammation, and hyperglycemia, require dual modulation of inflammatory (NF- $\kappa$ B) and pro-repair (PI3K/Akt, Nrf2) pathways. Radiation ulcers involve DNA damage, NLRP3-driven inflammation, and TGF- $\beta$ /Smad-mediated fibrosis, while burns trigger acute inflammation via DAMPs/PAMPs-TLR/NLR activation. Traditional Chinese medicine (TCM) and its bioactive components, such as *Scutellaria baicalensis*, curcumin, and *Panax notoginseng*, exhibit multi-target therapeutic effects by regulating oxidative stress, inflammation, angiogenesis, and extracellular matrix remodeling through key pathways, including Nrf2/ARE, MAPK, NF- $\kappa$ B, PI3K/Akt, HIF-1 $\alpha$ /VEGF, Wnt/ $\beta$ -catenin, and TGF- $\beta$ /Smad. Emerging supramolecular self-assembled biomaterials—nanofibrous scaffolds, hydrogels, and microneedles—address the hydrophobicity and low bioavailability of natural plant-derived macromolecules (NPHMs), enabling spatiotemporally controlled drug delivery. Innovative formulations, such as curcumin-loaded hydrogels and exosome-based systems, enhance antioxidant, anti-inflammatory, and pro-angiogenic activities, accelerating wound closure. Despite progress, challenges remain in optimizing multifunctional co-assembly systems, elucidating NPHM self-assembly mechanisms, and developing smart biomaterials responsive to dynamic wound micro-environments. Future research should focus on clinical translation by improving material stability, refining stimulus-responsive release systems, and integrating interdisciplinary insights from herbal medicine, nanotechnology, and regenerative biology. This review systematically summarizes the mechanistic roles of TCM in wound healing, highlights advancements in bioactive material design, and outlines future directions to bridge traditional knowledge with modern therapeutic innovations, offering a scientific foundation for advancing chronic wound management.

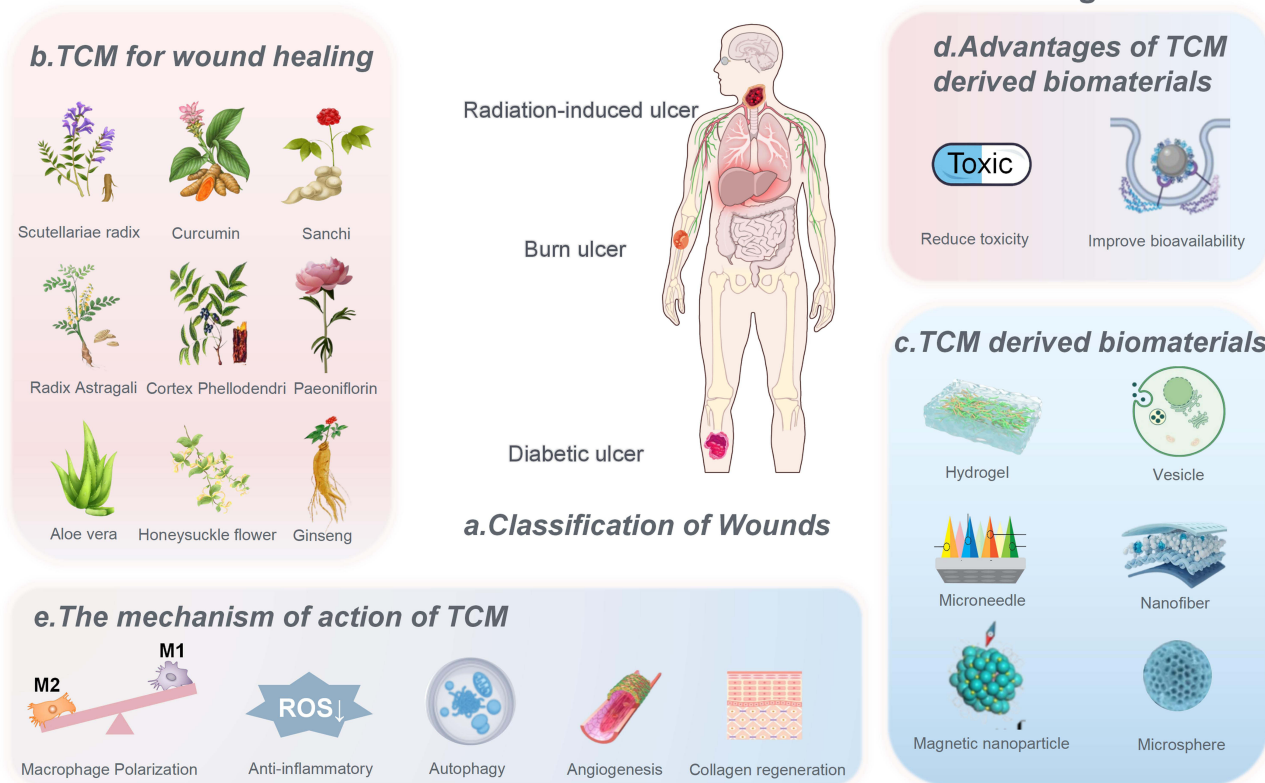
**Keywords:** chronic wounds, traditional Chinese medicine, biomaterials, signaling pathways, wound healing

## Introduction

It is reported that approximately 1–2% of the global population, particularly patients over the age of 65, are prone to chronic non-healing wounds.<sup>1</sup> Chronic wounds, such as diabetic ulcers (DU), have a global incidence rate of 0.02% to 10% among diabetic patients.<sup>2–7</sup> The presence of wounds severely affects people's physical functions and capabilities,<sup>8</sup> mental health,<sup>9</sup> and creates economic<sup>10</sup> and social burdens.<sup>11</sup> Wound healing has always been a challenge for clinicians, and there is an urgent need for new materials and methods. In recent years, extensive animal studies have focused on the impact of herbal compounds and active ingredients on the healing of diabetic wounds. The main advantage of TCM is that it usually contains a variety of effective components that can act on multiple targets simultaneously, producing synergistic effects. For example, TCM such as *Scutellaria baicalensis*, curcumin, *Panax notoginseng*, and *Astragalus membranaceus*, and their derived biomedical materials



## TCM and its derived biomaterials in Chronic Wound Healing



**Figure 1** TCM and its derived biomaterials in Chronic Wound Healing. (a) Classification of Wounds. (b) TCM for wound healing. (c) TCM derived biomaterials. (d) Advantages of TCM derived biomaterials. (e) The mechanism of action of TCM.

play roles including inhibiting the release of inflammatory factors, regulating oxidative stress, promoting macrophage polarization, inhibiting cell apoptosis, inducing autophagy, and involve multiple signaling pathways such as nuclear factor kappa-B (NF- $\kappa$ B), mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT). Additionally, research on composite reagents and new materials made from TCM components to promote healing is emerging. This article aims to review the mechanisms of TCM in regulating wound healing and summarizes reports, as shown in Figure 1, on the related signaling pathways of TCM reagents on wound healing, providing a scientific reference for further research on TCM treatment of wound healing and rational clinical application.

## The Basic Process of Wound Healing

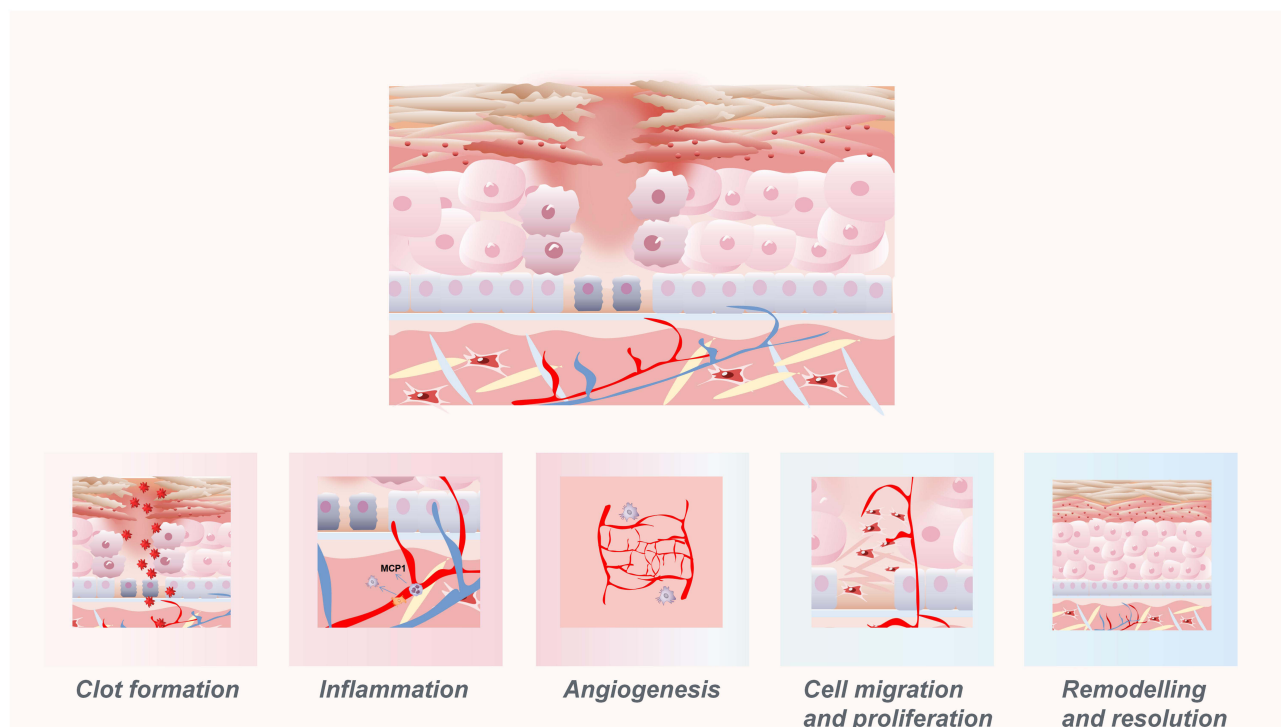
Wound healing requires the processes of blood clotting to stop bleeding, inflammation, epithelial regeneration, granulation tissue formation, and tissue remodeling.<sup>26,27</sup> Wound healing is a complex physiological process involving multiple stages and interactions of various cell types. The entire process of wound healing is depicted in Figure 2.

### Coagulation (Hemostatic Phase)

After skin injury, platelet function is activated, and platelets release granules. Concurrently, the coagulation cascade is activated, with various serine proteases being activated, ultimately leading to the conversion of fibrinogen to fibrin by thrombin, forming fibrin fibers.<sup>28</sup> The initiation of these cascades is crucially dependent on factor XI binding to negatively charged surfaces (such as collagen).<sup>29</sup> In this phase, platelets are not only involved in hemostasis but also release multiple effector factors through degranulation, activating the innate immune inflammatory response.

### Inflammatory Response Phase

The inflammatory phase follows the coagulation phase and lasts from hours to days. In this stage, neutrophils migrate to the wound interstitium under the influence of inflammatory signals,<sup>30,31</sup> releasing Monocyte Chemoattractant Protein-1 (MCP1),



**Figure 2** Wound healing occurs through five dynamically interconnected stages—clot formation, inflammation, angiogenesis, cell migration and proliferation, and tissue remodeling—collaboratively repairing damage and restoring tissue functionality.

Leukotriene B4 (LBT4), gasdermin, elastase, and myeloperoxidase, recruiting more inflammatory cells,<sup>32,33</sup> and dying after killing microbes. Subsequently, macrophages phagocytose neutrophils, promoting the transformation of macrophage phenotype and function, and inducing cell differentiation to ensure the restoration of vascular integrity,<sup>34–36</sup> preparing for the subsequent repair phase.

### Cellular Proliferation (Granulation Proliferation Phase)

In the late inflammatory response, fibroblasts and endothelial cells begin to proliferate, forming granulation tissue. In this stage, neovascularization, fibroblast migration, and new collagen matrix deposition are involved in the formation of granulation tissue.

### Re-Epithelialization

Concurrently with granulation tissue formation, the release from platelet degranulation, wound edges will enhance the migratory activity under the action of fibroblast growth factor 7 (FGF 7) heparin-binding epidermal growth factor (EGF) or hepatocyte growth factor (HGF), achieving re-epithelialization of the wound.<sup>37,38</sup> In this process, the level of ephrin B1 expressed by wound epidermal cells increases, activating the adjacent Eph receptors, allowing cells to move flexibly with loose desmosomal connections, achieving epidermal cell coverage of the wound and restoring the skin's barrier function.<sup>39</sup>

### Tissue Remodeling and Maturation (Scar Maturation/Remodeling Phase)

The final stage of wound healing includes the remodeling of collagen fibers and the reorganization of tissues, often leaving a scar. Scar formation is related to the deposition of new collagen by fibroblasts and myofibroblasts, and inflammation plays a fundamental role in driving the reaction of scarring and fibrosis. Throughout the healing process, multiple signaling pathways are involved in regulating to promote wound healing. For example, the PI3K/AKT signaling pathway affects the repair process with the activity of mTOR and GSK3 $\beta$ . Additionally, wound healing involves various

growth factors such as Platelet-Derived Growth Factor (PDGF), EGF, TGF- $\beta$ , etc., which coordinate intercellular and intracellular signal transmission, promoting cell proliferation, differentiation, migration, and protein synthesis.

## Classification of Wounds

Wounds are classified based on their etiology into DU, radiation ulcers (RU), and burn ulcers.<sup>40</sup>

### Diabetic Ulcers

DU are a serious complication in diabetic patients, mainly characterized by infection, ulceration, tissue necrosis, and clinical features such as lower limb vascular and neurological diseases. DU is one of the most dangerous complications of diabetes, severely affecting the quality of life and survival rate of patients. Its pathogenesis involves peripheral vascular disease, neuropathy, and infection, with molecular signaling pathways crucial to healing, including the PI3K-Akt signaling pathway, nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway, NF- $\kappa$ B signaling pathway.<sup>41,42</sup> Additionally, diabetes reduces the level of pro-angiogenic factors, increases the expression of anti-angiogenic factors, leads to apoptosis of vascular endothelial cells,<sup>43</sup> causes skin ischemia and hypoxia, and lacks nerve growth factors.

### Radiation-Induced Ulcers

Radiotherapy is an indispensable part of cancer treatment but also carries the risk of radiation-induced skin injury. Approximately 95% of patients undergoing radiotherapy will experience radiation-induced skin injury, with 85% of patients exhibiting moderate to severe skin injury reactions.<sup>44,45</sup> The clinical manifestations of RU include ulcers, erythema, desquamation, and these chronic wounds can persist for years, causing significant physical and psychological impact on patients.<sup>46–48</sup> The reason why RU are difficult to heal is that tissue fibrosis caused by radiation disrupts lymphatic and vascular drainage,<sup>49</sup> reducing tissue perfusion, leading to tissue hypoxia, which is prone to ulceration and slows down wound healing.<sup>50,51</sup> In addition, radiation directly acts on nuclear DNA and mitochondrial DNA, causing double-strand breaks, blocking the cell cycle of cell mitosis, inducing cellular senescence and damage. At the same time, DAMP molecules released by tissues and apoptosis interrupt skin tissue regeneration, produce inflammatory reactions, and the release of pro-inflammatory cytokines and inflammatory bodies such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Interleukin-1 (IL-1), Interleukin-6 (IL-6), and nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) further inhibits DNA repair, forming a vicious cycle. In addition, radiation injury is associated with changes in the expression of proteins such as tumor protein 53 (P53), bcl2-associated X protein (Bax), and B-cell lymphoma (Bcl-2). These complex biological processes work together to cause the development and persistence of RU, posing a serious threat to patient health and quality of life.

### Burn Ulcers

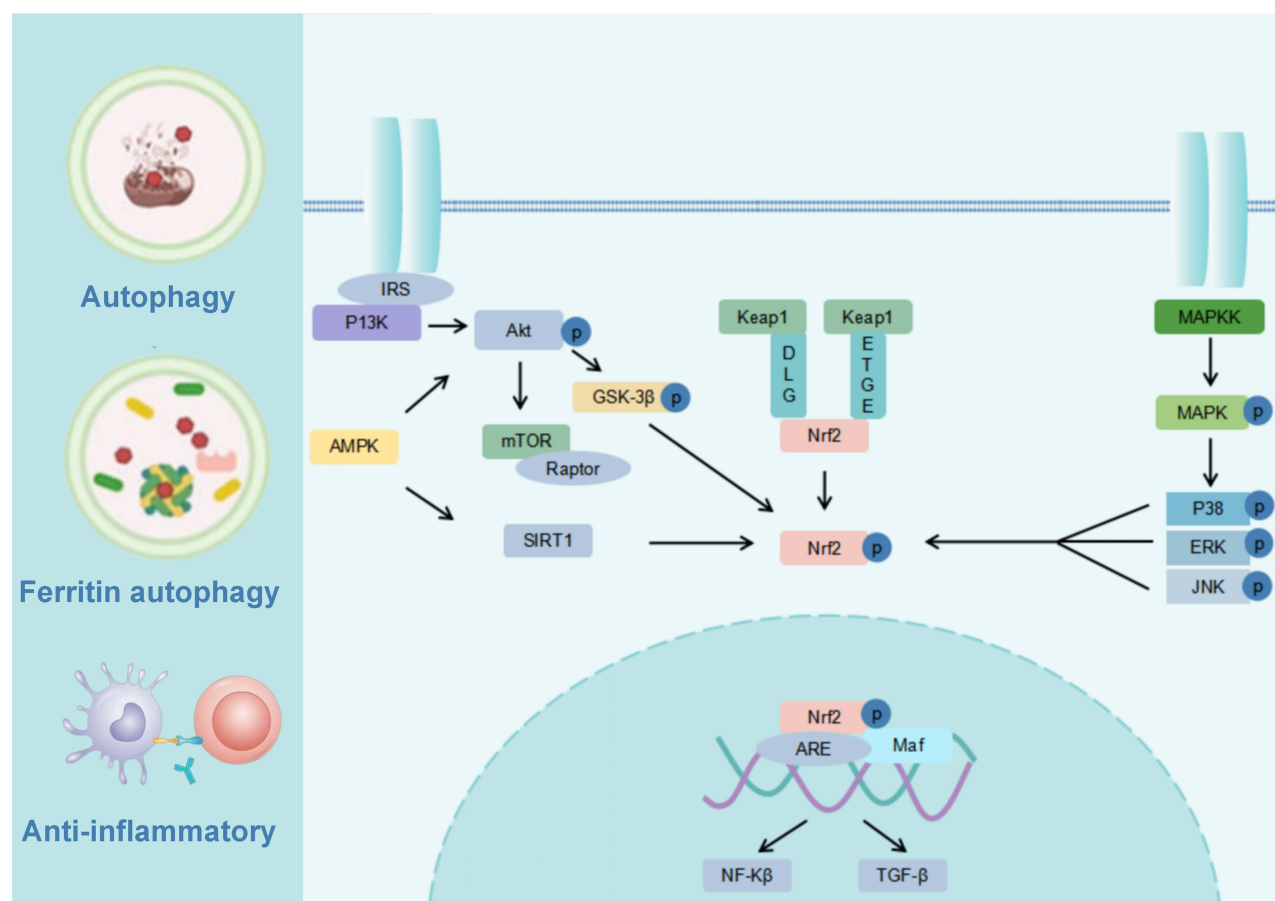
Burn ulcers are caused by friction, cold, heat, radiation, chemicals, or electricity, involving some energy transfer that leads to tissue structure destruction and cell death.<sup>52</sup> The clinical manifestations of burns include coagulative necrosis of the local skin, stagnant ischemia, and thermal inflammation. In severe burns,<sup>53</sup> DAMPs and their exogenous counterparts, pathogen-associated molecular pattern molecules (PAMPs), are recognized by pattern recognition receptors, namely Toll-like receptors (TLR) and NOD-like receptors (NLR). TLR and NLR activate NF- $\kappa$ B, and the transcription of various inflammatory mediators (such as IL-1, IL-6, IL-8) promotes the inflammatory cycle, leading to systemic inflammatory response syndrome.<sup>54,55</sup> It is worth noting that in this process, processes such as macrophage antigen presentation, neutrophil killing of pathogens,<sup>56,57</sup> T-cell proliferation, and IL-2 production are all inhibited.<sup>58–60</sup>

## Mechanisms of Wound Healing Promotion by TCM

### Nrf2/ARE Signaling Pathway

The Nrf2/ARE is one of the crucial intracellular signaling pathways that maintain cellular redox homeostasis.<sup>61–63</sup> Nrf2 is a key factor in antioxidant stress, capable of regulating the expression of cellular protective genes and antioxidants such as heme oxygenase 1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), to eliminate free

radicals.<sup>64</sup> The disruption of the body's antioxidant defense mechanisms is one of the factors delaying wound healing, and an increasing number of studies have shown that the activation of Nrf2 can regulate inflammatory factors, reduce oxidative stress damage, and promote the healing of diabetic wounds. After skin irradiation, the upregulation of NRF2 expression leads to persistent DNA damage and cellular senescence, inducing the occurrence of RU. The entire process of wound healing through the Nrf2/ARE pathway, MAPK pathway, and PI3K-Akt pathway is depicted in Figure 3. There are many Nrf2 activators in natural medicines. For example, curcumin,<sup>65–68</sup> baicalin,<sup>69–71</sup> berberine, and paeoniflorin (PF) all act on the Nrf2 pathway, involving the upregulation of Nrf2, inhibiting pro-inflammatory molecules matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 3 (MMP-3), regulating inflammatory factors TNF-1, IL-1, IL-8, promoting macrophage polarization, reducing the production of reactive oxygen species (ROS), alleviating inflammatory responses, and thus promoting skin healing. Unfortunately, the low solubility, bioavailability, and in vivo stability of curcumin hinder its efficacy as a clinical therapeutic drug. Curcumin is a hydrophobic molecule with low solubility in aqueous solutions. When taken orally, curcumin is degraded and rapidly metabolized under the acidic pH of the intestines. Similarly, after intravenous administration, it degrades within minutes and undergoes rapid first-pass metabolism, resulting in a short circulating half-life. Curcumin belongs to class IV of the biopharmaceutical classification system, characterized by low solubility and low permeability. These characteristics lead to reduced absorption, bioavailability, and stability.<sup>68</sup> Various curcumin composite preparations have been optimized, such as Bhattacharya optimizing a curcumin hydrogel scaffold with cerium oxide nanoparticles (CNP).<sup>72</sup> Liu C et al prepared a nanofiber wound dressing with a silver core and a curcumin surface using chitosan (CS) as the raw material, CS/Cur@ $\beta$ -CD/AgNPs,<sup>73</sup> which is highly biodegradable and allows rapid release of curcumin within 2 days. This dressing has a synergistic effect on wound healing while achieving antibacterial properties.<sup>74</sup> Gong et al combined curcumin with Mg<sup>2+</sup> to develop an exudate-



**Figure 3** The entire process of wound healing through the Nrf2/ARE pathway, MAPK pathway, and PI3K-Akt signaling pathways modulates autophagy, antioxidant responses, and anti-inflammatory reactions to promote wound healing.

absorbing and antibacterial hydrogel with a curcumin-loaded magnesium polyphenol network (Cur-Mg@PP), which has strong stability, high bioavailability, and high adaptability to complex-shaped wounds.<sup>75</sup> Curcumin, while achieving antioxidant and antibacterial effects,  $Mg^{2+}$  promotes macrophage polarization, thus promoting the healing of burn wounds. Tan W et al used curcumin and metformin loaded onto carboxymethyl chitosan (CMC) and oxidized hyaluronic acid (HA) to create a dual-drug loaded nanocomposite polysaccharide-based self-healing hydrogels (OCM@P) hydrogel for promoting diabetic wound healing, utilizing the principles of dynamic imine bonds and electrostatic interactions to form a porous structure, showing rapid release of Met and long-term sustained release of Cur, effectively inhibiting free radicals and significantly promoting re-epithelialization.<sup>76</sup> Li et al used exosomes with good biocompatibility, strong drug loading capacity, and immune inertia as an innovative fulcrum to construct macrophage exosomes loaded with curcumin (Exos-cur).<sup>65</sup> The study found that Exos-cur upregulated the expression of vascular endothelial growth factor (VEGF), platelet endothelial cell adhesion molecule 1 (PECAM-1, also known as CD31), and SMA proteins, repaired the mitochondrial membrane potential of human umbilical vein endothelial cells (HUVECs) and reduced oxidative damage, and accelerated wound healing in diabetic rats by activating the Nrf2/ARE pathway. Based on this, Yerneni SS et al further hypothesized that using dissolvable microneedle arrays (dMNA) to locally deliver curcumin-albumin-EV (CA-EV) can effectively control skin inflammation in vivo. In rat and mouse models, dMNA-delivered CA-EVs significantly reduced inflammation triggered by lipopolysaccharide and imiquimod by acting on inflammatory signal cascades such as NF- $\kappa$ B, MAPK, and janus tyrosine kinase (JAK)/signal transducer and activator of transcription (STAT).<sup>77</sup>

In terms of the application of baicalin, Masoud et al prepared a collagen hydrogel using fish skin extract and improved its mechanical properties through the PC method, incorporating baicalin into the luteolin hydrogel scaffold in an alkaline solution, increasing the Young's modulus to  $15.24 \pm 0.59$  kPa, achieving a wound closure rate of  $94.01 \pm 2.1\%$ . Compared with the swelling loading technology to incorporate baicalin into the hydrogel matrix, the new scaffold is more accurate and has a high incorporation efficiency, solving the problem of loading baicalin into collagen gels. In contrast, A Rang Kim et al reported incorporating baicalin into a HA/PNIPAM IPN hydrogel after synthesis with a baicalin solution, with a loading efficiency of 42.80%,<sup>78</sup> while the hydrogel treated with PC initially achieved a loading efficiency of up to 100%.

Berberine, the main chemical active components of PA, are flavonoids and alkaloids. Studies have confirmed that berberine ointment promotes wound healing, reduces advanced glycation end products (AGEs) and inflammatory factors such as IL-1 $\beta$ , while increasing the secretion of growth factors.<sup>79,80</sup> The compound berberine liquid dressing is currently well-researched and clinically applied. Xu et al found that compared with the clinically commonly used alginate calcium silver fiber dressing, the external application of the compound berberine liquid dressing is more conducive to solving the problem of multidrug resistance in diabetic foot. In addition, combining with *Centella asiatica* can improve wound healing and reduce scar formation. An anti-acne double-layer patch loaded with PA and *Centella CA* extracts was created. The experiment adopted the construction of a GC double-layer patch at  $-80^{\circ}\text{C}$ /room temperature, adding 1 mg/mL PA and 2.4 mg/mL CA, and found that after soaking for 150 hours, it had a good water retention rate of up to 3%. While improving the growth vitality of skin fibroblasts, it can absorb exudate from open acne wounds.<sup>81</sup>

PF has great potential in regulating M1 to M2 macrophages and can also accelerate wound healing through the Nrf2 pathway, reducing oxidative stress, increasing cell proliferation and migration, reducing apoptosis, and increasing the expression of VEGF and TGF- $\beta$ 1. Zhang et al designed a self-adaptive stimulus-responsive OBPG hydrogel, then added paeoniflorin-loaded micelles (MIC@Pae) to construct the OBPG&MP hydrogel drug delivery system, mainly acting on M2 macrophage polarization and extracellular matrix (ECM) remodeling processes.<sup>82</sup> Due to the dynamic reversibility and pH sensitivity of the Schiff base bond, the OBPG&MP hydrogel showed excellent injectability, self-healing ability, and responsiveness. It can also achieve sustained release of Pae for at least 72 hours, with scavenging rates of 68.1%, 74.6%, and 71.8% for  $\cdot\text{OH}$ ,  $\text{O}^{2-}$ , and  $\text{H}_2\text{O}_2$ , respectively. On the 14th day, the OBPG&MP hydrogel group's wound was almost completely healed, with a wound contraction rate of 98.1%. It has various properties, including protecting cells from oxidative damage. Hao et al developed a paeoniflorin hydrogel HA-PF (8%), and it was determined that signal transducer and STAT 1 were significantly inactivated, the expression of downstream protein iNOS was significantly inhibited, while STAT 6 was significantly activated, and the expression of downstream protein Arg-1 was significantly

enhanced, confirming the great ability of PF to regulate the STAT signaling pathway (a classic pathway for macrophage polarization).<sup>83</sup>

*Gynura divaricata* (L.) DC. (GD), known as “Bai Bei San Qi” in China, is used in TCM for its various pharmacological effects, including blood sugar-lowering effects, insulin sensitization, and blood pressure reduction. GD has been proven to enhance antioxidant activity in the body. Xu C et al showed that GD can activate Nrf2, prevent oxidative stress damage, promote angiogenesis, and thus promote wound healing in diabetic patients.<sup>84</sup>

## MAPK Signaling Pathway

The MAPK signaling pathway plays a crucial role in skin wound healing by finely regulating processes such as cell migration, proliferation, and differentiation, which promote tissue repair.<sup>85</sup> The MAPK family mainly includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. These kinases transmit signals through a phosphorylation cascade, affecting gene expression and cellular behavior.<sup>86</sup> During wound healing, the activation of the MAPK signaling pathway not only promotes angiogenesis but also regulates inflammatory responses and the reconstruction of the ECM. The ERK pathway is primarily associated with cell proliferation and differentiation, while JNK and p38 MAPK are closely related to cellular stress, inflammation, and apoptosis.<sup>87</sup>

Emu oil, extracted from the subcutaneous and retroperitoneal fat of emus, possesses strong anti-inflammatory properties. It may promote wound healing by fostering the growth of keratinocytes and re-epithelialization. Additionally, Ruyi Fan et al found in *in vitro* and *in vivo* experiments that emu oil enhances the secretion of IL-10, suppresses the secretion of IL-1 $\beta$ , promotes M2 macrophage polarization, and significantly reduces the phosphorylation of JNK and p38, thereby strengthening the anti-inflammatory response and promoting skin healing.<sup>88</sup>

Aloe vera is recognized as a wound healing promoter and has been shown to upregulate growth factors such as keratinocyte growth factor-1 (KGF-1), TGF- $\beta$ , cyclin D1, insulin-like growth factor 1 (IGF-1), VEGF, basic fibroblast growth factor (bFGF), and microfibril-associated glycoprotein 4 (MFAP4), as well as collagen, fibrillin, elastin  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), CD31, while downregulating the expression of MMPs. Aloe vera treatment for 48 hours shows increased expression of phosphorylated ERK (p-ERK) and increased cell proliferation.<sup>89</sup> Similarly, fibroblasts isolated from diabetic rats treated with aloe vera for 48 hours show increased JNK-1 mRNA expression. Aloeresin, an aromatic C-glucosyl-5-methylchromone found in aloe vera, possesses antioxidant activity. Iosageanu A et al found that aloesin promotes wound healing by participating in multiple processes, including cell migration, tissue development, angiogenesis, and cytokine release. Moreover, aloesin increases the phosphorylation of ERK and JNK in a concentration-dependent manner, leading to the activation of the MAPK signaling pathway, but has little effect on p38. In addition, aloesin strongly activates the effector proteins of TGF- $\beta$ 1 signaling, significantly increasing the phosphorylation of Smad2 and Smad3 in mouse skin samples, with little impact on Smad7 expression.<sup>90</sup> Furthermore, aloe emodin and  $\beta$ -sitosterol can bind to other MAPK signaling molecules, such as Myc and Jun, as well as Akt-1 from the PI3K/Akt pathway.<sup>91</sup> A silk protein/aloe vera gel wound dressing developed using silk protein and aloe vera, two natural extracts, enhances cell vitality, proliferation, migration, regulates VEGF secretion, inhibits cellular senescence, and activates the MAPK signaling pathway, particularly ERK1/2, thereby promoting the healing of DU.

## NF- $\kappa$ B Signaling Pathway

The NF- $\kappa$ B family of transcription factors plays a pivotal role in controlling gene expression involved in immune responses, inflammation, and cell survival, and is central to the regulation of wound healing.<sup>92</sup> Comprising five main components, these proteins form dimers that control a variety of genes associated with inflammatory responses. Typically, the NF- $\kappa$ B pathway is suppressed by inhibitors of the I $\kappa$ B family, but upon stimulation by inflammatory signals such as TNF- $\alpha$  or lipopolysaccharide (LPS), the I $\kappa$ B kinase (IKK) complex is activated, leading to the phosphorylation and degradation of I $\kappa$ B, thereby allowing NF- $\kappa$ B to translocate to the nucleus and induce the transcription of inflammatory cytokines.<sup>93</sup> In diabetic wounds, the upregulation of NF- $\kappa$ B into active transcription factors results in prolonged inflammation, hindering wound healing. The activation of NF- $\kappa$ B is also associated with the activation of the NLRP3 inflammasome, which further impedes the wound healing process in diabetic patients.<sup>94</sup> Additionally,

overexpression of NF- $\kappa$ B can alter the gene expression of angiogenesis-related factors, affecting vascular cell damage and neovascularization.<sup>95</sup>

Studies have shown that *Scutellaria baicalensis*, also known as Huang Qin, modulates macrophage polarization induced by oxidative stress through pathways such as NF- $\kappa$ B, PI3K/Akt/NRF2, and HO-1, thereby mediating inflammatory responses.<sup>96,97</sup> An ethanol composite of baicalin has been found to alleviate inflammatory pain induced by complete Freund's adjuvant (CFA) by suppressing the P2X3 receptor.<sup>98</sup> The combination of baicalin with SGC can activate the MAPK signaling pathway, promoting the proliferation of keratinocytes at the wound site to accelerate wound healing. A 3  $\mu$ M concentration of baicalin significantly enhances the effect of VEGF on the migration of keratinocytes, increasing the expression of MMP 9 induced by VEGF by about 30%. The optimal concentration of SGC is 0.5%, and its use in conjunction with 3  $\mu$ M baicalin increases the migration rate of keratinocytes by about 80%.<sup>99</sup> Innovative research from a chemical structure and molecular biology perspective has utilized non-covalent interactions between baicalin, which has similar scaffold and phenolic hydroxyl groups, and supramolecular hydrogel factors to construct co-assemblies. A new type of hydrogel dressing, CFPL, has been developed through chain-chain non-covalent interactions.<sup>100</sup> On the 11th day of treatment, the hydrogel continues to slowly release baicalin, with IL-6, IL-1 $\beta$ , and TNF- $\alpha$  levels dropping to 0.29%, 0.41%, and 0.94%, respectively. On the 7th and 14th days after wound induction, there is almost no distance between the epithelial tips in the acute wound tissue, indicating that the hydrogel containing chiral LBF has good anti-inflammatory properties, induces re-epithelialization, and promotes wound contraction. A hydrogel wound dressing prepared by Zhu Y et al, carboxymethyl chitosan-Sesbania gum@sesbania gum (CMCS-OSG@SE), promotes the healing of diabetic wounds by promoting epidermal regeneration, collagen deposition, and clearing ROS.<sup>101</sup> Liu X et al prepared ROS-sensitive nanoparticles loaded with baicalin polysaccharides (APS) based on the effective components of *Scutellaria baicalensis* (SB) and *Coptis chinensis* (CC), berberine (Bai) and berberine (Ber), and constructed a multifunctional TCM composite microneedle (C/B@APB@Ber). This microneedle downregulates the ROS-activated NF- $\kappa$ B pathway, thereby blocking the expression of pro-inflammatory cytokines and promoting the repolarization of M1 to M2 macrophages.<sup>102</sup>

*Panax notoginseng*, also known as San Qi, has the effect of promoting wound healing and reducing scar formation. *Panax notoginseng* and *Astragalus membranaceus* have been proven to promote the polarization of macrophages to the M2 phenotype by upregulating  $\beta$ -catenin and downregulating NF- $\kappa$ B, reducing inflammatory responses, and promoting wound healing in diabetic rats.<sup>103,104</sup> Rb1 significantly promotes skin wound healing in a second-degree burn rat model, with its potential mechanism related to the upregulation of FGF-2 by modulating the PDGF-BB/PDGF receptor beta (PDGFR- $\beta$ ) signaling pathway in wound tissue.<sup>105</sup> A review published in 2022 detailed the different signaling pathways affected by different active components of *Panax notoginseng*,<sup>106</sup> including the NF- $\kappa$ B pathway,<sup>107</sup> AMPK and endothelial nitric oxide synthase (eNOS) dependent signaling pathways,<sup>108</sup> hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) dependent pathways,<sup>109</sup> and Ang 2/Tie 2 signaling pathways.<sup>110,111</sup> Notoginsenoside (PNS), the main active component of *Panax notoginseng* (Burkill) F.H.Chen (PN) leaves, has been found to upregulate the expression of miR-146-5p in the NF- $\kappa$ B signaling pathway and downregulate the expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IRAK1, TRAF6, and p65, thereby reducing inflammatory responses and promoting skin healing.<sup>112</sup>

Jianting Li et al prepared ginger carbon dots (GCDs) from dried ginger solution using microwave-assisted hydrothermal method. GCDs effectively block the TLR4/NF- $\kappa$ B inflammatory trigger pathway, reducing the damage caused by inflammatory mediators, thus accelerating wound healing.<sup>113</sup>

Ginsenoside Rg5 can inhibit the activation of NF- $\kappa$ B p65 in keratinocytes and macrophages. NF- $\kappa$ B p65 is a transcriptional activator of SLC7A11. In this study, we confirmed that ginsenoside Rg5 dose-dependently reduced the expression of NF- $\kappa$ B p65, SLC7A11, as well as NRF2 and STAT3 in the wounded area of diabetic mice.<sup>114</sup>

Encapsulating Pae in microspheres and combining it with oxidized hyaluronic acid hydrogel to prepare a hydrogel loaded with Pae microspheres (Pae-MPs@OHA) promotes the healing of acute wounds in rats. Pae-MPs@OHA can reduce the number of M1 macrophages and increase the number of M2 macrophages, thereby regulating the release of inflammatory factors TNF- $\alpha$  and IL-1 $\beta$ . Molecular docking revealed that Pae can bind through various covalent bonds, reducing the expression of pro-caspase-1 and inhibiting the activation of caspase-1, thus reducing the degree of

inflammatory response. Western blot results further confirmed that Pae-MPs@OHA can reduce the expression of NF- $\kappa$ B, pNF- $\kappa$ B, NLRP3, ASC, and pro-caspase-1.<sup>115</sup>

Xia et al prepared Cur-GelMA hydrogels using 3D printing technology, which have good biocompatibility and promote tissue repair by alleviating ROS generation and ADSC cell apoptosis induced by AGE/AGER/NF- $\kappa$ B p65.<sup>116</sup>

Hu Y et al developed a novel 3D-printed dermal scaffold composed of decellularized ECM and copper-epigallocatechin gallate (Cu-EGCG), with a porous structure similar to that of natural human dermal matrix. This scaffold drives the expression of inflammatory-related genes in the HIF-1 $\alpha$ /VEGF pathway and the TNF- $\alpha$ /NF- $\kappa$ B/MMP9 pathway, promoting the healing of diabetic wounds and restoring the appearance, epidermal thickness, dermal thickness, number of skin appendages, and the arrangement and deposition of collagen in the dermis to a state similar to that of normal, undamaged skin, thereby reversing the scarring of diabetic wounds.<sup>117</sup>

Zhang P et al developed a novel berberine nanocolloidal hydrogel (BNH) that can inhibit the expression of NF- $\kappa$ B, TNF- $\alpha$ , and IL-6, and by activating Sirt1, increase the expression of VEGF, CD31, and SMA, which are beneficial for the wound healing of diabetic rats.<sup>118,119</sup>

Honeysuckle is an effective free radical scavenger that can promote wound healing. Baicalein, an active component of honeysuckle, can promote the mRNA levels of inflammatory cytokines IL-6, IL-1 $\beta$ , and TNF- $\alpha$ , which can be transcriptionally regulated by NF- $\kappa$ B and STAT3 to alleviate skin inflammation.<sup>120</sup> Lonicera japonica Thunb, from which chlorogenic acid is isolated, is a type of flavonoid glycoside. Silent information regulator 1 (Sirt1) is a highly conserved nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase, which is related to various intracellular signals such as aging, inflammation, apoptosis, and autophagy. Honeysuckle extract increases the autophagy flux in HUVECs and alleviates oxidative stress and reduces the ability to induce cell apoptosis by promoting the Sirt1-autophagy pathway, thereby accelerating the healing process of wounds both in vitro and in vivo.<sup>121</sup> TCM, such as Ma Nian, promotes the proliferation of HaCaT cells and promotes healing through active components like linoleic acid glycerides, betulin, L-lysine, and morin, acting on targets such as TNF, SRC, and TP3. Liu et al used network pharmacology methods to predict the targets of Ma Nian acting on wound healing and found that TNF induces autophagy flux and the expression of autophagy genes in epidermal keratinocytes through NF $\kappa$ B, and other targets are associated with various validated signaling pathways such as the JAK/STAT pathway and the NF- $\kappa$ B pathway.<sup>122</sup>

## PI3K/AKT Signaling Pathway

The PI3K/AKT signaling pathway plays a central role in skin wound healing, activated by growth factors and cytokines such as PDGF and EGF through their interaction with receptor tyrosine kinases (RTKs).<sup>123</sup> The autophosphorylation of RTKs recruits PI3K to the cell membrane, converting phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3), which in turn activates AKT. The activation of AKT promotes mTORC1, influencing biological activities such as proliferation, growth, and survival, while also regulating downstream proteins like mTOR and GSK3.<sup>124</sup> In patients with diabetes mellitus (DM), impaired PI3K/AKT signaling is associated with the progression of DM and its complications, including lower limb ulcers. Abnormal PI3K/AKT signaling may lead to abnormalities in cell migration, proliferation, differentiation, apoptosis, and excessive degradation of the ECM. (Pentaerythritol tetranitrate) PTEN, a negative regulator of the PI3K/AKT pathway, when absent, can increase epithelial cell proliferation and migration, accelerating wound healing.<sup>125</sup> Therefore, the precise regulation of the PI3K/AKT signaling pathway is crucial for maintaining tissue homeostasis and promoting the healing of acute wounds, and its balanced activation in skin wound healing has potential clinical significance for the treatment of chronic wounds related to diabetes.<sup>126</sup>

Chen L et al found that periplocin can induce the sequential phosphorylation of Src, PI3K, Akt, and ERK1/2 in a dose- and time-dependent manner, mediated by Na/K-ATPase, leading to the activation of Src/ERK1/2 and PI3K/Akt pathways and accelerated wound repair.<sup>127</sup> Scholars have synthesized a multifunctional chitosan/sodium alginate/velvet antler blood peptide (VBPs) hydrogel (CAVBPH). Treatment with this hydrogel activates the PI3K/AKT/mTOR and SIRT1/NF- $\kappa$ B pathways, thereby enhancing cell proliferation, angiogenesis, and ECM secretion, and alleviating inflammation at the wound site.<sup>128</sup>

A hyaluronic acid hydrogel containing Poria (Schw). Wolf terpenoid compounds can significantly accelerate the healing of diabetic wounds, with anti-inflammatory effects and enhanced angiogenesis. Using network pharmacology and

molecular docking, Ding X et al identified 74 potential target genes (JUN, MAPK1, STAT3, AKT1, and CTNNB1) related to the treatment of diabetic ulcers with Poria (Schw). Wolf, showing significant enrichment in the PI3K-AKT signaling pathway. In vitro experiments showed that Poria polysaccharides (10 mg/L) promote the migration of HUVECs and increase the expression of CD31 and VEGF mRNA, while also activating the expression of p-PI3K and p-AKT. Additionally, PTE reduces the expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and NF- $\kappa$ B mRNA in THP-1 cells and promotes M2 macrophage polarization, indicating the potential therapeutic effect of PTE in the treatment of diabetic ulcers.<sup>129</sup>

Danmu can promote the proliferation of HUVECs, upregulate the expression levels of VEGF in HUVECs, and regulate the PI3K/AKT/mTOR pathway to promote cell repair and wound healing.<sup>130</sup> Xu Y constructed a magnetically attracted thermosensitive hydrogel (FDA-TA) based on polyether F127 diacrylate (F127) and tannic acid (TA). Under pre-iron enrichment conditions, the PI3K-AKT pathway is activated to inhibit the autophagy mediated by nuclear receptor coactivator 4, promoting tissue healing.<sup>131</sup> Furthermore, a composite hydrogel (GBTF)<sup>3+</sup> was synthesized through one-step photopolymerization of gelatin methacrylate (GelMA), Bletilla striata polysaccharide (BSP), and tannic acid/iron(III) complex (TA/Fe), which rapidly promotes wound healing through anti-inflammatory and pro-angiogenic effects.<sup>132</sup>

Ginseng-derived nanoparticles (GDNPs) possess the basic characteristics of exosomes, enhancing the migration of HaCaT cells and HUVECs, as well as angiogenesis in HUVECs, and promoting skin wound healing and reducing inflammation in mice through the ERK and AKT/mTOR pathways.<sup>133,134</sup>

Moist Exposed Burn Ointment (MEBO), an effective drug for treating diabetic trauma, has been shown to improve microcirculation, clear necrotic material, reduce inflammation, and increase the expression of vascular endothelial factors. Zheng et al studied its mechanism and found that in a rat ulcer wound model, the MEBO group first enhanced and then weakened the regulatory effect on autophagosomes. The expression levels of key factors in the mTOR signaling pathway, such as PI3K, Akt, and mTOR, were relatively low, increased and then decreased, and were significantly higher than those in the model group. It is speculated that MEBO may activate the PI3K-Akt-mTOR signaling pathway, activate autophagy inhibition, reverse the expression levels of PI3K, Akt, and mTOR, and participate in the repair and healing of ulcer wounds.<sup>135</sup>

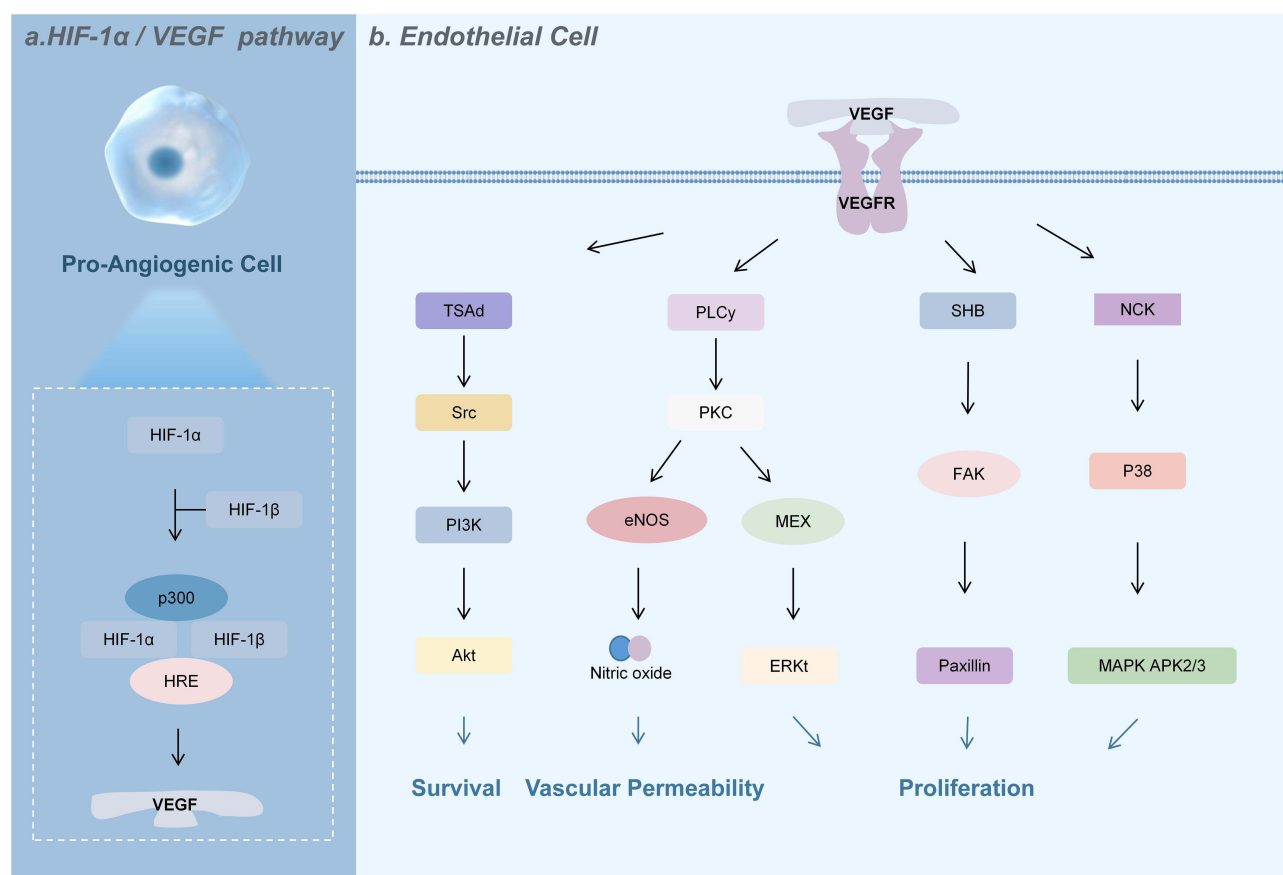
## HIF-1 $\alpha$ /VEGF Signaling Pathway

VEGF plays a central role in wound healing, not only promoting angiogenesis but also regulating vascular permeability and endothelial cell function.<sup>136</sup> The expression of VEGF is regulated by HIF-1 $\alpha$ , which activates receptors such as VEGFR-2 and downstream signaling pathways, including PLC- $\gamma$ /PIP2/DAG/IP3, MAPK/ERK, PI3K/AKT, and FAK/Paxillin, to promote cell proliferation and migration.<sup>137</sup> The dysfunction of the HIF-1 $\alpha$ /VEGF axis is a primary mechanism of impaired vascularization in diabetes. Additionally, HIF-1 $\alpha$  is widely recognized as a major regulator of oxygen homeostasis. The entire process of wound healing through the HIF-1 $\alpha$ /VEGF pathway is depicted in Figure 4.<sup>138</sup>

The active component of Asperosaponin VI (ASA VI) from *Dipsacus asperoides*, a traditional Chinese medicinal plant, promotes cell proliferation, migration, and enhances angiogenic capacity by upregulating the HIF-1 $\alpha$ /VEGF pathway, ultimately facilitating wound healing.<sup>139</sup> Jamun honey (JH) (0.1% v/v) significantly improves wound closure, migration, and the expression of  $\alpha$ -SMA. Local application of JH in a diabetic mouse model promotes re-epithelialization, collagen deposition (I/III), and balanced myofibroblast formation, while also upregulating angiogenic markers (HIF-1 $\alpha$ , VEGF, VEGF R-II).<sup>140</sup>

Ji M et al reported the synthesis of dandelion-shaped mesoporous strontium-gallium particles (GE@SrTPP) through dopamine-mediated biomineralization and self-assembly, followed by functionalization with a gallium metal polyphenol network. GE@SrTPP can release bioactive ions in a spatiotemporal manner akin to dandelion seeds. In the early stages of wound healing, it exhibits rapid and effective hemostasis and antibacterial properties. During the inflammatory phase, GE@SrTPP promotes M2 polarization of macrophages, suppresses the expression of pro-inflammatory factors, and reduces oxidative stress in the wound. In the proliferation and tissue remodeling stages, GE@SrTPP promotes angiogenesis by activating the HIF-1 $\alpha$ /VEGF pathway.<sup>141</sup>

Pae, a major active component found in *Paeonia lactiflora*, has demonstrated angiogenic properties in endothelial cells with vascular dysfunction and zebrafish models. Pae reportedly enhances the secretion of angiogenic growth factors and promotes



**Figure 4** HIF-1 $\alpha$ /VEGF Signaling Axis in Wound Healing-Associated Angiogenesis. (a) Promoting angiogenesis by targeting the HIF-1 $\alpha$ /VEGF pathway facilitates wound healing. (b) Angiogenesis is a complex and highly orchestrated process that relies on elaborate intercellular and intracellular signaling networks between endothelial cells (ECs) and pro-angiogenic cells.

the proliferation, migration, and tube formation of endothelial cells. He J et al developed a multifunctional sponge dressing based on copper, Bletilla striata polysaccharide (BSP), and Peony leaf extract (PLE), known as BSP-Cu-PLE sponge. The BSP-Cu-PLE sponge exhibits excellent antimicrobial activity and hemostatic properties, and significantly ( $p < 0.05$ ) accelerates the healing process of skin wounds by stimulating collagen deposition, promoting angiogenesis, and reducing inflammatory cells.<sup>142</sup> A stimulus-responsive sugar-peptide hydrogel, termed OBPG&MP, was constructed from oxidized Bletilla striata polysaccharide (OBSP), tannic acid-grafted  $\epsilon$ -polylysine (PLY-GA), and Pae-loaded micelles (MIC@Pae). This hydrogel mimics the glycoprotein fiber structure of the ECM, demonstrating excellent injectability, self-healing ability, and biocompatibility. It adaptively responds to the inflammatory microenvironment of chronic wounds, sequentially releasing therapeutic agents to eradicate bacterial infections, neutralize ROS, modulate macrophage polarization, suppress inflammation, and promote angiogenesis and ECM remodeling, playing a key role in the inflammatory, proliferative, and remodeling phases of wound healing.<sup>82</sup>

As recorded in the “Compendium of Materia Medica” the fruit of the Chinese herb CFI can be moistened with wine, baked, mashed (flesh and kernel), and ground into a fine powder with borneol to treat persistent oral ulcers.<sup>143</sup> As a flavonoid-rich traditional Chinese medicinal plant, CFI has been found to possess anti-ulcer, antioxidant defense enhancement, protection against UV-induced skin damage, prevention of endothelial cell dysfunction, antibacterial, and wound healing properties, and can alleviate ischemia/reperfusion injury in mouse intestines by activating PPAR $\alpha$  and inhibiting the NF- $\kappa$ B signaling pathway.<sup>144–146</sup> Feng et al validated through research that CFIE may promote the healing of diabetic wounds through the PI3K/AKT and HIF-1 $\alpha$  pathways.

## Wnt Signaling Pathway

The Wnt/ $\beta$ -catenin signaling pathway is a widely conserved cellular signaling network present in both invertebrate and vertebrate animals, playing crucial roles in various physiological processes such as embryonic development, tumorigenesis, and wound healing.<sup>147</sup> This pathway includes core components such as Wnt proteins, Frizzled family receptors, LRP5/6, and GSK-3 $\beta$ , which control cell proliferation, differentiation, and tissue homeostasis by regulating the stability and nuclear localization of  $\beta$ -catenin.<sup>148</sup> In wound healing, the Wnt/ $\beta$ -catenin signaling pathway is involved in the regulation of inflammatory responses, cell proliferation and migration, angiogenesis, hair follicle regeneration, and skin fibrosis, with its activity changes being closely related to the healing outcome.<sup>149</sup> Activation and inhibition factors of the Wnt signaling pathway play significant roles at different stages of wound healing, affecting inflammation, proliferation, differentiation, and tissue regeneration, indicating the complex regulatory role of the Wnt signaling pathway in wound healing and tissue regeneration, making it an important area of research and application in wound therapy and tissue engineering.<sup>150</sup>

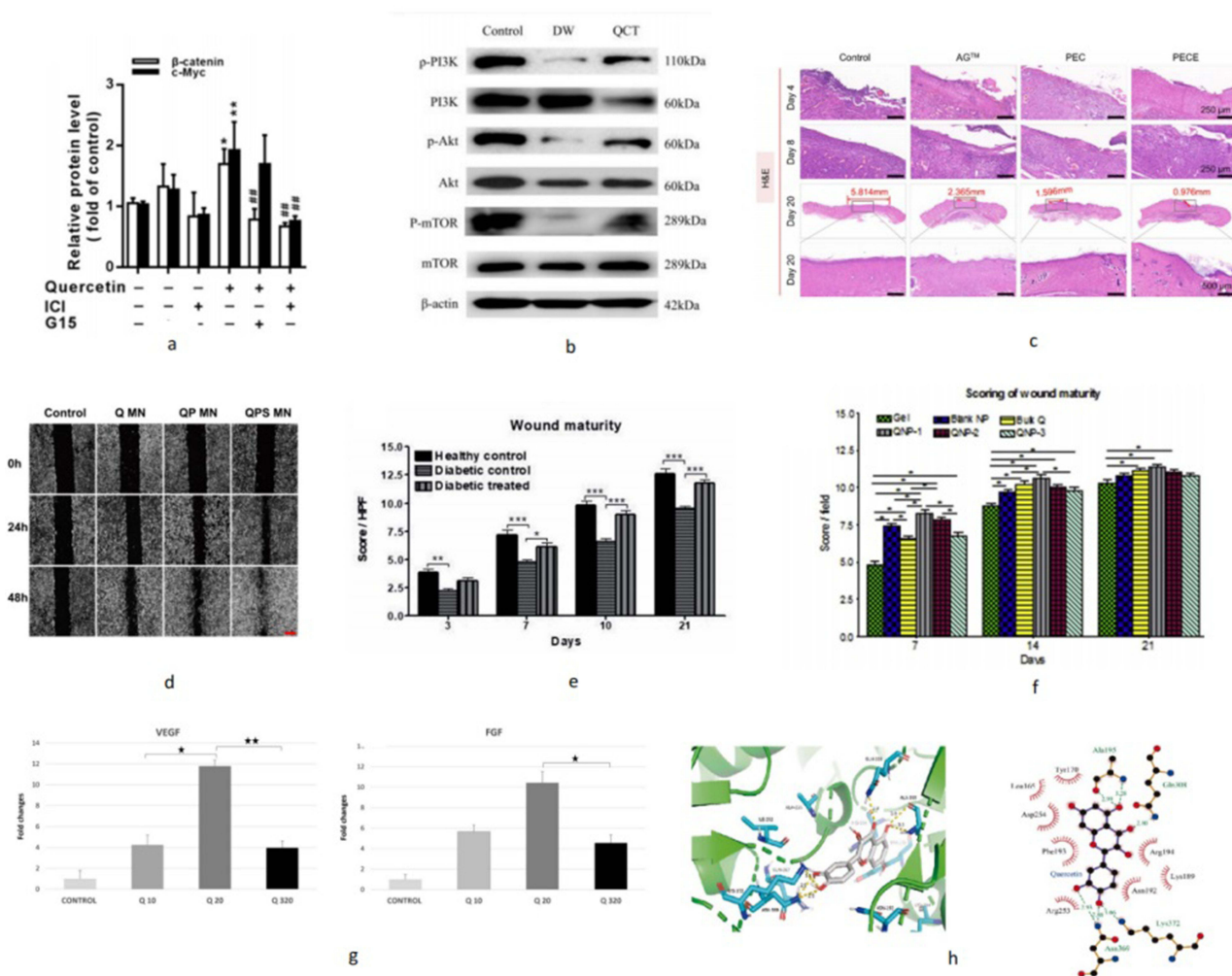
In skin wounds treated with quercetin, the expression levels of VEGF, fibroblast growth factor, and  $\alpha$ -SMA are positively correlated in a dose-dependent manner. Molecular docking analysis also reveals that hydrogen bonds formed between quercetin and residues Ala195, Gln308, Asn369, and Lys372 of TERT suggest that the telomerase RNA component catalytic element (TERT) plays an indispensable role in enhancing wound healing capabilities. Quercetin can stimulate the proliferation of human epidermal stem cells and promote wound healing through the estrogen receptor (ER $\alpha$ )/ $\beta$ -catenin/c-Myc signaling pathway.<sup>151–153</sup> Studies have also shown that quercetin can regulate the PI3K-AKT-mTOR signaling pathway to accelerate wound healing.<sup>154–156</sup> Compared to the direct application of quercetin, Xing et al developed a polysaccharide-based injectable hydrogel (PECE) loaded with quercetin. A 1% concentration of PECE showed the maximum release within the first 12 hours, with the best antibacterial effect, and almost no bacteria present by the fourth day. By the 20th day, the narrowest wound measured only 0.976 mm, with the best epidermal recovery and the observation of new hair follicle formation. The clearance rate for DPPH was over 99%, and there was a significant reduction in IL-6 and TNF- $\alpha$ .<sup>157–159</sup> The hydrogel exhibited high antioxidant properties and excellent antibacterial performance. Another microneedle system, QPS MN, released about 47% in vitro within the first hour, with a scratch migration rate of  $61.4 \pm 3.25\%$ , ten times that of the control group. Expression of IL-6 and TNF- $\alpha$  was reduced, while VEGF protein expression increased. Quercetin chitosan tripolyphosphate nanoparticles can achieve better healing quality and maturity of granulation tissue,<sup>160</sup> with the optimal quercetin nanoparticle concentrations identified as 0.3% and 0.1%.<sup>161,162</sup> Additionally, a composite of polycaprolactone (PCL) and chitosan oligosaccharides was prepared and mixed with quercetin to construct a PCL-COS-Qe membrane.<sup>163</sup> The loading efficiency was 97.0%, and it had high water vapor permeability, which is beneficial for wound drying. The application of quercetin and its derived biomaterials in wound healing is depicted in Figure 5.

Lucidone can effectively heal skin wounds in mice. The activation of Wnt/ $\beta$ -catenin signaling by GSK3 $\beta$  leads to an increase in c-Myc and cyclin D1 gene activation. Lucidone increases cell cycle regulatory proteins to accelerate keratinocyte proliferation and triggers EMT/MMP activation, promoting the loosening of tight junctions and facilitating migration/invasion. Furthermore, lucidone also participates in the inflammatory phase of wound healing through NF- $\kappa$ B-mediated iNOS/COX-2/NO production and VEGF expression in macrophages.<sup>164</sup>

Tan D et al developed a multifunctional hydrogel wound dressing composed of royal jelly-derived extracellular vesicles (RJ-EV) and methacryloyl sericin (SerMA). RNA sequencing results indicate that the SerMA/RJ-EVs hydrogel dressing mainly accelerates wound healing by inhibiting inflammation and promoting vascular repair through Wnt signaling and Hippo signaling pathways.<sup>165</sup>

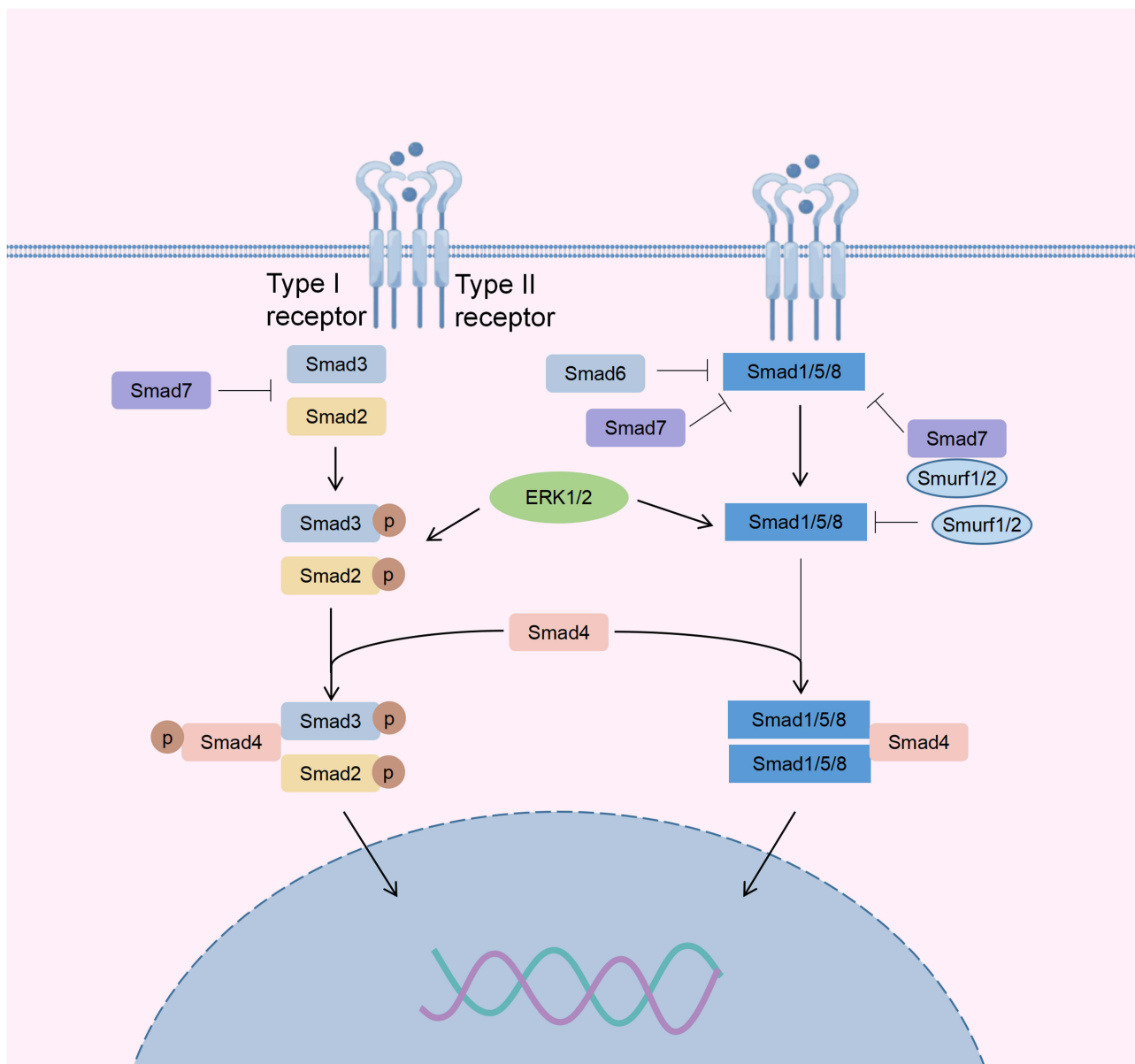
## TGF- $\beta$ /Smad Signaling Pathway

TGF- $\beta$ /mothers against decapentaplegic (Smad) signaling pathway plays a central role in skin wound healing. TGF- $\beta$  is a key cytokine synthesized by damaged tissue, fibroblasts, and M2 macrophages, and it is crucial in the generation of myofibroblasts, cells responsible for substantial collagen deposition and wound contraction.<sup>166</sup> Growth factors such as VEGF, PDGF, and TGF- $\beta$  released by M2 macrophages promote the proliferation, migration, and differentiation of fibroblasts, which is essential for capillary growth and granulation tissue formation in the reparative



**Figure 5** Investigations on the Effects of Quercetin and Related Treatments on Wound Healing. (a) Detection of  $\beta$ -catenin and c-Myc in human embryonic stem cells (EpSCs) treated with 1  $\mu$ M quercetin for 24 hours after pre-treatment with ICI 182780 for 30 minutes. Reprinted from Wang Z, Zhang G, Le Y, et al. Quercetin promotes human epidermal stem cell proliferation through the estrogen receptor/ $\beta$ -catenin/c-Myc/cyclin A2 signaling pathway. *Acta Biochim Biophys Sin.* 2020;52(10):1102–1110.<sup>151</sup> (b) Western blot (WB) analysis to detect changes in proteins related to the PI 3-kinase-AKT-mTOR signaling pathway after QCT treatment. Reprinted from Zhang Z, Wang L, Li X, Miao Y, Li D. Integrating network pharmacology, molecular docking and experimental validation to explore the pharmacological mechanisms of quercetin against diabetic wound. *Int J Med Sci.* 2024;21(14):2837–2850. Published under Creative Commons 4.0, <https://creativecommons.org/licenses/by/4.0/>.<sup>156</sup> (c) Hematoxylin and eosin (HE) staining to observe the degree of inflammatory cell infiltration and the condition of granulation tissue formation. Reprinted with permission from Xing D, Du Y, Dai K, Lang S, Bai Y, Liu G. Polysaccharide-based injectable hydrogel loaded with quercetin promotes scarless healing of burn wounds by reducing inflammation. *Biomacromolecules.* 2024;25(11):7529–7542. Copyright 2024, American Chemical Society.<sup>158</sup> (d) Scratch assay to test the ability of DMN to promote the migration and repair of HUVECs.<sup>159</sup> (e) Wound maturity evaluation when quercetin ointment is applied directly. Reprinted from Kant V, Jangir BL, Sharma M, Kumar V, Joshi VG. Topical application of quercetin improves wound repair and regeneration in diabetic rats. *Immunopharmacol Immunotoxicol.* 2021;43(5):536–553. Reprinted by permission of the publisher (Taylor & Francis Ltd, <http://www.tandfonline.com>).<sup>157</sup> (f) Wound maturity scoring for quercetin chitosan tripolyphosphate nanoparticles at different drug concentrations. Reprinted from *European Journal of Pharmacology*, 880, Choudhary A, Kant V, Jangir BL, Joshi VG. Quercetin loaded chitosan tripolyphosphate nanoparticles accelerated cutaneous wound healing in Wistar rats, 173172, Copyright 2020, with permission from Elsevier.<sup>160</sup> (g) Expression of VEGF and FGF in HUVEC cells exposed to 10, 20, and 320 nM doses of quercetin. Reproduced from Kartal B, Alimogullari E, Elci P, et al. The effects of Quercetin on wound healing in the human umbilical vein endothelial cells[J]. *Cell Tissue Bank.* 2024;25(3):851–860. Springer Nature, <https://link.springer.com/article/10.1007/s10561-024-10144-1>.<sup>152</sup> (h) Molecular docking analysis. Quercetin forms hydrogen bonds with the Ala195, Gln308, Asn369, and Lys372 residues of TERT. Reprinted from *Journal of Ethnopharmacol*, 290, Mi Y, Zhong L, Lu S, et al. Quercetin promotes cutaneous wound healing in mice through Wnt/ $\beta$ -catenin signaling pathway. *J Ethnopharmacol.* 2022;290:115066, Copyright 2022 with permission from Elsevier.<sup>153</sup>

dermis.<sup>167</sup> TGF- $\beta$  initiates signaling by binding to cell surface type I and II receptors, leading to the phosphorylation of Smad2 and Smad3, which then mediate gene expression, promote collagen deposition, and lead to fibrosis.<sup>168</sup> However, the abnormal regulation of the TGF- $\beta$  signaling pathway can lead to scarring and fibrosis, characterized by abnormal synthesis and deposition of collagen, as well as an increased ratio of type I to type III collagen.<sup>169</sup> Therefore, modulating the TGF- $\beta$ /Smad signaling pathway is of significant importance for controlling abnormal skin scarring and promoting wound healing. The entire process of wound healing through the TGF- $\beta$ /Smad pathway is depicted in Figure 6.



**Figure 6** The entire process of wound healing through the TGF- $\beta$ /Smad pathway.

Astragalus (AR) and Rehmannia (RR) in a 2:1 ratio form NF3, which affects the migration of skin fibroblasts and the activation of selected genes and proteins related to wound healing. A concentration of 4 mg/mL of NF3 promotes the migration of human skin fibroblasts and upregulates the synthesis of TGF- $\beta$ 1 and BMP-6. qRT-PCR analysis shows that NF3 regulates genes including TGF- $\beta$  superfamily ligands and downstream effector genes, as well as genes involved in the TGF/Smad pathway and Ras/MAPK (non-Smad) pathways. Additionally, in ECM-related molecules, NF3 upregulates the expression of type I and III collagen, fibronectin, and TIMP-1, and downregulates the expression of MMP-9 in skin fibroblasts.<sup>167</sup>

Salvia miltiorrhiza, a commonly used medicinal plant, is reported to have anti-inflammatory effects. Studies have found that the water extract of Salvia miltiorrhiza (RSM) increases the levels of serum epidermal growth factor (EGF), transforming growth factor (TGF)- $\beta$ , and hydroxyproline (Hyp), and increases the protein expression of bFGF, TGF- $\beta$ 1, and EGF, playing anti-inflammatory roles, improving local wound microcirculation, and accelerating wound surface

metabolism to promote wound healing (WH).<sup>170</sup> Tanshinone IIA (TSA), a bioactive component of *Salvia miltiorrhiza*, has been shown by Zhan Y et al to prepare TSA self-dissolving microneedles (TSA-MN) that inhibit the proliferation and migration of HSF cells in a dose-dependent manner, significantly reduce the secretion of TGF- $\beta$ 1, and increase the expression of Smad7.<sup>171</sup> Luan X et al prepared microneedles with *Tripterygium wilfordii* hook F (TP)/Pae tips and BP-hydrogel bases. The combined administration of TP and Pae not only provides anti-inflammatory, detoxifying, and immunomodulatory effects but also, with the addition of BPs, exhibits good biocompatibility and near-infrared (NIR) responsiveness, endowing MN with photothermal controlled drug release capabilities. TP/Pae loaded responsive MNs can effectively improve skin fibrosis and capillary dilation, reduce collagen deposition, and decrease epidermal thickness.<sup>172</sup> *Alpinia galanga* has been shown to enhance TGF- $\beta$ 1-mediated growth inhibition by inhibiting the phosphorylation of the Smad3 linker region threonine 179 residue and can be used locally for the treatment of abnormal skin scars.<sup>173</sup>

## Conclusion

Natural products, including herbs, are among the most precious treasures left to us by nature and have played an indelible role in the history of human health and development. Our research elucidates the mechanisms and potential of TCM in promoting wound healing from the perspective of signaling pathways. This work is relatively novel and holds significance for in-depth study. The unclear composition and mechanisms of action of TCM are one of the reasons it is rarely used in large-scale clinical treatments, yet the regulation of signals in skin regeneration and wound healing by TCM is still in its infancy. Further research and a deeper understanding of the mechanisms involved in healing are required. However, the mechanisms by which TCM and derived biomaterials promote healing vary, and there is still a lack of systematic summarization of this system. Our goal is to bridge this gap by contributing to the field. This article focuses on categorizing the mechanisms involved in the promotion of wound healing by Chinese medicine and its derived biomaterials into the following seven pathways: I) Nrf2/ARE, II) MAPK signaling pathway, III) NF- $\kappa$ B pathway, IV) PI3K/AKT signaling pathway, V) HIF-1 $\alpha$ /VEGF signaling pathway, VI) Wnt pathway, and VII) TGF-Smad. It systematically summarizes the specific mechanisms by which these seven pathways play a role in wound healing and how Chinese medicine and its derived materials regulate different pathways to promote wound healing. Additionally, it summarizes the etiological classification of wounds and the pathogenesis of different types of wounds. In the final part, it also briefly outlines several basic stages involved in the wound healing process. In summary, the promotion of wound healing based on natural products and their derived biomaterials is an emerging system worth further development. Next, we will discuss the current bottlenecks in the field and potential exploration directions that could further advance our understanding and application of this area.

## Future Directions and Exploration

Chronic wounds, including DU, radiation-induced ulcers, and burns, exhibit distinct pathological mechanisms, necessitating tailored therapeutic interventions. DU are characterized by impaired angiogenesis, persistent inflammation, and a hyperglycemic microenvironment, requiring dual modulation of inflammatory (NF- $\kappa$ B) and pro-repair (PI3K-Akt, Nrf2) pathways. Combinatorial therapies employing *Astragalus membranaceus* and *Salvia miltiorrhiza* to regulate macrophage polarization and suppress inflammation show exceptional therapeutic promise. Radiation ulcers involve DNA damage, chronic NLRP3-driven inflammation, and TGF- $\beta$ /Smad-mediated fibrosis, where interventions such as curcumin (activating Nrf2/ARE signaling) combined with hyperbaric oxygen therapy target inflammatory pathways to promote healing. Burns trigger acute inflammatory cascades via DAMPs/PAMPs-TLR/NLR activation (elevated IL-6, TNF- $\alpha$ ), necessitating immediate anti-inflammatory/antimicrobial dressings followed by epidermal regenerative enhancers like *Panax notoginseng* (NF- $\kappa$ B pathway inhibition and keratinocyte migration mediation). Beyond single herbs or their simple combinations, compound TCM formulations represent a significant therapeutic approach in wound management (Table 1). These formulations are meticulously designed by integrating multiple herbs according to TCM principles—such as achieving synergistic effects and attenuation of toxicity—to enable comprehensive regulation of the complex wound microenvironment through simultaneous multi-target and multi-pathway actions.

The unique value of natural plant-derived herbal macromolecules (NPHMs) in skin repair is increasingly recognized, yet their clinical translation is hindered by hydrophobicity and low bioavailability. Supramolecular self-assembled bioactive materials—nanofibrous scaffolds, hydrogels, vesicles, and microneedles—offer innovative solutions.

**Table 1** Traditional Chinese Medicine Compound Preparation Promotes Wound Healing

Traditional Chinese Medicine Formula	Signaling Pathway	Composition	Function
Yangyin Shengji San <sup>12</sup>	COX-2/PGE2 Signaling Pathway	Contains realgar 0.025g, calcined gypsum 0.3g, indigo naturalis 0.15g, peppermint 0.05g, magnolia bark 0.075g, pu Huang 0.1g, atractylodes macrocephala 0.05g, licorice 0.1g, and additional licorice 0.15g per gram of the formula.	Antioxidant stress, anti-inflammatory, and analgesic effects.
NF3 <sup>13</sup>	TGFβ/Smad and Wnt Pathways	Astragalus and licorice in a 2:1 ratio.	Promotes angiogenesis and suppresses inflammation to enhance the healing of diabetic ulcers.
Di'ao Xinxuekang Capsule <sup>14</sup>	NF-κB/COX-2 Pathway	Extracted from the rhizome of <i>Tripterygium wilfordii</i> . Approved since 1989 for the treatment of cardiovascular diseases.	DXXK has a significant anti-inflammatory effect, which may be related to the inhibition of the NF-κB/COX-2 pathway and related inflammatory mediators PGE2, NO, TNF-α, IL-1β, and IL-6.
Rosuvastatin combined with Danshen <sup>15</sup>	Increases protein expression of VEGF and CD31 in wound tissue, reduces protein expression of IL-6, TNF-α, IL-1β, and promotes protein expression of EGFR, HIF-1α.	Danshen, the dried root and rhizome of <i>Salvia miltiorrhiza</i> from the Lamiaceae family. Rosuvastatin is an HIF prolyl hydroxylase inhibitor.	Promotes angiogenesis, reduces inflammatory responses, and thereby promotes the healing of full-thickness skin defect wounds in diabetic rats.
Du Zhong Wan <sup>16</sup>	Induces the production of pro-angiogenic factor SLIT 3.	Eucommia and Dipsacus in a 1:1 ratio.	DZW promotes the healing of osteoporotic fractures by enhancing osteoblastogenesis and H-type angiogenesis.
Photobiomodulation combined with LBP <sup>17</sup>	Reduces ROS production, leading to the activation of transcription factors AP-1 and NF-κB.	A polysaccharide-rich hydrogel preparation extracted from the fruits of <i>Lycium barbarum</i> .	The combined treatment inhibits uvr-induced skin thickening, reduces the expression of c-Fos and c-Jun, as well as MMP-1, -2, and -9, while increasing the levels of collagen I, III, and FGF2.
Jia Wei Si Miao Yong An Tang (JWSMYA)	MAPK/ERK Pathway	Honeysuckle 90g, Radix Scrophulariae 90g, Angelica sinensis 60g, licorice 10g, dandelion 30g, purple root 30g, Bletilla striata 30g, Astragalus membranaceus 30g, borneol 10g.	JWSMYA improves the quality of radiative wound healing, which may be mediated by the MAPK/ERK pathway.
Traditional Chinese Medicine Hydrogel Microneedles <sup>18</sup>	Blocks bacterial infection, reduces inflammatory responses, promotes collagen deposition, and increases angiogenesis to significantly accelerate the healing of infected wounds.	Starch-aloe hydrogel microneedles loaded with berberine.	Possesses antibacterial promotion of healing and drug release capabilities, along with mechanical strength and adjustability.

(Continued)

Table 1 (Continued).

Traditional Chinese Medicine Formula	Signaling Pathway	Composition	Function
CS-PVA-ANE Nanofiber Mat <sup>19</sup>	Significantly improves wound closure rate, accelerates excellent angiogenesis, promotes re-epithelialization, and collagen matrix deposition.	Prepared by electrospinning chitosan-polyvinyl alcohol (CS-PVA) nanofiber mat. Added the active ingredient anemarrhasaponin B4 (ANE) from traditional Chinese medicine <i>Anemarrhena asphodeloides</i> .	Significantly inhibits the differentiation of lipopolysaccharide (LPS)-stimulated pro-inflammatory (M1) macrophage subpopulations, reduces the production of reactive oxygen species (ROS), and the release of inflammatory cytokines.
She Xiang Yu Hong Ointment <sup>20</sup>	Increases the quantity of granulation tissue, regulates the release of pro-inflammatory cytokines (eg, IL-6 and TNF- $\alpha$ ). Improves collagen fiber deposition and tissue hyperplasia at the wound site.		Accelerates wound healing, promotes angiogenesis, and inhibits inflammation. The mechanism may be the result of VEGF acting alone or in combination.
Pien Tze Huang (PZH)	ROS/Bcl-2/Bax/Caspase-3 Pathway		PZH promotes the expression of growth factors and regulates oxidative stress. <sup>21</sup> Its mechanism involves reducing intracellular ROS levels through the ROS/Bcl-2/Bax/Caspase-3 pathway, activating the Nrf2/ARE signaling pathway to regulate oxidative stress, increasing ATP synthesis, thereby promoting energy production and the healing of diabetic wounds. <sup>22,23</sup> The important active components for promoting the healing of diabetic wounds include Notoprotein R1, deoxycorticosterone, ursolic acid, and 4-methoxyphenol. <sup>24</sup>
Qing Re Huo Xue Tang (QHD)	PI 3 K/AKT Signaling Pathway		Li et al found that the traditional Chinese medicine formula Qing Re Huo Xue Tang (QHD) significantly reduces the expression of angiogenesis proteins HIF-1 $\alpha$ , FLT-1, and VEGF; lowers cytokine levels, increases the expression of IL-10 and wound repair genes, promoting wound healing with anti-inflammatory effects. The effects and mechanisms of QHD on other types of wounds such as radiation injury and diabetic ulcers require further research and exploration. <sup>25</sup>

Nanofibrous scaffolds mimic the extracellular matrix, providing high surface area for cell adhesion and growth factor delivery, while hydrogel microneedles enable painless, efficient transdermal drug administration. Future challenges include elucidating NPHM self-assembly mechanisms, optimizing multifunctional co-assembly systems for synergistic multi-target therapy, and designing smart biomaterials responsive to spatiotemporal cues in the wound

microenvironment. Clinically oriented research must enhance material stability, develop stimulus-responsive release systems, and refine precision drug delivery. Targeting cytoskeletal dynamics (eg, tissue fluidity) and signaling pathways (JAK/STAT, TLR) may further modulate healing.<sup>174,175</sup> Notably, NPHM self-assembly principles may bridge traditional herbal medicine and modern science, offering novel insights into regenerative potential through microenvironmental modulation. Although challenges persist, advanced delivery strategies hold promise to unlock host-driven healing and improve therapeutic outcomes in chronic wound management.

## Data Sharing Statement

Data will be made available on request from the corresponding author, Peng Liu and Zilin Wang.

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## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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