The combination of bioactive herbal compounds with biomaterials: A review on promising opportunities for regenerative medicine

Guoying Zhou[1§], Ruojiao Xu[1§], Thomas Groth[2], Yanying Wang[3], Hua Ye[4,*], Xiaobing Dou[1,*]

[1]College of Life Sciences, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, China

[2]Department Biomedical Materials, Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Halle (Saale) D-06099, Germany

[3]The Second Clinical Medical College, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, China

[4]Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Oxford OX1 2JD, UK

*Address correspondence to:

Xiaobing Dou, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou, 310053, PR China. E-mail address: xbdou77@163.com

Hua Ye, Institute of Biomedical Engineering, Department of Engineering Science, University

of Oxford, Oxford OX1 2JD, UK. E-mail address: hua.ye@eng.ox.ac.uk

Abstract

Regenerative medicine aims to restore the function of diseased or damaged tissues and organs by cell therapy, gene therapy, and tissue engineering, along with the adjunctive application of bioactive molecules. Traditional bioactive molecules such as growth factors and cytokines have shown great potential in regulation of cellular and tissue behavior, but have the disadvantages of limited source, high cost, short half-life and side effects. In recent years, herbal compounds extracted from natural plants/herbs have gained increasing attention. This is not only because herbal compounds are easily obtained, inexpensive, mostly safe and reliable, but also owing to their excellent effects including anti-inflammatory, antibacterial, antioxidative, proangiogenic behavior and abilty to promote stem cell differentiation. Such effects also play important roles in the processes related to tissue regeneration. Furthermore, the moieties of the herbal compounds can form physical or chemical bonds with the scaffolds, which contributes to improved mechanical strength and stability of the scaffolds. Thus, the incorporation of herbal compounds as bioactive molecules in biomaterials is a promising direction for future regenerative medicine applications. Herein, an overview on the use of bioactive herbal compounds combined with different biomaterial scaffolds for regenerative medicine application is presented. We firstly introduce the classification, structures and properties of different herbal bioactive components and then provide a comprehensive survey on the use of bioactive herbal compounds to engineer scaffolds for tissue repir/regeneration of skin, cartilage, bone, neural, and heart tissues. Finally, we highlight the challenges and prospects for the future development of herbal scaffolds towards clinical translation. Overall, it is believed that the combination of bioactive herbal compounds with biomaterials could be a promising perspective for next generation of regenerative medicine.

Keywords

Regenerative medicine, Herbal compounds; Biomaterials, Skin regeneration, Bone regeneration, Neural regeneration, Myocardial repair

The combination of bioactive herbal compounds with biomaterials: A review on promising opportunities for regenerative medicine

Guoying Zhou[1][§], Ruojiao Xu[1][§], Thomas Groth[2], Yanying Wang[3], Hua Ye[4,*], Xiaobing Dou[1,*]

Graphic abstract
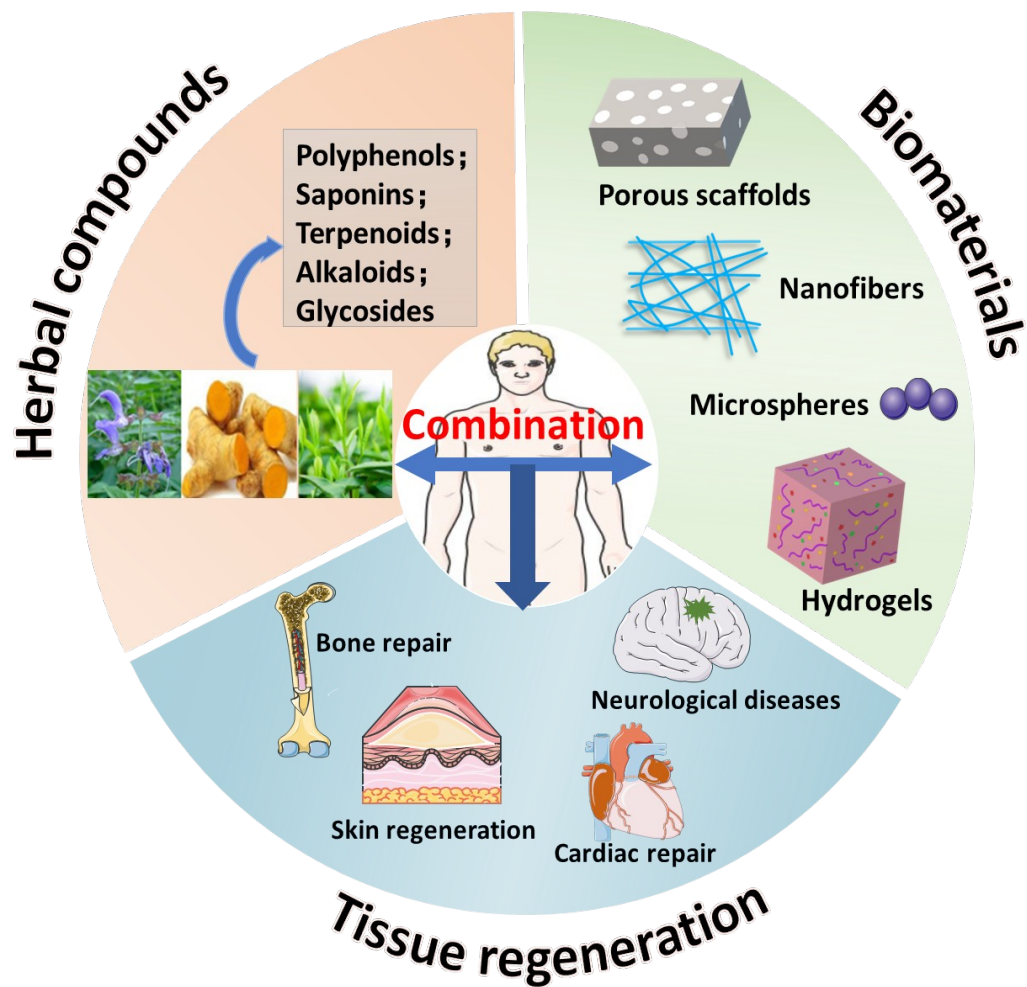
1. Introduction

Tissue and organ dysfunction caused by trauma, diseases and aging is a great challenge for human's health and life quality[1]. Once the tissue is damaged, the microenviroment surrounding the cells is also destroyed, which normally leads to highly disordered repair and loss of function of the tissue[2]. Therefore, one of the key considerations for tissue repair/regeneration is to construct biomaterials with appropriate bioactive molecules to modulate the microenviroment, cell ingrowth and benefit for effective tissue repair/regeneration and functional recovery[3].

To address this issue, enormous amounts of studies have focused on the delivery of various cytokines to endow the scaffolds with improved cell/tissue affinity and regenerative ability[4]. Cytokines are a class of active proteins or peptides that are produced in living organisms, which have extensive regulatory effects on cell growth, cell differentiation, apoptosis, inflammation, wound healing, blood vessel formation and so on[5]. Such functions are also important for the processes of tissue integration and functional restoration. Despite of the significant evidence by in vivo and in vitro studies, the strategy for delivery of cytokines have limitations such as the limited source, high production cost and short half-life[6].

Chinese herbs have been used in clinical practice for prevention and treatment of diseases for thousands of years[7]. Especially, since Tu Youyou won the Nobel Prize due to the discovey of artemisinin (an active compound isolated from Artemisia annu), the study of herbal extracts/compounds has become a research hotspot. A large amount of studies have demonstrated the superior pharmacological effects of herbal extracts/compounds on various diseases like dermatitis, wound healing, osteoarthritis, bone fracture, neurological diseases, heart diseorders and so on[8-10]. These benefit effects can be attributed to the multiple effects of herbal extracts such as anti-inflammation, anti-bacterial, antioxidation, anti-tumor, immunomodulation and pro-angiogenesis properties, which may also promote regeneration during regenerative medicine applications[11,12]. At the same time, the herbal extracts have the advantages of good safety, high effectiveness and low production cost. Therefore, the combination of bioactive herbal extracts/coumpounds with biomaterials has been considered as a promising direction in the field of regenerative medicine[8,13].

In this review, we provide a broad overview on the use of bioactive herbal compounds combined with biomaterial scaffolds in tissue repair and regeneration including skin, cartilage, bone, neural and heart tissues. Firstly, we start with the introduction of the herbal bioactive compounds, focusing on their chemical structures and properties related to tissue repair/ regeneration. Afterwards, we will focus on recent insights gained from various herbal compounds combined with functional materials which are developed by different fabrication methods and their applications in regenerative medicine. Finally, we will discuss the

challenges and opportunities for use of bioactive herbal compounds in regenerative medicine for clinal application in the future.

2. Bioactive herbal compounds: classification, structures and properties

Herbal extracts represent a mixture of active ingredients obtained after extraction and concentration using modern technologies and are used in herbal medicine. Indeed, various crude herbal extracts have been employed previously to construct herbal scaffolds for tissue repair and regeneration which is reported elsewhere[8,14]. Here, we limit our review on the engineering of scaffolds by using various herbal compounds of well-defined composition. Phytochemicals of interest can be classified into polyphenols, saponins, terpenoids, anthraquinones, alkaloids and glycosides[15,16]. The chemical structures of the different herbal compounds that have been used in tissue repair/regeneration were summarized in Figure 1.
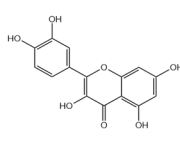
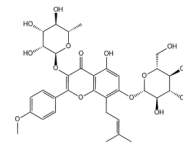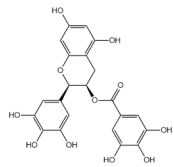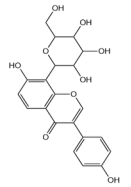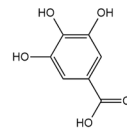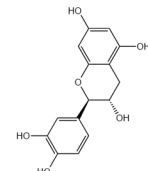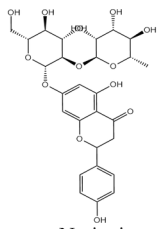(A) Polyphenols
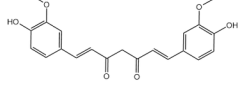
Curcumin
Resveratrol
Quercetin
Icariin
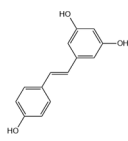
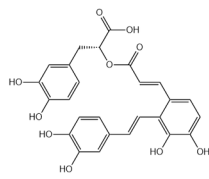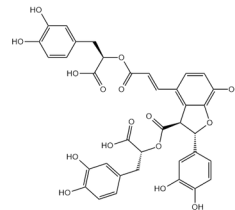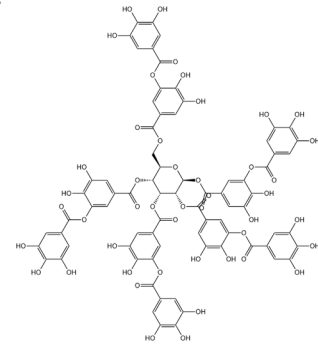Epigallocatechin-3-gallate (EGCG)
Puerarin
Gallic acid
Catechin

Naringin
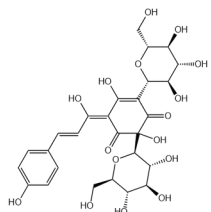Salvianolic acid A
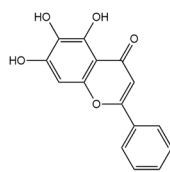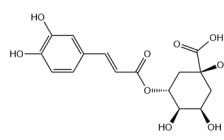Salvianolic acid B

Hydroxysafflor yellow A
Baicalin
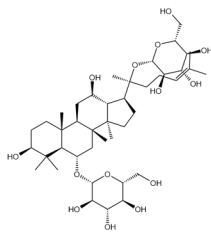Chlorogenic acid
Tannic acid

(B) Saponins
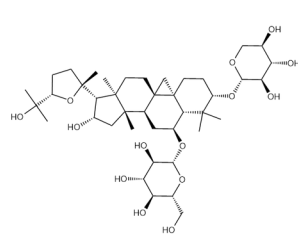
(C) Terpenoids

Ginsenoside
Astragaloside
Ursolic acid
Paeoniflorin
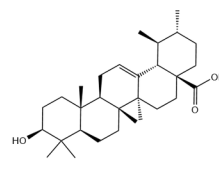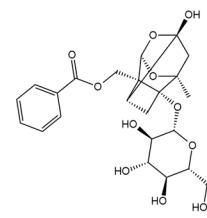
(D) Anthraquinones
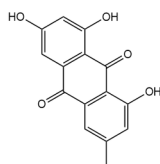
(E) Alkaloids
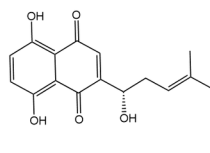
(F) Glycosides
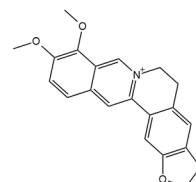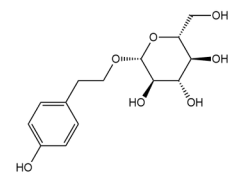
Emodin
Shikonin
Berberine
Salidroside

Figure 1. The chemical structures of the various herbal coumpounds including polyphenols (A), saponins (B), terpenoids (C), anthraquinones (D), alkaloids (E) and glycosides (F).

2.1 Polyphenols

Polyphenols are phenolic compounds that carry one or more hydroxyl group and are widely used in herbal medicines. Examples of herbal polyphenols applied in tissue regeneration include curcumin, resveratrol, quercetin, icariin, epigallocatechin-3-gallate (EGCG), tannic acid, puerarin, gallic acid, catechin, naringin, salvianolic acid A and B, baicalin, chlorogenic acid and hydroxysafflor yellow A (Figure 1A).

Polyphenols have shown numerous biological activities and health benefits such as excellent antioxidant, anti-inflammatory, and anti-microbial activities [17]. It is known that free radicals such as reactive oxygen species (ROS) play important roles in alterations of macromolecular and cellular elements in tissues which can exacerbate tissue damage[18]. Additionally, tissue damage always induces inflammation. A moderate inflammatory response activates the body's defenses against microorganisms, foreign materials, and damaged cells, which are favorable for tissue regeneration[19]. However, excessive inflammatory responses upon tissue injury, especially in the case of bacterial infection, will lead to further damage of the tissue and result in unpleasant outcomes for tissue repair[20]. The hydroxyl groups in polyphenols serve as hydrogen donors to reduce oxygen from excited state to a more stable trilinear state, leading to reduction of oxygen radical production[21]. Besides, polyphenols can inhibit the activity of free radical-producing enzymes such as cyclooxygenase (COX), lipoxygenase (LOX) and NADPH oxidase (NOX) and up-regulate endogenous antioxidant enzymes to reduce oxidative damage[22]. Additionally, polyphenols can inhibit macrophage function by inhibition of enzymes associated with pro-inflammatory properties, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), thereby reducing the expression of pro-inflammatory factors tumor necrosis factor-alpha (TNF-α), interleukin-1(IL-1) and IL-6 secreted by macrophages[23]. Furthermore, polyphenols down-regulate NF-κB signalling pathway, modulate mitogen-activated protein kinase (MAPK) and also suppress toll-like receptor (TLR) and pro-inflammatory genes' expression[24]. Moreover, polyphenols exert also antibacterial activities which might be related to its

inhibition of nucleic acid synthesis, inhibition of microbial energy metabolism and destruction of biofilm function[25]. Therefore, the herbal polyphenols have been considered as ideal candidates for improving tissue regeneration outcomes. To date, a number of studies have delivered different herbal polyphenols in both in vivo and in vitro experiments for different tissue repair/regeneration applications including skin, cartilage, bone, neural, heart tissues and so on. The detailed information of the findings will be provided in the next section.

2.2 Saponins

Saponins are a large family of herbal isolated compounds containing a steroid or triterpenoid aglycone linked to one or more oligosaccharide moieties (Figure 1B). For instance, ginsenoside and astragaloside are two examples of herbal saponins that have been used for tissue regeneration. For example, ginsenoside Rg1, ginsenoside Rb1 and astragaloside IV have been shown to possess anti-inflammatory, neuroprotective and cardioprotection effects, which hold great therapeutic potential for neural regeneration in diseases like stroke, traumatic brain injury, Parkinson's disease, as well as myocardial repair and regeneration[26,27]. The action mechanism of anti-inflammatory effects of ginsenoside was attributed to the negative regulation of pro-inflammatory cytokine expressions (TNF-α, IL-1β, and IL-6) and enzyme expressions (iNOS and COX-2), but also the anti-inflammation and pro-healing effects derived by M2-polarized macrophages[28]. Astragaloside IV can significantly increase the phosphorylation levels of JAK2 and STAT3, reduce the expression levels of inflammatory factors such as IL-1β, IL-6 and TNF-α, decrease the content of malonaldehyde (MDA) and ROS, and increase the concentration of SOD, thus reducing inflammation and oxidative stress[29]. In addition, ginsenoside Rb1, Rh3 and astragaloside IV have also been reported to be helpful in healing of myocardial infarction[30]. Ginsenoside Rb1 prevents spinal cord ischemia-reperfusion injury (SciI) -induced apoptosis of rat spinal nerve cells by down-regulating Ask-1 phosphorylation, caspase-3 levels and Bax/Bcl-2 ratio[31]. Ginsenoside Rh3 inhibits Caspase-3 in myocardial tissue, up-regulates the expression of anti-apoptotic protein Bal-2 and inhibits the expression of Bax protein in cardiomyocytes, thereby reducing the apoptosis of cardiomyocytes, and improving the myocardial ischemia reperfusion[32]. Astragaloside IV has been confirmed to promote angiogenesis and

cardioprotection after myocardial infarction partly through the activation of PTEN/PI3K/Akt signalling pathway[33].

2.3 Terpenoids

Terpenoids represent a large class of herbal compounds with a basic structure of isoprene units such as ursolic acid and paeoniflorin (Figure 1C). Ursolic acid has been confirmed to have several biological and pharmacological effects including anti-inflammatory, anti-cancer, anti-tumor as well as neuroprotective effects, which are employed for neural regeneration after sciatic nerve injury[34]. The anti-inflammatory mechanisms of ursolic acid mainly include suppression of the activities of lipoxygenase, cyclooxygenase and phospholipase, and decrease of the production of nitric oxide and reactive oxygen species, inhibition of the activation of the signal pathway, downregulation of the expression of inflammatory factors, as well as the inhibition of the activities of elastase and complement[35]. The anti-inflammatory effects of paeoniflorin have been evident by many experimental models related to different inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma[36]. The mechanism of its anti-inflammatory activity is that paeoniflorin inhibits the infiltration of neutrophils and macrophages, reduces the number of F4/80+CD68+ macrophages and the production of related cytokines (TNF-α, IL-1β, IL-6, IL-12, IL-23, and iNOS), as well as down-regulates the production of Th1/Th17 cell-related cytokines[37]. Moreover, paeoniflorin has been reported to be promising not only for treatment of neurodegenerative diseases via modulation of Ca^{2+} and ROS homeostasis, but also for promoting diabetic wound repair through reducing inflammation, promoting collagen deposition and microvascular formation[38], suggesting the great potential of paeoniflorin in various tissue regenerations.

2.4 Anthraquinones

Anthraquinones are derived from anthracenes with two keto groups at positions 9 and 10 as seen in Figure 1D. The examples of herbal anthraquinones include emodin and shikonin. Anthraquinones are also attracting much attention during medical applications due to their good pharmacological activity[39]. Firstly, anthraquinones play antibacterial role by inhibiting

bacterial respiration and metabolism, destroying bacterial cell membrane and cell wall, as well as affecting the synthesis of protein nucleic acid and other biological macromolecules[40]. In addition, anthraquinones could inhibit activation of NF-κB and activator protein-1 (AP-1) pathways by suppression of upstream signaling including IL-1 receptor-associated kinase 4 (IRAK1), p38, Src, and spleen tyrosine kinase (Syk), and thus exert anti-inflammatory activities [41]. Furthermore, it was demonstrated that the anthraquinones possess excellent antioxidant properties, which for both emodin and aloe-emodin was attributed to their reducing and scavenging ability on hydroxyl radicals[42].

2.5 Alkaloids

Alkaloids are a class of nitrogen-containing alkaline organic compounds with berberine as an example (Figure 1E). For instance, berberine is the main active ingredient of the Chinese medicine Huanglian, which has been widely known due to its excellent antibacterial, anti-fungal and antiviral properties, and thus are well suitable for infected diseases such as infected wounds, gastrointestinal infections and conjunctivitis[43]. The mechanism of its antibacterial activity is due to the inhibition of the synthesis of bacterial proteins associated with the growth of bacteria, which ultimately induced cytoplasm pyknosis and bacterial death[44]. In addition, the antifungal activity of berberine was reported to be related with mitochondrial dysfunction[45]. Berberine stimulates formation of ROS in fungal mitochondria, followed by production of oxidative stress and destruction of mitochondrial structure, leading to fungal apoptosis through mitochondrial pathway[45]. In addition, berberine is commonly used in the treatment of gastrointestinal diseases such as enteritis, which is attributed to the reduced levels of pro-inflammatory cytokines such as TNF, IFN-γ, KC and IL-17 in colon tissues[46,47].

2.6 Glycosides

Glycosides represent a group of compounds formed by connecting a sugar or a glycolic acid with another non-sugar substance through its terminal carbon atom (Figure 1F). They are reported to play several known functions, including anti-inflammatory, antibacterial, immunomodulatory and neural protective effects[48]. For instance, salidroside, a phenylpropanoid glycoside derived from Rhodiola rosea L, has been demonstrated a

significant role in neural tissue engineering to promote nerve regeneration[49]. Studies have reported that salidroside reduces inflammation and neuronal damage after middle cerebral artery occlusion (MCAO) with reperfusion by selectively inhibition of endothelial complement activation, suggesting the protection potential of salidroside in cerebral ischemia-reperfusion injury[50].

3. Application of bioactive herbal compounds in various tissue repair/regeneration applications

The combination of bioactive herbal compounds with biomaterial scaffolds can not only integrate the advantages of both components, but also endow sustained release of herbal compounds and thus improve the bioavailability[51]. On the other hand, the incorporation of herbal compounds can improve the biocompatibility and pharmacological effects of the biomaterial scaffolds. Furthermore, the herbal compounds also contribute to the physiochemical properties of the biomaterials including microstructure, wetting properties, mechanical strength, biodegradation behavior and so on[52]. Such physiochemical properties are also of particular importance since they can modulate the cellular and tissue behaviors during tissue repair[53,54]. Therefore, the combination of bioactive herbal compounds with biomaterial scaffolds can serve as a promising strategy for various tissue repair/regeneration fields, to create bioactive scaffolds with better regenerative capacities[55,56].

Currently, different fabrication techniques have been developed to engineer herbal constructs including hydrogel formation, electrospinning, drug carrier microsphere, decellularized scaffolds, freeze-drying, 3D printing and so on[57-60]. Hydrogels are three-dimensional (3D) networks of hydrophilic polymers which can hold large amounts of water and offer a stable and favourable environment for cell growth[61]. Additionally, hydrogels can endow sustained release of the loaded pharmacologically active molecules which can improve the retention time and thus exert a better treatment outcome for tissue repair and regeneration [62]. However, herbal compounds with poor solubility cannot be incorporated directly to the hydrogel. In this respect, microspheres, micelles and nanoparticles can overcome this problem and load the compounds at a high encapsulation efficiency, and at the same time, enhance the drug durability and stability[63-65]. Thus, the lipophilic herbal compounds can be loaded into

microspheres, micelles and nanoparticles firstly and incorporated into hydrogel[66,67]. Electrospinning is a widely used method for fabrication of nanofibrous scaffolds mimicking the nature structure of extracellular matrix (ECM), which has been also employed to construct herb-containing scaffolds. Both hydrophilic and lipophilic herbal compounds can be incorporated to fibers by choosing different solvents or different electrospinning methods like simple blending, coaxial or emulsion electrospinning for skin and other tissue repair applications[68,69]. In addition, decellularized scaffolds that are composed by a number of ECM components such as collagen, elastin and glycoproteins, can endow the scaffolds with advantages including low immunogenicity, high biocompatibility, excellent structural functions as well as biological functions[70]. Therefore, the combination of herbal compounds together with decellularized scaffolds has also been considered as a promising strategy for applications in regenerative medicine. Besides, freeze-drying or lyophilization is a method to produce porous scaffolds through dehydration of mostly heat-sensitive materials, through which the herbal compounds can also be incorporated[71]. The combination of different bioactive herbal compounds with biomaterials through various fabrication techniques and their applications in tissue repair and regeneration is then reported herein.

3.1 Skin tissue regeneration and wound healing

Although skin has a quite high regeneration capacity, the repair efficiency was inhibited particularly in the cases of large area of skin loss, severe trauma, as well as chronic wounds such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers[72]. The conventional methods to treat skin damage such as autologous/allograft split or full-thickness skin graft are constrained by limited sources, infections and scar formation[73]. In this regard, development of wound dressing from biomaterials has been emerged as a promising alternative approach to treat various skin-related disorders[74]. The studies that combined different herbal compounds with biomaterials for skin tissue repair/regeneration applications were summarized in Table 1.

3.1.1 Curcumin

Curcumin is a polyphenol compound isolated from turmeric with numerous pharmacological effects such as anticoagulant, antioxidant, anti-cancer and anti-inflammatory

activities[59]. It has been reported that the anti-inflammatory and antioxidant properties are accountable for the favorable effects of curcumin on skin wound healing[75]. Curcumin can reduce inflammation through inhibition of the action of inflammatory mediators such as cyclooxygenase-2 (COX-2), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α)[60]. Additionally, curcumin can control the expression of the gene for nuclear transcription factor-κB (NF-κB), which lowers the amounts of reactive oxygen species (ROS) and weakens the oxidative stress response at damaged sites[76]. Despite of the multiple benificial activities, it has the limitations of poor water solubility, rapid drug metabolism and unsatisfactory drug stability[66]. In order to solve these problems, curcumin was loded into different macro- or nanocarriers such as microspheres, micelles and nanoparticles, which were then combined with different dressing systems such as hydrogels, nanofibers, and decellularized scaffolds to treat damaged skin, illustrating a promising therapeutic strategy for skin tissue repair/regeneration [77-80].

Various hydrogel systems have been applied for delivery of curcumin to improve the wound healing outcomes. For this purpose, curcumin nanoparticles (CNPs) were encapsulated in gelatin microspheres (CNPs@GMs) and subsequently added to thermal-sensitive hydrogels to explore the effects on chronic cutaneous wound repair[81]. The results illustruated that the hydrogel system can respond to matrix metalloproteinases (MMPs) and releases curcumin specifically at non-healing wound sites to increase the drug effects, resulting in improved healing of diabetic wounds[81] (Figure 2A). Zhang et al. designed a hydrogel delivery system based on glycosaminoglycans to regulate the wound microenvironment, where the curcumin was encapsulated in the hydrogel by micellization to achieve ROS scavenging and anti-

inflammatory function[82]. In another study, curcumin nanoparticles were loaded in hydrogel ,

which was found improved healing process on diabetic wounds, characterized by enhanced re-epithelization, intact dermo-epidermal junction, reorganization of the dermis with significantly increased collagen deposition and VEGF expression[83]. In addition, encapsulation of nanotechnologically-modified curcumin and epidermal growth factor (EGF) into hydrogel was shown to exhibit significantly antioxidant, anti-inflammatory and migration-promoting

effects in vitro, as well as improved wound healing effects in terms of ideal re-epithelialization, granulation tissue formation, and skin appendage regeneration in vivo[84] (Figure 2B). Such hydrogel systems laden with curcumin could serves as drug delivery platforms for sustained and targeted delivery of hydrophobic compounds for skin regenenration[83-85].

Besides, Yang et al. applied electrostatic spinning technique to incorporate curcumin/ lithospermi radix extracts with a bilayer nanofiber scaffold, which was found improved wound healing speed in a rat model with diabete[86]. The results revealed that curcumin acted as an anti-inflammatory agent by lowering the expression of interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), so as to accelarate wound healing[86]. Besides, silver@curcumin nanoparticles and electrospun chitosan nanofiber developed by Liu et al. demonstrate remarkable inhibition of bacteria and promote wound healing and reduce scar formation[87] (Figure 2C). In addition to the effects for accelerated wound closure, the regeneration of skin appendages such as skin follicles and sebaceous glands can also be enhanced by curcumin-loaded cellulose nanocrystal film[88].

In addition, the combination of herbal compounds together with decellularized scaffolds has also been considered as a promising strategy for applications in tissue engineering. For instance, in a study by Hemant et al, the goat small intestine submucosa (G-SIS) was decellularized, followed by curcumin incorparation[89]. The fabricated curcumin-embedded DG-SIS scaffolds demonstrated sustained release of curcumin and improved biodegradable, biocompatible, antibacterial and free radical scavenging capacities, suggesting a potential herbal construct for wound healing and skin tissue engineering[89]. Singh et al. fabricated a nanoceria laden decellularized extracellular matrix-based curcumin releasing nanoemulgel system and the results showed the system allowed sustained release of curcumin with free radical scavenging ability and antibacterial properties for full-thickness wound healing[90] (Figure 2D).

It's also worth noting that curcumin treatment can also affect the physicochemical properties of the nanofibrous scaffold[91]. For instance, the addition of curcumin resulted in increase in the hydrophilicity of the nanofibers, which is favorable for cell adhesion and

proliferation[92]. Additionally, Jirofti et al. reported that curcumin could enhance the mechanical properties of nanofibres, leading to a 2-3 fold increase in tensile strength, which enabled improved adaptability to the contours of the wound[93].

Overall, the application of curcumin combined with different biomaterial scaffolds provides a promising prospect to effectively promote wound healing and accelarate skin tissue regeneration.
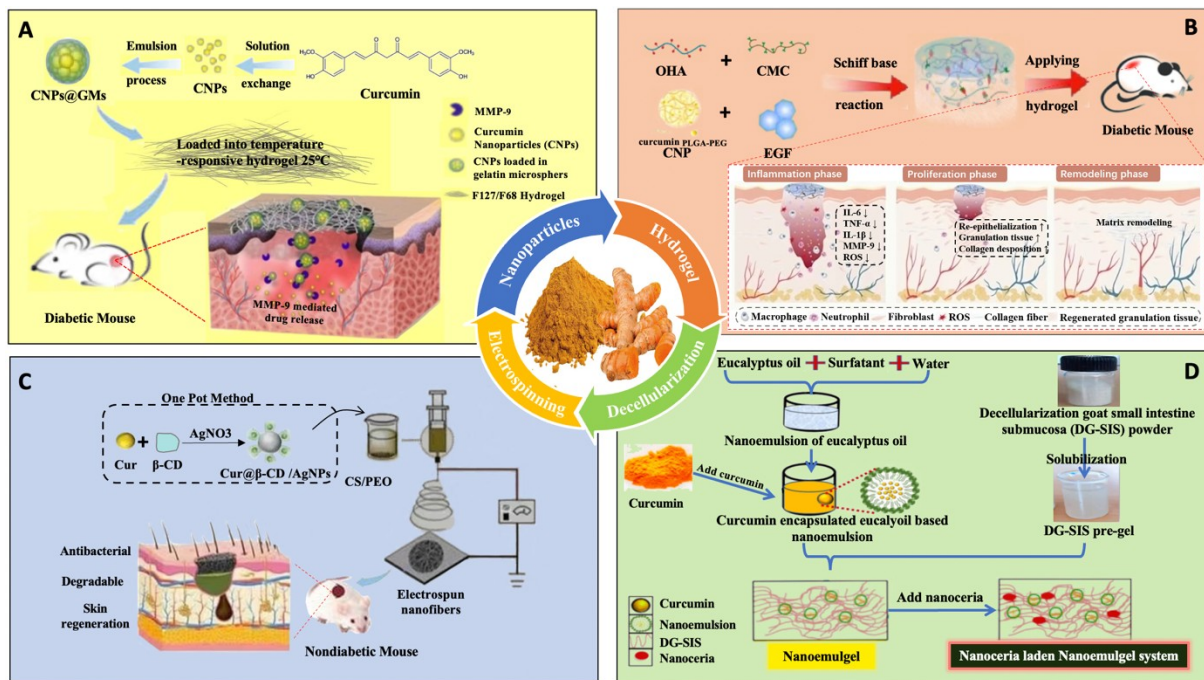
Figure 2. Combined application of curcumin and different biomaterials to accelerate wound healing and skin tissue regeneration. (A) Curcumin nanoparticles (CNPs) were fabricated using the solution exchange approach firstly and then loaded into gelatin microspheres (CNPs@GMs) using the emulsification procedure, followed by mixing with thermosensitive hydrogel to fabricate the final CNPs@GMs/hydrogel for improving dermal wound healing through matrix metalloproteinase-9 (MMP-9) mediated curcumin release[81]. (B) Hyaluronic acid (HA) and chitosan hydrogels (OHA-CMC) were prepared by Schiff base reaction and then encapsulated with nanotech modified curcumin and epidermal growth factor (EGF) in hydrogels to address the major issues in the various stages of diabetic wound healing[84] (Figure 2B). (C) A composite chitosan electrospun nanofibrous material containing curcumin@β-cyclodextrin nanoparticles (Cur@β-CD/AgNPs) made of silver and curcumin showed

synergic effects on anti-bacterial and wound healing process[87]. (D) The decellularized ECM of caprine small intestine submucosa (DG-SIS), curcumin-encapsulated eucalyptus oil-based nano emulsion (Ce), and nanoceria (NC) were combined together to create DG-SIS/Ce/NC nanoemulgel system targeting for promotion of full-thickness wound healing[90]. Reproduced with permission[81,84,87,90].

3.1.2 Tannic acid

Tannic acid is a polyphenolic compound isolated from a variety of plants and possesses excellent pharmacological functions containing antibacterial, antiviral, anti-inflammation and antioxidant properties[94,95]. Owing to beneficial therapeutic effects, tannic acid has been used widely in the treatment of bacterial infections, skin herpes, pharyngitis and many other diseases[96]. The combination of tannic acid as a functional component with hydrogels to prepare different hydrogel systems has been confirmed as an effective avenue for skin regeneration[97]. Notably, due to the presence of hydroxyl and carboxyl groups, TA can act as a natural cross-linking agent for biomaterials through hydrophobic interaction and hydrogen bonding[98,99]. As a result, the biomaterials are endowed not only with the pharmacological effects of TA, but also improved physiochemical proprties such as enhanced mechanical strength, increased adherent capacity, as well as effects on the biodegradability, porosity and morphology of biomaterial scaffolds[99,100].

For example, a bioactive skin-mimicking hydrogel was fabricated through the combination of tannic acid (TA) and imidazolidinyl urea reinforced polyurethane (PMI) (TAP hydrogel) [101]. The TAP hydrogel was shown to possess excellent mechanical properties, sufficient adhesion, outstanding hemostatic activity, anti-inflammatory, antibacterial, and antioxidant properties, which resulted in outstanding therapeutic efficiency with even infected skin wounds on diabetic mice[101]. Besides, the incorporation of iron ions/TA chelates into hydrogels can improve the performance in inflammation modulation, angiogenesis, and tissue regeneration[102]. However, conventional metal-phenolic materials (MPNs) crosslinked only by physical hydrogen or coordination bonds, exhibit poor solution stability[103]. Li et al. prepared copper-coordinated poly(tannic acid) nanoparticles (Cu-PTA NPs) by dual cross-linking methods of covalent and coordination bonds, showing a long-lasting controlled release of

tannic acid, and leading to excellent antimicrobial, antioxidant, and anti-inflammatory effects. Additionally, plenty of other studies have confirmed the wound healing-promoting effects of hydrogels loaded with TA, such as TA-modified gelatin (gel-TA) hydrogel[104], TA-bound sodium alginate/poly(N-vinylcaprolactam) (AG/PVCL) hydrogel[105], TA-Fe(III)(TA-Fe) nanoparticles-contained agarose (AG)-based hydrogel[106] and so on.

In addition to the hydrogel system, TA has been incorporated to electrospun nanofibers for wound treatment. In the study by Albright et al., polypeptide-based block copolymer micelles were deposited onto the surfaces of PCL/collagen nanofibers using TA as a binding partner and this system suggested great promise as infection-mitigating skin graft for wound healing[107].

3.1.3 Gallic acid

. Gallic acid is one of the main active ingredients in several traditional Chinese medicines such as gallnut, dogwood, peony bark, saxifraga stolonifera, and rheum palmatum. Its well-known pharmacological activities include anti-inflammatory, anti-cancer, antioxidant and cardiovascular disease(CVD) preventing effects[108]. It was reported that gallic acid is a broad-spectrum inhibitor of NLRP3 inflammatory vesicles and inhibits NLRP3 inflammatory vesicle activation by reducing mitochondrial reactive oxygen species (mtROS) production through upregulation of Nrf2 expression[109]. In addition, the researchers performed intervention studies with gallic acid and monitored alterations in DNA stability in lymphocytes by single cell gel electrophoresis (SCGE) analysis. The results indicated that a small amount of gallic acid could prevent oxidative DNA damage and reduce inflammation[110]. Therefore, gallic acid has also been considered as one of the candidate herbal compounds for skin repair/regeneration.

In a recent study, gallic acid modified chitosan hydrogel (CS-GA) was prepared by glow discharge plasma (GDEP) technique, which was shown to exhibit excellent antioxidant properties, high biocompatibility and haemocompatibility, as well as fast haemostasis and wound healing-promoting activities[111]. Similarly, the GA-HGC hydrogel formed by coupling thermosensitive hexanoyl glycol chitosan (HGC) with gallic acid (GA) was demonstrated to

possess good self-healing properties, high compressive strength, strong tissue adhesive scapacity and suitable biodegradability[112]. Besides, cryogels generated from chitosan (CS), oxidized gallic acid (OGA), and heme (HE) showed excellent cytocompatibility and better hemostatic properties than gauze and gelatin sponges[113]. In addition, nanocomposite scaffold with gallic acid-loaded chitosan nanoparticle was synthesized by ionic gel method using tripolyphosphate (TPP) as cross-linking agent. Results showed the nanocomposite scaffold enhanced re-epithelialization, accelerated fibroblast migration, angiogenesis, hexosamine synthesis, collagen deposition and promoted wound healing, revealing a promising wound dressing material for skin tissue regeneration[114].

3.1.4 Quercetin

Quercetin is a flavonoid extracted from many plants, which possesses a wide range of pharmacological activities including anti-cancer, anti-inflammatory, antiviral properties and so on[115,116]. Thus, it has also been discovered and applied widely in skin repair/regeneration. Vedakumari et al. constructed a new quercetin-chitosan-fibrin (Q-CF) scaffold through imersion of chitosan-fibrin scaffold in quercetin, followed by homogenized and lyophilized[117]. The results indicated that the Q-CF scadffold exhibited suitable mechanical strength, good biocompatibility and bactericidal activities as well as excellent wound healing-promoting effects, which can serve as a promising wound dressing material[117]. To combat antibiotic abuse, Wang et al. developed a non-antibiotic wound dressings constructed by semi-interpenetrating network (semi-IPN) hydrogels based on quaternized chitosan (QCS) and polyacrylamide (PAM), which were found enhanced antimicrobial activity against Staphylococcus aureus and Escherichia coli after quercetin incorporation[118]. In another study, inspired by ancient Chinese medicine for hair regeneration in burned skin, the researchers fabricated PCL/gelatin electrospun fibrous membranes composed by quercetin-copper (Qu-Cu) chelates, which were found stimulated hair follicle regeneration and wound healing[119]. Such fibrous membrane was found to promote wound healing and particularly stimulate the regeneration of skin accessory structures such as sweat glands and hair follicles[119]. These findings reveals the values of analysis of bioactive components in ancient Chinese

prescription for the design of novel bioactive materials in tissue repair/regeneration applications.

3.1.5 Puerarin

Puerarin, a natural isoflavone, is the main active component of Pueraria lobata[120]. It has been confirmed that puerarin attenuates oxidative damage in vascular endothelial cells by improving mitochondrial respiratory function and attenuates inflammation by regulating NLRP3 inflammatory vesicle activation[121,122]. Zeng et al. constructed a chitosan-based hydrogel containing puerarin (Chitosan@Puerarin hydrogel) to accelerate diabetic wound healing through inhibition of miR-29ab-mediated inflammatory axis, evidenced by the suppression of M1-polarization and pro-inflammatory cytokine production[123]. Ou et al. incorporated puerarin via polydopamine nanoparticles into polyethylene glycol diacrylate (PEG-DA) hydrogel. This hydrogel was found to accelerate wound healing by reducing oxidative damage[124]. Likewise, polydopamine/puerarin (PDA/PUE) nanoparticles were doped into polyethylene glycol diacrylate hybrid hydrogels (PEG-DA/PDA/PUE), and the hydrogels exhibited good cell proliferation and antioxidant activities[125]. Inspired by the grinding technique of traditional Chinese medicine, Chen et al. fabricated Chinese-herb-based (CS@PUE) hydrogels by self-assembly of chitosan (CS) and puerarin (PUE)[126]. The CS@PUE hydrogels exhibited extraordinary antibacterial and wound closure rate in mouse full-thickness and infected full-thickness wound models[126]. Notably, different amounts of PUE incorporation exerted a fine control on the hydrogel formation process, physicochemical properties as well as biological activities[126]. This finding also reveals the importance of using Chinese herbal components to construct novel bioactive materials for tissue repair/regeneration.

3.1.6 Berberine

Berberine is a quaternary alkaloid extracted from the Chinese herb Huanglian, which has been demonstrated to possess hypoglycemic, anti-tumor, anti-inflammatory and antibacterial properties that are well suitable for skin-related disorders particularly like infected wounds[43,127]. In a recent study, Li et al. constructed a temperature-sensitive in situ gel in which

berberine liposomes functioned as a barrier to bacterial toxins, resulting in a reduction in the number of wound biofilms to promote healing of infected wounds[128]. Besides, berberine was loaded into biologically active microalga spirulina to create a bioactive hydrogel[129]. Based on this method, synergistic quorum sensing blockade and chemical-photodynamic therapy were achieved to destroy the biofilm, down-regulate expression of virulence factors, which accelerated the methicillin-resistant staphylococcus aureus (MRSA)-infected diabetic wound healing[129]. Additionally, it has been demonstrated that berberine-included nano-hydrogels increase the expression of VEGF, CD31 and SMA while decrease the expression of NF-κB, TNF-α, and IL-6 by activating Sirt1, which promote wound healing in diabetic rats[130]

3.1.7 Others

Aiaticoside (derived from Apiaceae) was incorporated into polyvinyl alcohol/polyethylene glycol (PVA/PEG) hydrogel and the resulting hydrogel effectively accelerated wound healing in terms of epithelial and granulation formation and moderate collagen deposition[131]. Besides, asiatic acid was combined with porous electrospun fibrous scaffold (AA-PL) to accelerate epithelial re-epithelialization by alleviating high oxidative stress and inflammation in diabetic wounds[132]. Additionally, to overcome the low solubility of astragaloside, it was firstly incorporated into solid lipid nanoparticles (SLNs) nanoparticles by solvent evaporation method followed by loading of the nanoparticles into the carbomer gel to prepare the astragaloside IV-loaded nanoparticle-enriched hydrogel. The resulting hydrogel system was confirmed to have multiple beneficial effects for wound healing including the maintaining of type III/type I collagen ratio, promotion of angiogenic effects as well as inhibition of scarring complications[133]. In another study, hydroxy saffron yellow pigment A (HSYA) was included to the hydrogel together with desferrioxamine (DFO) and was shown to promote angiogenesis and upregulate HIF-1α secretion[134]. Paeoniflorin (PF), a major bioactive ingredient extracted from Paeonia lactiflora roots, has been incorporated into a hyaluronic acid (HA)-based hydrogel to form HA-PF[135]. It was found the HA-PF hydrogel promoted macrophages shift from M1 (pro-inflammatory) to M2 (anti-inflammatory and pro-healing) phenotype, thereby promoting diabetic wound healing[135]. Similarly, another micro-environmentally responsive hydrogel loaded with Nano-ZnO and PF-encapsulated micelles

also showed significant promotion of wound healing in chronically infected diabetic wounds through sequential haemostatic, antibacterial and angiogenic abilities[136]. In our work, a hyaluronic acid-based self-healing hydrogel loaded with salvianolic acid B was fabricated to accelerate diabetic wound healing via anti-inflammatory and pro-angiogenic properties[137].

Altogether, these improvements suggest the great potential of combination of bioactive herbal compounds with biomaterials for promoting skin regeneration under normal cutaneous wounds as well as chronically infected wounds. However, the research done so far is limited to mouse or rat models, which differ significantly from human skin. Therefore, further exploration is needed to mature the use of biomaterials loaded with herbal compounds for clinical applications.

Table 1. Application of bioactive herbal compounds together with biomaterials for skin tissue regeneration.

Herbal bioactive components	Sources	Application method	Experimental models		Main effects	Ref
			In vivo	In Vitro		
Curcumin and Shikonin	Curcuma longa L. and Arnebia	Bilayer nanofibrous scaffolds	Chronic wounds model in STZ-induced diabetic rats	L929 cells	Increase collagen synthesis and TGF-β production, anti-inflammatory	86
Curcumin	Curcuma longa L.	Cellulose nanocrystal film	Chronic wounds model in STZ-induced diabetic rats	/	Improve the regeneration of hair follicles and sebaceous glands	88
Curcumin	Curcuma longa L.	Electrospun nanofibrous mat	Chronic wounds model in STZ-induced diabetic rats	/	Rapid wound healing efficacy	91
Curcumin	Curcuma longa L.	Electrospun nanofibrous membranes	/	Fibroblast cells	Antibacterial properties and induction of cell growth, attachment, and proliferation	92
Curcumin	Curcuma longa L.	Electrospun Nanofibers	Full-thickness wound healing model in rats	HDFs	Faster wound-healing process, higher recovery percentage (wound-healing rate), and decreased risk of infection	93
Curcumin	Curcuma longa L.	Nanoparticlesand electrospun chitosan nanofiber	Full-thickness wound healing model in mice	Mouse erythrocyte and L929 cells	Antibacterial action and accelerated wound healing	87
Curcumin	Curcuma longa L.	Hydrogel	Chronic wounds model in STZ-induced diabetic rats	/	Complete re-epithelization, intact dermo-epidermal junction, reorganization of the dermis，increased collagen deposition and VEGF and AQP3 expression	83

Curcumin	Curcuma longa L.	Hydrogel	Chronic wounds model in STZ-induced diabetic mice	NIH-3T3 cells and RAW 264.7 cells	Attenuated intracellular oxidative stress and inflammation, and promoted cell migration and downstream MMP9	84
Curcumin	Curcuma longa L.	Gelatine microspheres (GMs)、thermos-sensitive hydrogel	Chronic wounds model in STZ-induced diabetic rats	BJ and HaCat cells	Anti-oxidants and promotions of cell migration.	81
Curcumin	Curcuma longa L.	Extracellular Matrix-Based Scaffolds	/	L929 fibroblast cells	Inhibit bacterial growth and scavenge the free radicals	89
Curcumin	Curcuma longa L.	Extracellular matrix nanoemulsion system loaded with nanoceria	Full-thickness wound healing study on rabbit model	L929 cells	Scavenge ROS and antibacterial, promote collagen synthesis and improve wound healing rate	90
Tannic acid	Rhus chinensis Mill.	Hydrogel	Chronic wounds model in STZ-induced diabetic mice	/	Antibacterial, anti-inflammatory, promote collagen deposition and vascularization	101
Tannic acid	Rhus chinensis Mill.	Enzyme catalysed hydrogel	Tail amputation model in rats and wound healing model in mice	3T3 cells	Haemostasis and promotes wound adhesion	104
Tannic acid	Rhus chinensis Mill.	Supramolecular hydrogel	Bleeding liver model in rats and full-thickness wound healing model in rats	NIH 3T3 and RAW 264.7	Antibacterial, anti-inflammatory, antioxidant, enhanced ECM synthesis, collagen deposition and granulation tissue thickening	105
Tannic acid	Rhus chinensis Mill.	Electrospun nanofibers	Tail amputation model in mice and full-thickness wound healing model in rats	Human fibroblasts	Antibacterial，stimulates cell migration and differentiation	107
Gallic acid	Rheumpalmat um L.	Gallic acid-modified chitosan-based (CS-GA)	Full-thickness wound healing model in rats	L929 and Rat red blood cells	Antibacterial, anti-inflammatory, antioxidant	111

		hydrogel	and bleeding liver model in rats			
Gallic acid	Rheumpalmatum L.	Hydrogel	liver trauma in mice model and tail amputation model in mice and mice wound infection model	HaCaT cells	Antibacterial, anti-inflammatory, promotes collagen deposition and angiogenesis	138
Gallic acid	Rheumpalmatum L.	Chitosan-based cryogel	Mice-tail amputation model and mice wound infection model	C2C12 cells	Antibacterial, anti-inflammatory, homeostatic, promotes vascularization of wounds	113
Gallic acid	Rheumpalmatum L.	Gallic acid -hexanoyl glycol chitosan (GA-HGC) hydrogel	Full-thickness wound healing model in mice	NIH-3T3 cells	Upregulation of growth factors and recruitment of fibroblasts	112
Gallic acid	Rheumpalmatum L.	Collagen-fibrin scaffold	Wound healing model in rats	NIH/3T3 mouse fibroblast cell	Accelerates angiogenesis, hexosamine synthesis, collagen deposition and recruitment of immune cells	114
Quercetin	Sophora flavescens Ait.	Chitosan–fibrin composite (CF) scaffolds	Wound healing model in rats	NIH 3T3 cells	Promotes migration of fibroblasts and epithelial cells to the wound site	117
Quercetin	Sophora flavescens Ait.	Electrospun nanofibers	Deep second-degree scald model in rats	HUVECs and HDFs	Induce proliferation, migration and differentiation of skin and hair follicle related cells	119
Puerarin	Kudzu root	Chitosan@Puerarin hydrogel	Chronic wounds model in STZ-induced diabetic rats	RAW264.7	inhibition of inflammation and regulation of miR- 29 expression	123
Puerarin	Kudzu root	Nanoparticle-incorporated	Wound healing model	hPDLSCs	improve the activity of superoxide dismutase	124

		hybrid hydrogels	in mice		and glutathione peroxidase and reduce the levels of ROS and malondialdehyde	
Puerarin	Kudzu root	Nanoparticle-incorporated hybrid hydrogels	Wound healing model in rats	DPSCs and periodontal ligament stem PDLSCs	Reduced ROS and increased activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) under oxidative stress conditions	125
Puerarin	Kudzu root	Chitosan@puerarin (CS@PUE) hydrogels	Full-thickness wound healing model and infected full-thickness wound healing model	L929 cells	Antibacterial, anti-inflammatory	126
Berberine	Coptis chinensis	Nano-colloids hydrogel	Chronic wounds model in STZ-induced diabetic rats	HFF-1 and HaCaT cells	Reducing inflammation and promoting angiogenesis	130
Asiatic acid	Centella asiatica	Electrospun fibrous scaffold	Chronic wounds model in STZ-induced diabetic rats	HaCaTs and RAW 264.7	Reduces cellular oxidative stress damage, down-regulates pro-inflammatory cytokines and inhibits bacterial growth	132
Astragaloside	Astragalus	Nanoparticle-enriched hydrogel	Full-thickness wound healing model in rats	immortalized human fibroblast line and immortalized keratinocyte line	Regulates the stages of re-epithelialization, angiogenesis and extracellular matrix remodelling, enhances the migration and proliferation of keratinocytes, and inhibits scar formation	133
Hydroxysaffl-or yellow A	Carthamus tinctorius L.	Hydroxysafflor yellow A/ deferoxamine (HSYA/DFO) hydrogels	Chronic wounds model in STZ-induced diabetic rats	immortalized human keratinocytes line, human fibroblast cells, and human umbilical vein	promote angio- genesis and up-regulate HIF-1a secretion	134

				endothelial cells		
Paeoniflorin	Paeoniflorin	Hyaluronic acid-based hydrogel	Chronic wounds model in STZ-induced diabetic rats	L929 cells and HUVECs	Promote the conversion of macrophages from M1 to M2 type	[135]
Paeoniflorin	Paeoniflorin	Microenvironment-Responsive hydrogel	Chronic wounds model in STZ-induced diabetic rats	L929 cells and HUVECs	Haemostatic, antibacterial, and angiogenic	[136]
Salvianolic acid B	Salvia miltiorrhiza	Salvianolic acid B/ hyaluronic acid hydrogel	Chronic wounds model in STZ-induced diabetic rats	NIH/3T3 cells	Anti-inflammatory and promote angiogenesis	[137]

3.1 Bone and cartilage tissue regeneration

Large-volume bone defects and articular cartilage damage remain great challenges in the fields of orthopaedic medicine due to the unsatisfactory outcomes of current therapy[139]. Biomaterials-based approaches to enhance bone and cartilage regeneration have been considered as promising strategies[140]. Thereupon, the incorporation of exogenous growth factors such as bone morphogenetic proteins (BMPs) and transforming growth factor beta (TGF-β) into scaffolds was found to effectively accelerate the healing process. However, their clinical application was limited due to the high cost, low stability and high dose-induced side effects[141]. Alternatively, herbal compounds are not only inexpensive and safety, but also can effectively promote the restoration of bone and cartilage defects owing to their anti-inflammation, antimicrobial, angiogenesis as well as enhanced osteogenic and chondrogenic differentiation capacities[142,143]. Accordingly, a large number of bioactive herbal compounds have been constructed into biomaterials targeting a better restoration of bone and cartilage. The key findings are summarized in Figure 3 and Table 2.
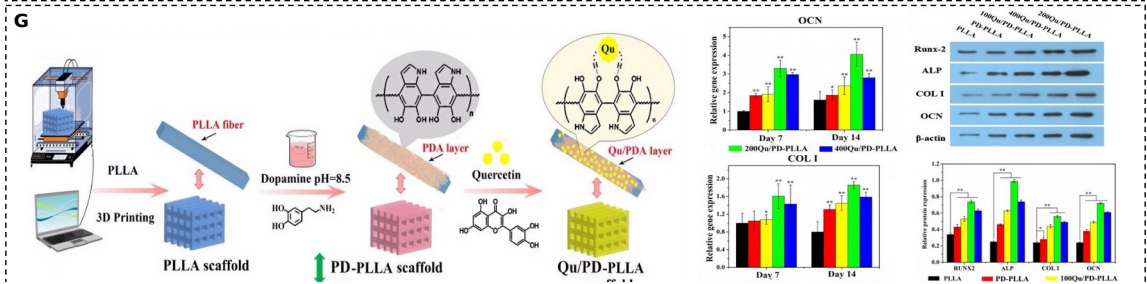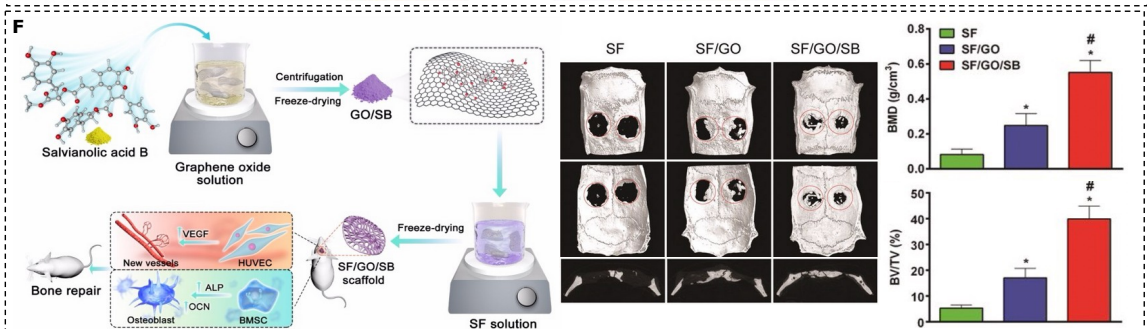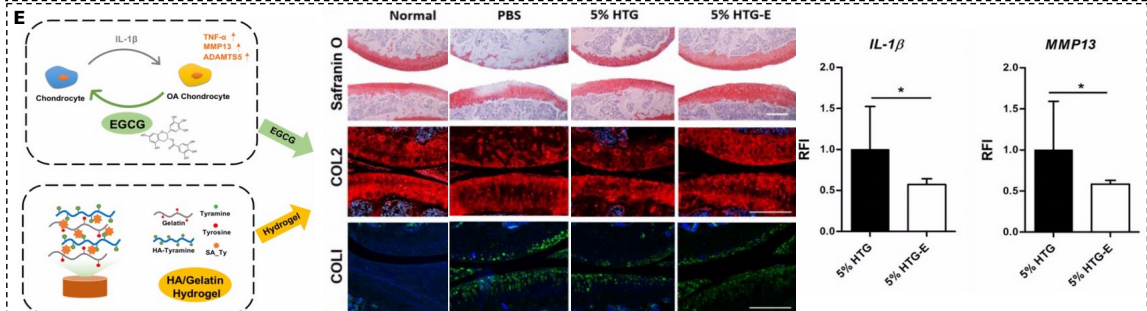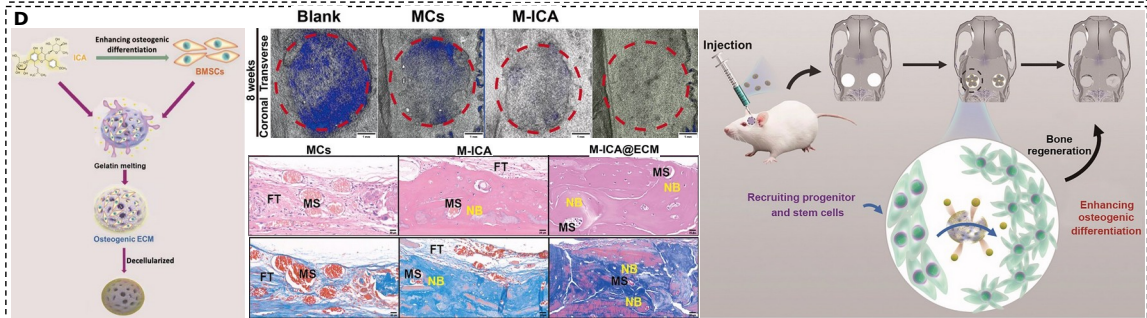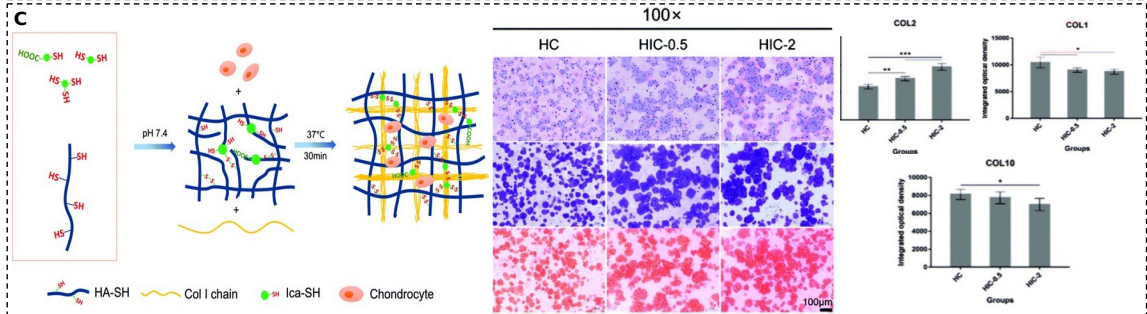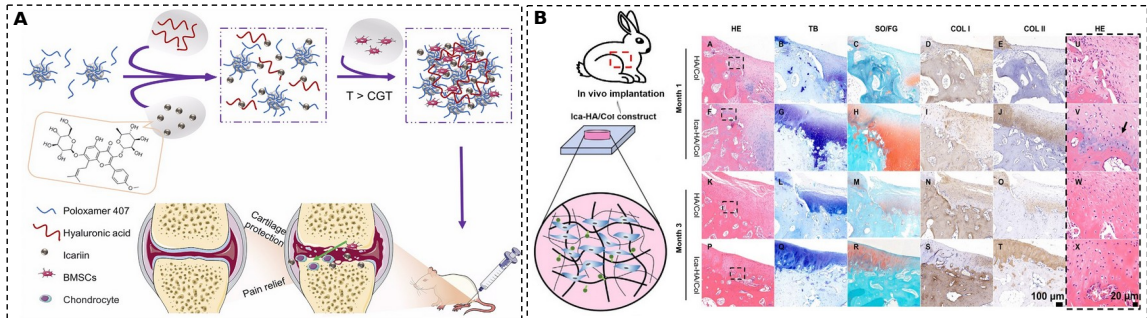
Figure 3. Combined application of bioactive herbal compounds and different biomaterials for bone and cartilage tissue regeneration. (A) Schematic illustration of Icariin-loaded Poloxamer 407 and HA (PHa) hydrogels combined with bone marrow mesenchymal stem cells (BMSCs) for cartilage protection and pain relief in osteoarthritis (OA)[144]. (B) Histological analysis and immunohistochemical staining showing Icariin (Ica)-conjugated hyaluronic acid/collagen hydrogels (Ica-HA/Col) promote the osteochondral restoration in a rabbit model with osteochondral defect[145]. (C) Histological and immunohistochemical staining showing the thiolated icariin (Ica-SH) functionalized HA/Col hydrogel (HIC) could facilitate cartilage matrix secretion and further promote the cartilage formation[146]. (D) Icariin (ICA)-incorporated porous microcarriers combined with decellularized extracellular matrix derived from bone marrow mesenchymal stem cells promote bone regeneration synergistically through recruitment of progenitor and stem cells as well as enhancement of osteogenic differentiation[147] (E) The incorporation of epigallocatechin-3-gallate (EGCG) into HA/Gelatin hybrid hydrogel (HTG-E) reduces inflammation and enhances cartilage regeneration in surgically induced OA model[148].(F) The incorporation of salvianolic acid B (SB) into the silk fibroin/graphene oxide (SF/GO) scaffold contributed to better bone regeneration and significantly higher bone mineral density (BMD)[149]. (G) 3D printed quercetin (Qu) and polydopamine (PDA) modified poly(L-lactide) (PLLA) scaffolds could stimulate bone tissue engineering illustrated by the increase of osteogenic-related genes and proteins expression[150]. Reproduced with permission[144-150].

3.2.1 Icariin

Herb Epimedium (HEP) is a traditional Chinese herb that is widely used to treat osteoporosis in China, Japan and Korea[151]. Icariin (Ica), the main component of Epimedium, has been shown to promote chondrogenesis of bone marrow mesenchymal stem cells (BMSCs) in both 2D and 3D cell cultures[152]. Wang et al. cultured BMSCs in self-assembled peptide nanofiber hydrogel scaffolds and the results suggested that Ica treatment promotes chondrogenic differentiation of BMSCs[153]. Zhu et al. fabricated hydrogels containing Ica by in situ crosslinking of hyaluronic acid and Poloxamer 407, which was shown to promote proliferation and chondrogenesis of BMSCs as well as prevention of cartilage destruction and pain relief in osteoarthritis (OA) model[144] (Figure 3A). Yang et al. conjugated Ica to hyaluronic acid/collagen (Ica-HA/Col) hydrogel to promote the osteochondral interface restoration, characterized by upregulation of chondrogenic genes, as well as calcium and collagen deposition[145] (Figure 3B). The injectable sulphated epimedium functionalized

collagen/hyaluronic acid hydrogel prepared by Liu et al. can stimulate chondrocyte proliferation and promote secretion of cartilage matrix, which has great potential in articular cartilage repair[146] (Figure 3C).

Besides the promoting ability for cartilage repair, Ica has also been applied to promote bone regeneration. Zhou et al. prepared Ica-conjugated poly(glycolide-co-caprolactone) (PGCL) porous microcarriers, followed by coating with BMSC-derived decellularized extracellular matrix (dECM)[147] (Figure 3D). It was reported that initially released Ica regulated osteogenic ECM production in BMSCs, while in vivo results showed that Ica and dECM exhibited good synergy in repairing rat with calvarial defects[147]. In another study, researchers loaded Ica into 3D-printed reconstructed rod, which was shown to facilitate osteogenesis and neovascularization, and finally increased the bone mass and bone density[154]. Additionally, Hu et al. prepared Ica-loaded nano-hydroxyapatite-enhanced hybrid scaffolds (Ica-loaded nHAP/CMCS/PLGA) using a combination of organic /inorganic hybrid technology and emulsion template method and used it to treat calvarial defects in rats[155]. It was found that the incorporation of Ica into scaffolds not only improved the in vitro bioactivity and accelerated the repair capacity in vivo, but also improved the mechanical properties of scaffolds[155]. In another study, Ica was added to a bioactive composite scaffold to provide structural and mechanical support as well as to facilitate bone regeneration[156], revealing that the incorporation of Ica to biomaterials is a promising potential strategy for bone and cartilage tissue engineering and regeneration.

3.2.2 Berberine

In addition to the application in skin tissue repair/regeneration, berberine (Ber) also plays an important role in bone and cartilage regeneration. For instance, Chen et al. fabricated an interpenetrating polymer network (IPN) of a sodium hyaluronate and sodium alginate (HA/SA) scaffold combined with Ber to explore the effects on osteochondral repair. The results showed the system could activate the Wnt signalling pathway to partially repair subchondral bone and protect cartilage from degeneration through upregulation of autophagy[157]. In the study by Ma et al., Ber/polycaprolactone/collagen (Ber/PCL/COL) scaffold was developed by electrospinning technique, which was shown to promote osteogenic differentiation and accelerate bone repair[158]. Similarly, a bilayer membrane composed of mineralized collagen (MC) and chitosan (CS) cast film was coated with Ber-loaded PCL/PVP electrospun nanofiber to form Ber@PCL/PVP-MC/CS bilayer membrane[159]. It was found enhanced attachment and proliferation of MC3T3-E1 cells in vitro and improved

bone regeneration in a rat model with femoral bone defect[159]. Furthermore, Chen et al. reported a Ber-encapsulated poly(lactic-co-glycolic acid)-hydroxyapatite (PLGA/HA) microspheres which could promote bone regeneration with DOPA-IGF-1 via the IGF-1R/PI3K/AKT/mTOR pathway, suggesting a promising system for cartilage tissue regeneration[160].

Biomimetic calcium phosphate (CaP) ceramics have been considered as ideal biomaterials for bone tissue repair due to their good biocompatibility, osseointegration and osteoconduction activities[161]. Thus, the systems by combination of bioactive compounds with CaP ceramics have also been developed for effective bone repair. For instance, Hu et al. designed a Ber/nAg/SF biomimetic CaP scaffold by composition with Ber, Ag nanoparticles (nAg), and silk fibroin (SF) and tested it with pre-osteoblast MC3T3-E1 cells in vitro. The results showed that the scaffold exhibited enhanced osteogenesis and antibacterial functions[162]. Different from the scaffolds made by the sintering process mentioned above, Sun et al. proposed a 3D printed degradable calcium phosphate scaffold with controlled release of Ber, which was found to be beneficial for the adhesion and proliferation of MC3T3 cells and showed promise for jaw repair[163].

3.2.3 EGCG

Epigallocatechin-3-gallate (EGCG), which is normally extracted from green tea, is a polyphenolic bioactive compound with multiple pharmacological activities[164]. Firstly, EGCG has been reported to promote the proliferation and osteogenic differentiation of several types of stem cells[165,166]. In addition, EGCG could regulate inflammation and eliminate free radicals, so that it can be used as an effective compound for treating osteoarthritis (OA)[167]. Jin et al. prepared an EGCG-HA/Gelatin hybrid hydrogel and implanted it into mice with OA[148]. It was proven that the hybrid hydrogel promoted chondrogenic regeneration in vitro and minimized cartilage loss in surgically induced OA model[148] (Figure 3E). In addition to hydrogel system, EGCG was incorporated to membranes. Chu et al. reported an EGCG-modified collagen membrane with nano-hydroxyapatite (nano-HA) coating, and found the modified membrane increased mechanical strength and promoted bone regeneration compared to the unmodified collagen membrane[168]. Furthermore, the mechanism studies have shown that EGCG-modified collagen membrane promoted bone regeneration in vivo by recruitment of M2 macrophages, promotion of growth factor secretion as well as osteogenic differentiation[52]. Besides, composite sponges have also been used as biomaterials for bone regeneration. Gao et al.

developed an EGCG-modified gelatin sponge, which was shown to enhance the bone-forming ability in rats with calvarial defects[169].

3.2.4 Resveratrol

Resveratrol (RSV) is a natural polyphenol existing in various plants, including grapes, berries and peanuts[170]. In addition to the routine functions as other bioactive herbal compounds such as anti-cancer, antioxidant, anti-inflammatory properties, RSV can also stimulate osteoblast differentiation[171]. Yu et al. prepared RSV-PLA-gelatin porous nanoscaffolds and used them to treat rats with articular cartilage defects[172]. The results showed that the RSV-PLA-gelatin porous scaffold promoted the repair of cartilage injury probably via the PI3K/AKT signalling pathway[172]. Wang et al. fabricated and implanted collagen/RSV scaffold in rats with critical-size calvarial defects and found the collagen/RSV scaffold accelerated wound closure and contraction more effectively than collagen scaffold[173]. In another study, Li et al. prepared RSV/SIS scaffolds by combination of acellular small intestinal submucosa (SIS) and RSV skull defects. Results showed that RSV functionalization significantly affected the osteogenic properties of the SIS scaffolds and induced more vascular and new bone tissue formation in rats with skull defects[174].

3.2.5 Naringin

Naringin (Ng) is an active flavonoid extracted from Citrus fruit, which has also been included into biomaterials for bone and cartilage repair[175]. In order to reduce the burst release of naringin (Ng), Yang et al. prepared Ng-loaded microsphere/sucrose acetate isobutyrate (Ng-m-SAIB) depots by electrospray technique and was shown to enhance osteogenic differentiation in rats with calvarial defects[176]. In another study, a naringin-inlaid composite silk fibroin/hydroxyapatite (Ng/SF/HAp) scaffold was fabricated based on salt-leaching technology[177]. The results showed that Ng facilitated human umbilical cord mesenchymal stem cells (hUCMSCs) ingrowth into the SF/HAp scaffold and promoted osteogenic differentiation[177]. Besides, Wu et al. reported a 3D printed mesoporous bioactive glass/sodium alginate/gelatin scaffold loaded with Ng and calcitonin gene-related peptide can effectively promote cell proliferation and osteogenesis-related gene expression[178], suggesting a potential method for bone tissue engineering.

3.2.6 Others

Other herbal compounds used in bone and cartilage tissue regeneration include salvianolic acid B (SAB), catechin, quercetin, curcumin, gallic acid and so on. Ji et al.

reported a SAB-loaded chitosan/hydroxyapatite (SAB-CS/HA) bone scaffold with controlled release as well as osteogenic and angiogenic bioactivities[179]. Wang et al. constructed a silk fibroin/graphene oxide (SF/GO) scaffold loaded with SAB to form SF/GO/SAB scaffold which was shown to repair bone defects by promoting osteogenic differentiation and angiogenesis[149] (Figure 3F). The quercetin/polydopamine-poly(L-lactide) scaffold fabricated by Chen et al. through 3D printing technology can continuously release quercetin, which can promote the expression of genes and proteins related to osteogenesis[150] (Figure 3G). Similarly, catechin-conjugated mesoporous hydroxyapatite nanoparticles (Cat@MHAP) were proved with enhanced antioxidant and osteogenic properties[180]. Quercetin-modified electrospun fibrous scaffold[181], and injectable quercetin-loaded hydrogel[182] were both confirmed to enhance cartilage regeneration. Besides, an anti-inflammatory hydrogel that contained gelatin methacryloyl (GelMA) loaded with curcumin (Cur) was fabricated to deliver microtissues, which resulted in cartilage tissue regeneration that close to natural hyaline cartilage[183]. Gallic acid has been inserted onto chitosan via free radical-mediated grafting and found to promote osteogenesis through blocking the canonical Wnt/β-catenin signalling pathway[184].

To sum up, the combination of bioactive herbal compounds and biomaterials can improve the release profile of herbal compounds, and on this basis, the drugs can be maintained at an appropriate concentration and a sustained manner to promote the proliferation and osteogenic differentiation of various cells with osteogenic potential[185], providing great potentials for bone and cartilage regeneration.

Table 2. Application of biomaterials loaded with bioactive herbal compounds in bone and cartilage tissue regeneration

Herbal bioactive components	Sources	Application method	Experimental model		Main effects	Ref
			In Vivo	In Vitro		
Icariin	Epimedium	Self-assembling peptide nanofiber hydrogel scaffold	/	Rat BMSCs	Promote chondrogenic differentiation of BMSCs, and inhibit the side effect of growth factor activity	[153]
Icariin	Epimedium	Hydrogel	OA rat model	BMSCs and chondrocytes	Inducing chondrogenic differentiation of BMSCs	[144]
Icariin	Epimedium	Ica conjugated hyaluronic acid/collagen (Ica-HA/Col) hydrogel	Rabbit cartilage defect model	Rabbit chondrocytes	Promoting restoring of osteochondral defect.	[145]
Icariin	Epimedium	Hyaluronic acid/collagen hydrogel	Subcutaneous transplantation model of nude mouse	Rabbit chondrocytes	Promotes chondrocyte proliferation, maintains chondrocyte phenotype and promotes secretion of cartilage extracellular matrix	[146]
Icariin	Epimedium	Polyglycolide-co-caprolactone (PGCL) porous microcarriers	Full-thickness calvarial defect model in rats	BMSCs	Promotes bone regeneration synergistically with dECM derived from BMSCs	[147]
Icariin	Epimedium	Ica-loaded nHAP/CMCS/PLGA	Rat calvarial critical size defect model	Osteoblasts	Promotes adhesion, proliferation and differentiation of osteoblasts	[155]
Icariin	Epimedium	PLGA/TCP/Ica scaffold	SAON rabbit model	MC3T3-E1 cells	Enhances the mechanical properties of new bone tissue and improves angiogenesis	[156]
Berberine	Coptis chinensis	HA/SA IPN scaffold	Rat cartilage defect model	BMSCs	Activation of the Wnt signaling pathway partially repairs subchondral bone and protects cartilage from degeneration through upregulation of autophagy.	[157]

Berberine	Coptis chinensis	BBR/PCL/COL scaffold	Rat calvarial bone defect model	PDLSCs	Accelerates bone defect repair	[158]
Berberine	Coptis chinensis	BER@PCL/PVP-MC/CS Bilayer Membrane	Rat femur defect model	MC3T3-E1 cells	Induce bone regeneration	[159]
Berberine	Coptis chinensis	BBR/nAg/SF biomimetic CaP scaffolds	/	MC3T3-E1 cells	Enhances osteogenic and antibacterial functions	[162]
Berberine	Coptis chinensis	3D printed degradable calcium phosphate scaffolds	/	MC3T3 cells	Facilitates the adhesion and proliferation of MC3T3 cells	[163]
EGCG	Green tea	EGCG-HA/Gelatin hybrid hydrogel	Mouse OA model	OA chondrocytes	Anti-inflammatory and promote cartilage regeneration	[148]
EGCG	Green tea	Nano-HA modified EGCG-collagen membranes	Rat skull defect model	/	Promote bone regeneration	[168]
EGCG	Green tea	EGCG-modified collagen membranes	Rat skull defect model	M2 macrophages	Aggregates M2 macrophages, promotes growth factor secretion and osteogenic differentiation	[52]
EGCG	Green tea	vhEc-GS-β hydrogel	Rat skull defect model	Rat osteoblast	Enhanced osteogenesis	[169]
Resveratrol	Grape	Resveratrol-PLA-gelatin porous nanoscaffolds	Rat model of articular cartilage defect	BMSCs	Promote cartilage repair	[172]
Resveratrol	Grape	RSV and collagen scaffolds	Rat critical size skull defect model	Human adult stem cells	Promote bone regeneration	[173]
Resveratrol	Grape	RSV/SIS scaffolds	Rat model of articular cartilage defect	hBMSCs	Promotes blood vessel and new bone formation	[174]
Naringin	Citrus fruit	Ng-microspheres and Ng-m-SAIB depots	Rat skull defect model	Osteoblasts	Enhanced osteogenic differentiation	[176]
Naringin	Citrus fruit	Naringin/SF/HAp scaffolds	Rabbit distal femoral bone defect model	hUCMSCs	Promotes osteogenesis and blood vessel formation	[177]
Naringin	Citrus fruit	3D printing mesoporous bioactive glass/sodium alginate/ gelatin sustained release scaffolds	/	MG-63 cells	Effectively promotes cell proliferation and the expression of osteogenesis-related genes	[178]

Salvianolic acid B	Salvia miltiorrhiza	Sal B-CS/HA scaffold	Rabbit radial defect model	MC3T3 E1	Promotes vascular and bone formation	[179]
		SF/GO/SB scaffold	Rat cranial defect model	EA-hy9.26	Promotes vascular and bone formation	[149]
Catechin	Tea	Cat@MHAP	/	Saos-2	Enhances cell proliferation and osteogenic differentiation	[180]
Quercetin	Sophora flavescens Ait.	Qu/PD-PLLA scaffolds	/	MC3T3-E1	Promotes attachment and proliferation of MC3T3-E1 cells and the expression of osteogenic-related genes and proteins	[150]
Quercetin	Sophora flavescens Ait.	PHBV-g-QUE fibrous scaffold	Nude mice model	Rabbit chondrocytes	Promotes maturation of new cartilage tissue and cartilage regeneration	[181]
Quercetin	Sophora flavescens Ait.	The Que-BG hydrogel	SD rat cartilage defect model	RAW 264.7 cells	Promote cartilage formation and maintain anti-inflammatory activity, promote macrophage polarization to M2 type, and effectively inhibit the degradation of ECM	[182]
Curcumin	Curcuma longa L.	anti-inflammatory hydrogel that contained gelatin methacryloyl (GelMA) loaded with curcumin (Cur)	Rabbit full-thickness cartilage defect model	MSCs	Regulates the hypertrophic and inflammatory environment at the defect site	[183]
Gallic acid	Rheumpalmatum L.	GAC	/	mBMMSCs	Promotes osteogenesis through canonical Wnt/β-catenin signaling pathway	[184]

3.2 Neural tissue regeneration

Neural damage remains one of major factors contributing to the high disability and mortality worldwide[186]. Currently, there is no effective treatment for restoring the lost tissue and function. The combined application of biomaterials and bioactive molecules, represents a promising approach for regeneration following neural damage such as stroke, traumatic brain injury (TBI), spinal cord injury (SCI), and peripheral nerve tissue injury[187,188]. The application of herbal compounds as bioactive molecules together with biomaterials has also been confirmed to make contributes for neural repair and regeneration. Some key findings were summarized in Figure 4 and Table 3.

Firstly, we reviewed the findings combining herbal compounds and biomaterials for treatment of central nervous system trauma. In a previous study, curcumin was combined with autologous nerve stem/progenitor cells (NS/PCs) and found to reduce the lesion size, astrogliosis, microglial reaction and the number of apoptotic cells, while improve the neurological status of injured animals in rats with brain injury[189]. Besides, the synergistic effect of induced neural progenitor cells (iNPCs) and the nanoconjugated form of curcumin was demonstrated[190]. When combined with PuraMatrix hydrogel, they exert anti-inflammatory effects, not only reducing the extent of injury area, but also increasing neurite growth, thus providing a more promising approach for the treatment of acute SCI[190] (Figure 4A). In addition, the study by Luo et al. revealed that Fmoc-grafted chitosan/ Fmoc peptide (FC/FI) hybrid hydrogels could release curcumin slowly and continuously, which not only enhanced Schwann cell (SC) migration and interacted with neurites in vitro, but also reassembled the extracellular matrix, regulated local inflammatory responses, and promoted the regeneration of myelin sheath and repair of spinal cord injury (SCI) in vivo[191] (Figure 4B).

The combination of biomaterials and herb compounds is also effective in restoration of peripheral nerve tissue. Jahromi et al. designed an artificial neural guidance conduit (NGC) as a carrier to transplant allogeneic Schwann cells (SCs) and curcumin encapsulated chitosan nanoparticles (nanocurcumin)[192] (Figure 4C). It was found that the NGC/SCs/nanocurcumin system significantly increased the number of sciatic nerve axons and promoted nerve regeneration, suggesting a promising strategy for improving nerve regeneration[192]. Quercetin, another herbal compound that is known to have anti-inflammatory, antioxidant and anti-apoptotic effects, which can also promote nerve recovery[193]. Huang et al. reported hydrogels with a sustained release of quercetin could significantly increase the number of motor and functional neurons, improve the survival rate of neurons in injured rat model, thereby

promoting nerve regeneration and motor function recovery[194]. Moreover, the neuroprotective effects of salidroside have also been demonstrated[195]. In the study by Liu et al., salidroside on engineered nerve constructed by Schwann cells (SCs) and Poly (lactic-co-glycolic acid) (PLGA) can dramatically enhance the proliferation and function of SCs through modulation of neurotrophic factors and promote nerve regeneration and functional improvements[49] (Figure 4D).

Figure 4. Combined application of bioactive herbal compounds and different biomaterials for neural tissue regeneration. (A) PuraMatrix™ peptide hydrogel (PM)-embedded iNPCs with curcumin (CURC) placed within an HA demilune scaffold containing polypyrrole-coated fibers (PPY) supported a significant increase in neuro-preservation and decrease in the injured area. [190]. (B) The curcumin (Cur)-loaded hybrid fmoc-grafted chitosan (FC)/fmoc peptide (FI) hydrogel (FC/FI-Cur) showed controlled release of Cur and promoted the regeneration of myelin sheath and repair of spinal cord injury (SCI)[191]. (C) Poly-L-lactic acid/multi-wall carbonnanotube neural guidance conduit containing Schwann cells (SCs) and curcumin encapsulated chitosan nanoparticles (nanocurcumin) showed good cell biocompatibility in vitro and enhanced sciatic nerve regeneration in a rat model with sciatic nerve injury[192]. (D)

Engineered nerve constructed by Schwann cells (SCs) and Poly (lactic-co-glycolic acid) (PLGA) combined with salidroside (SDS) promoted nerve regeneration and recovery of sciatic nerve function[49]. Reproduced with permission [49,190-192].

Table 3 Application of biomaterials loaded with bioactive herbal compounds in neural tissue regeneration.

Herbal bioactive components	Sources	Application method	Experimental models		Main effects	Ref.
			In Vivo	**In Vitro**		
Curcumin	Curcuma longa L.	Nanoscale scaffold	Rat model of brain injury	Nerve stem/progenitor cells (NS/PCs)	Reduce the lesion extent and the number of apoptotic cells	189
Curcumin	Curcuma longa L.	Fmoc-grafted chitosan / Fmoc peptide (FC/FI) hybrid hydrogels	Rat model of spinal cord injury (SCI)	Schwann cells (SCs)	Enhance SCs migration，reassemble the extracellular matrix and promote myelin regeneration	191
Curcumin	Curcuma longa L.	PuraMatrix hydrogel	Rat model of SCI	Induced neural progenitor cells (iNPCs)	Reduce the extent of injury area and increase neurite growth	190
Curcumin	Curcuma longa L.	Artificial neural guidance conduit (NGC)	Rat model of sciatic nerve injury	SCs	Increase the number of sciatic nerve axons and promote nerve regeneration	192
Quercetin	Sophora flavescens Ait.	Hydrogels	Rat model of brachial plexus injury	/	Increases the number and survival rate of motor and functional neurons	194
Salidroside	Rhodiola rosea	Poly lactic-co-glycolic acid (PLGA) polymer	Rat model of sciatic nerve injury	SCs	Enhance the proliferation and function of SCs	49

3.3 Myocardial repair

Myocardial infarction (MI) is another factor leading to morbidity and mortality which poses significant therapeutic challenges[196]. The main obstacles are due to the limited regenerative capacity of the adult mammalian heart[196]. There, the overproduction of reactive oxygen species (ROS) and excessive expression of hypoxia-inducible factor-1 alpha (HIF-1α) following MI can further lead to disruption of cellular homeostasis, apoptosis of cardiac cells, inflammatory cell infiltration, dilatation of ventricular and heart failure[197]. Current methods for treating MI include the transplantation of stem cells, remodelling of fibroblasts, delivery of growth factors and so on[198]. These methods are benefit for myocardial repair but the efficiency is limited. In recent years, the bioactive components of TCM have been proved to promote myocardial repair[199]. Thereupon, it was found the combination of TCM components and biomaterials can improve the efficacy for treating MI, which were then summarized in Figure 5 and Table 4.

Baicalin (BN) is one of the main bioactive components of Scutellaria baicalensis, a well-known Chinese herbal medicine since ancient times[200]. Recent studies have shown that BN can reduce MI by inhibiting apoptosis or by exerting its antioxidant properties[201]. Zhang et al. loaded BN to polyethylene glycol (PEG) nanocarriers and injected it into rats with MI, which significantly reduced the infarct area[202]. Furthermore, the researchers developed BN and puerarin (PU) co-loaded nanoparticulate system and observed significantly improved therapeutic efficiency compared with the drug solution formulations[203]. Their studies suggested that the bioactive TCM components-loaded nanoparticulate system could be a promising strategy for the treatment of MI.

In addition to the nanoparticulate system, injecting hydrogels with delivery of bioactive herbal components have been shown to promote cardiac repair after MI[204-206]. Hydrogels can not only provide an extracellular matrix-like microenvironment for damaged cardiomyocytes, stabilize the structures of ventricular, but also can enable the sustained release of drugs, so as to improve the post-MI functions[207,208]. For instance, the excellent self-healing ability of SAB-loaded EMP hydrogel allowed increased retention time of SAB in the beating ventricular wall and thus can inhibit ventricular remodelling and promote angiogenesis for MI treatment in a long-term manner[204] (Figure 5A). In another study, puerarin (PUE) combined with rat bone marrow mesenchymal stem cells (rBMSCs) were embedded in highly hydrophilic polyzwitterionic microgels using a microfluidic system, and then injected into the infarcted

areas of rat MI model[209] (Figure 5B). The results showed the PUE- and rBMSCs-loaded microgels maintained the stemness of rBMSCs and exerted both anti-inflammation and angiogenesis effects, which synergistically accelerated the highly efficient restoration of cardiac function[209]. Furthermore, Liao et al. prepared an injectable hydrogel system EGCG@Rh-gel using epigalcatechin-3-galate (EGCG) and rhein-peptide hydrogel (Rh-gel)[206] (Figure 5C). The abundant noncovalent interactions of π-π stacking and hydrogen bonding between EGCG and Rh-gel enabled the EGCG@Rh-gel with good mechanical strength and long-term sustained release of EGCG[206]. Thereupon, the EGCG@Rh-gel effectively blocked ROS-inflammatory cycle by scavenging ROS and inhibiting TLR4, improved the survival rate of neonatal rat cardiomyocytes (NRCMs), reduced fibrosis, and thus promoted myocardial repair in rat model[206]. Moreover, astragaloside IV(AST) was firstly fabricated to AST nanoparticles and then loaded to an injectable conductive hydrogel[205] (Figure 5D). This hydrogel system was found to inhibit left ventricular remodelling and myocardial dysfunction effectively in rats with MI through upregulation of angiogenesis in infarct margin, decrease of cell apoptosis, and increase the expression of Connexm43 (Cx43)[205]. Overall, the above examples using injectable hydrogels with delivery of bioactive herbal compounds provide promising strategies for cardiac repair in myocardial disease.

Table 4 Application of biomaterials loaded with bioactive herbal compounds in myocardial repair.

| Herbal bioactive components	Sources	Application method	Experimental models		Main effects	Ref.
			In Vivo	In Vitro		
Baicalin	Scutellaria baicalensis	Polyethylene glycol nanocarriers	Rat model of myocardial infarction (MI)	/	Reduce the infarct area	[202]
Baicalin; Puerarin	Scutellaria baicalensis; Kudzu root	Nano-particles	Rat model of MI	Human cardiomyocytes (HCMs) and HUVECs	Reduce the infarct area	[203]
Salvia acid B	Salvia miltiorrhiza	Elastin-mimic peptide hydrogel (EMH)	Rat model of MI	HUVECs	Repair ischemic damage and promote angiogenesis	[204]
Astragaloside IV	Astragalus membranaceus	Composite hydrogel	Rat model of MI	/	Inhibit myocardial apoptosis, reduce infarct size and promote angiogenesis	[205]
EGCG	Green tea	Rhein-peptide hydrogel	Rat model of MI	Neonatal rat cardiomyocytes (NRCMs)	Block ROS-inflammatory cycle, improve the survival rate of NRCMs and reduce fibrosis	[206]
Puerarin	Kudzu root	Microgel	Rat model of MI	Rat bone marrow mesenchymal stem cells (rBMSCs)	Reduce inflammation and promote angiogenesis	[209]
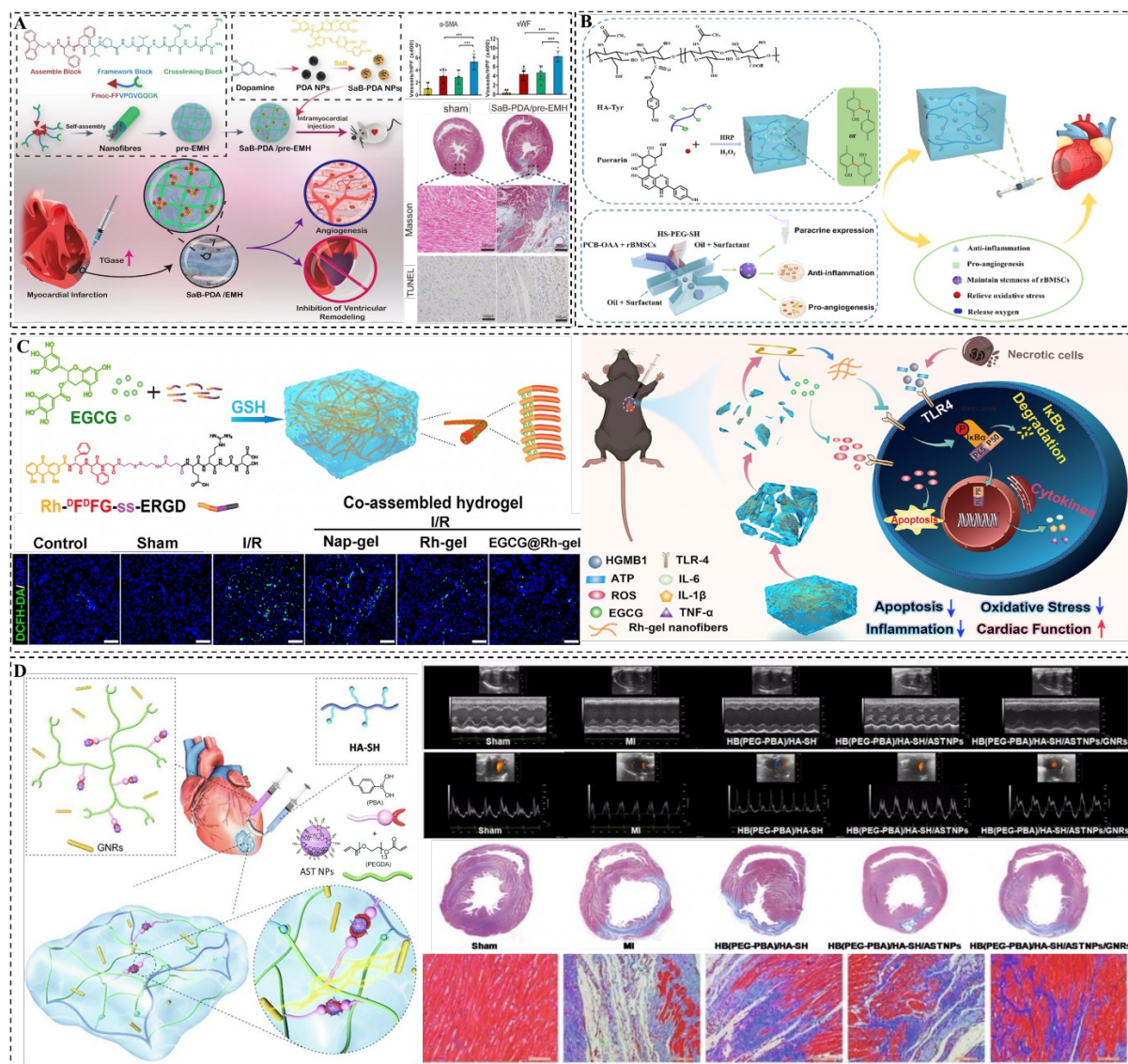
Figure 5. Combined application of bioactive herbal compounds and different biomaterials for myocardial repair and regeneration. (A) The self-healing elastin-mimic peptide hydrogel (EMH) allows for an increase in retention time of salvianolic acid B (SaB) in the beating ventricular wall, which can then inhibit ventricular remodeling and promote angiogenesis for myocardial infarction (MI) treatment[204]. (B) Puerarin-crosslinked hydrogel bearing rat bone marrow mesenchymal stem cells (rBMSCs)-embedded polyzwitterionic microgels (HA-Tyr-PUE@rBMSCs@microgels) can modulate microenvironment, reduce inflammation, maintain of stemness of rBMSCs and increase paracrine effect on treatment of MI[209]. (C) An injectable hydrogel system of EGCG@Rh-gel by co-assembling epigallocatechin-3-gallate (EGCG) and the rhein-peptide hydrogel (Rh-gel) blocked the ROS-inflammation cycle, reduced cell apoptosis, improved cardiac function, and significantly reduced the formation of scarring after cardiac ischemia-reperfusion (I/R)[206]. (D) An injectable conductive hydrogel loaded with

Astragaloside IV nanoparticles (AST NPs) effectively inhibited left ventricular remodeling and myocardial dysfunction through stimulating angiogenesis, promoting cell–cell signaling transduction, and inhibiting cell apoptosis[205]. Reproduced with permission [204-206,209].

3.4 Other tissue regeneration applications

In addition to the skin, bone, neural and cardiac repair/regeneration mentioned above, the combination of herb compounds and biomaterials has also been used in other tissue regeneration. Studies have shown that icariin loaded β-cyclodextrin sulfate can significantly promote the proliferation and migration of endothelial progenitor cells, accelerate the speed of vascular endothelialization, and effectively prevent thrombosis, demonstrating great potentials in the treatment of cardiovascular diseases[210]. In the study by Wang et al., astragaloside IV (AT) and ferulic acid (FA) were loaded into poly(ethylene glycol)-poly(DL-lactide) electrospun fiber scaffolds[211]. The results showed that AT and FA synergistically enhanced the activities of endothelial cells and smooth muscle cells, remodeled the extracellular matrix and significantly promoted angiogenesis, which provided clinical relevance for engineering of blood vessel substitutes[211]. In recent years, salvianolic acid B (SAB), an active component extracted from salvia miltiorrhiza, has been gradually discovered and applied in tissue regeneration areas. It was found that the combination of SAB and heparin in electrospun artificial vessels promoted the proliferation and migration of human umbilical vein endothelial cells (HUVECs) and reduced oxidative stress, thereby promoting rapid endothelialization of the artificial vascular grafts[212]. Besides, SAB was incorporated into a bioactive composite scaffold consisting of poly (lactic-co-glycolic acid) and β-tricalcium phosphate (PLGA/β-TCP) to evaluate the effects of SAB-incorporated scaffold on spinal fusion models[213]. Results showed that the release of SAB from the scaffold promoted osteogenesis and angiogenesis in a dose-dependent manner to enhance spinal fusion[213].

4. Concluding remarks and future prospects

In conclusion, the combination of bioactive herbal compounds and biomaterials provides a powerful strategy for tissue regeneration of skin, bone, cartilage, neural, heart, blood vessel and other tissues. On one hand, the biomaterial scaffolds provide a carrier matrix for sustained delivery and controlled release of the different herbal compounds to the damaged tissue sites. On the other hand, the incorparation of bioactive herbal compounds endows herbal scaffolds with beneficial effects such as anti-inflammtatory, antioxidant, antibacterial, pro-angiogenic as well as the stem cell differentiation promoting abilities, which improve the regenerative

potential. Thereupon, physical or chemical bonds can be formed between the groups of herbal compounds (like hydroxyl, carboxyl) and scaffolds (like amino), leading to enhanced mechanical strengh and improved stabilty of the scaffolds. These avenues are of particular attactive for material researchers working in the field of tissue regeneration.

In spite of the great advancements achieved by in vitro and in vivo studies, there has been no herbal-constructed scaffolds applied in clinics yet. Given that, several prospective improvements must be considered for future clinical applications. Firstly, understanding the precise targets and mechanism of different herbal compounds in various tissue regeneration is of great importance to gain deeper theoretical knowledge. In addition, the stability and release profile of the loaded herbal compounds should be well-controlled, to ensure the safety and effectiveness in clinic applications. Furthermore, novel approaches toward the fabrication of herbal-scaffolds that can further improve the bioavailability of the herbal compounds are highly on demand. Moreover, more types of bioactive herbal compounds should be tested or the ones that have been used in one tissue repair can be tested in other one in order to seek for more potential and appropriate herbal compounds for various tissue regeneration applications. Last but importantly, to overcome the shortcomings of single herbal component effect, the combination of two or more herbal compounds with biomaterials to meet the complicated tissue regeneration application requirements is also worthy of consideration.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest for publishing this review.

References

1.   Steffens D, Braghirolli DI, Maurmann N, et al. Update on the main use of biomaterials and techniques associated with tissue engineering. Drug Discov Today 2018;23(8):1474-1488, doi:10.1016/j.drudis.2018.03.013
2.   Mack M. Inflammation and fibrosis. Matrix Biol 2018;68-69(106-121,

doi:10.1016/j.matbio.2017.11.010

3.	Leal-Egaña A, Díaz-Cuenca A, Boccaccini AR. Tuning of cell-biomaterial anchorage for tissue regeneration. Advanced materials (Deerfield Beach, Fla) 2013;25(29):4049-57, doi:10.1002/adma.201301227

4.	Babensee JE, McIntire LV, Mikos AG. Growth factor delivery for tissue engineering. Pharmaceutical research 2000;17(5):497-504, doi:10.1023/a:1007502828372

5.	Tayalia P, Mooney DJ. Controlled growth factor delivery for tissue engineering. Advanced materials (Deerfield Beach, Fla) 2009;21(32-33):3269-85, doi:10.1002/adma.200900241

6.	Wang CY, Hou WX, Guo XR, et al. Two-phase electrospinning to incorporate growth factors loaded chitosan nanoparticles into electrospun fibrous scaffolds for bioactivity retention and cartilage regeneration. Mater Sci Eng C-Mater Biol Appl 2017;79(507-515, doi:10.1016/j.msec.2017.05.075

7.	Yan F, Li F, Liu J, et al. The formulae and biologically active ingredients of Chinese herbal medicines for the treatment of atopic dermatitis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2020;127(110142, doi:10.1016/j.biopha.2020.110142

8.	Li H, Wu R, Yu H, et al. Bioactive Herbal Extracts of Traditional Chinese Medicine Applied with the Biomaterials: For the Current Applications and Advances in the Musculoskeletal System. Front Pharmacol 2021;12(778041, doi:10.3389/fphar.2021.778041

9.	Li XZ, Zhang SN. Recent advance in treatment of osteoarthritis by bioactive components from herbal medicine. Chinese medicine 2020;15(80, doi:10.1186/s13020-020-00363-5

10.	Chen BH, Zhang HF, Qiu JJ, et al. Mechanical Force Induced Self-Assembly of Chinese Herbal Hydrogel with Synergistic Effects of Antibacterial Activity and Immune Regulation for Wound Healing. Small 2022;18(21):13, doi:10.1002/smll.202201766

11.	Bu L, Dai O, Zhou F, et al. Traditional Chinese medicine formulas, extracts, and compounds promote angiogenesis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2020;132(110855, doi:10.1016/j.biopha.2020.110855

12.	Zhao W, Zhang R, Ma C, et al. Study on the wound healing, anti-inflammation and anti-bacterial activities of Jinjianling cream: A Chinese herbal compound. Pakistan journal of pharmaceutical sciences 2019;32(3 Special):1361-1370

13.	Kumar M, Keshwania P, Chopra S, et al. Therapeutic Potential of Nanocarrier-Mediated Delivery of Phytoconstituents for Wound Healing: Their Current Status and Future Perspective. AAPS PharmSciTech 2023;24(6):155, doi:10.1208/s12249-023-02616-6

14.	Tarun Agarwal S-AT, Valentina Onesto, Jia Xian Law, Garima Agrawal, Sampriti Pal, Wei Lee Lim, Esmaeel Sharifi, Farnaz Dabbagh Moghaddam, Tapas Kumar Maiti. Engineered herbal scaffolds for tissue repair and regeneration Recent trends and technologies. Biomedical Engineering Advances 2021;2(doi:10.1016/j.bea.2021.100015

15.	Adewole KE, Attah AF, Adebayo JO. Morinda lucida Benth (Rubiaceae): A review of its ethnomedicine, phytochemistry and pharmacology. J Ethnopharmacol 2021;276(114055, doi:10.1016/j.jep.2021.114055

16.	Adewole KE. Nigerian antimalarial plants and their anticancer potential: A review. J Integr Med 2020;18(2):92-113, doi:10.1016/j.joim.2020.01.001

17.	Latos-Brozio M, Masek A. Structure-Activity Relationships Analysis of Monomeric and Polymeric Polyphenols (Quercetin, Rutin and Catechin) Obtained by Various Polymerization Methods. Chem Biodivers 2019;16(12):e1900426, doi:10.1002/cbdv.201900426

18.	Bergamini CM, Gambetti S, Dondi A, et al. Oxygen, reactive oxygen species and tissue damage. Current pharmaceutical design 2004;10(14):1611-26, doi:10.2174/1381612043384664

19.	Worsley AL, Lui DH, Ntow-Boahene W, et al. The importance of inflammation control

for the treatment of chronic diabetic wounds. Int Wound J 2023;20(6):2346-2359, doi:10.1111/iwj.14048

20. Janakiram NB, Valerio MS, Goldman SM, et al. The Role of the Inflammatory Response in Mediating Functional Recovery Following Composite Tissue Injuries. Int J Mol Sci 2021;22(24), doi:10.3390/ijms222413552

21. Charlton NC, Mastyugin M, Török B, et al. Structural Features of Small Molecule Antioxidants and Strategic Modifications to Improve Potential Bioactivity. Molecules 2023;28(3), doi:10.3390/molecules28031057

22. Croft KD. Dietary polyphenols: Antioxidants or not? Arch Biochem Biophys 2016;595(120-4, doi:10.1016/j.abb.2015.11.014

23. Yahfoufi N, Alsadi N, Jambi M, et al. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients 2018;10(11), doi:10.3390/nu10111618

24. Khan H, Sureda A, Belwal T, et al. Polyphenols in the treatment of autoimmune diseases. Autoimmunity reviews 2019;18(7):647-657, doi:10.1016/j.autrev.2019.05.001

25. Coppo E, Marchese A. Antibacterial activity of polyphenols. Current pharmaceutical biotechnology 2014;15(4):380-90, doi:10.2174/138920101504140825121142

26. Zhao D, Zhang M, Yuan H, et al. Ginsenoside Rb1 protects against spinal cord ischemia-reperfusion injury in rats by downregulating the Bax/Bcl-2 ratio and caspase-3 and p-Ask-1 levels. Experimental and molecular pathology 2018;105(3):229-235, doi:10.1016/j.yexmp.2018.09.001

27. Xu Z, Yang D, Huang X, et al. Astragaloside IV Protects 6-Hydroxydopamine-Induced SH-SY5Y Cell Model of Parkinson's Disease via Activating the JAK2/STAT3 Pathway. Frontiers in neuroscience 2021;15(631501, doi:10.3389/fnins.2021.631501

28. Im DS. Pro-Resolving Effect of Ginsenosides as an Anti-Inflammatory Mechanism of Panax ginseng. Biomolecules 2020;10(3), doi:10.3390/biom10030444

29. Qi Y, Gao F, Hou L, et al. Anti-Inflammatory and Immunostimulatory Activities of Astragalosides. The American journal of Chinese medicine 2017;45(6):1157-1167, doi:10.1142/s0192415x1750063x

30. Singh D, Chaudhuri PK. Structural characteristics, bioavailability and cardioprotective potential of saponins. Integrative medicine research 2018;7(1):33-43, doi:10.1016/j.imr.2018.01.003

31. Zheng Q, Bao XY, Zhu PC, et al. Ginsenoside Rb1 for Myocardial Ischemia/Reperfusion Injury: Preclinical Evidence and Possible Mechanisms. Oxidative medicine and cellular longevity 2017;2017(6313625, doi:10.1155/2017/6313625

32. Zarneshan SN, Fakhri S, Khan H. Targeting Akt/CREB/BDNF signaling pathway by ginsenosides in neurodegenerative diseases: A mechanistic approach. Pharmacological research 2022;177(106099, doi:10.1016/j.phrs.2022.106099

33. Cheng S, Zhang X, Feng Q, et al. Astragaloside IV exerts angiogenesis and cardioprotection after myocardial infarction via regulating PTEN/PI3K/Akt signaling pathway. Life sciences 2019;227(82-93, doi:10.1016/j.lfs.2019.04.040

34. Lee SY, Kim YJ, Chung SO, et al. Recent studies on ursolic acid and its biological and pharmacological activity. EXCLI journal 2016;15(221-8, doi:10.17179/excli2016-159

35. Luan M, Wang H, Wang J, et al. Advances in Anti-inflammatory Activity, Mechanism and Therapeutic Application of Ursolic Acid. Mini reviews in medicinal chemistry 2022;22(3):422-436, doi:10.2174/1389557521666210913113522

36. Xin Q, Yuan R, Shi W, et al. A review for the anti-inflammatory effects of paeoniflorin in inflammatory disorders. Life sciences 2019;237(116925, doi:10.1016/j.lfs.2019.116925

37. Zhang L, Wei W. Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony. Pharmacology & therapeutics 2020;207(107452, doi:10.1016/j.pharmthera.2019.107452

38. Yu H, Gong W, Mei J, et al. The efficacy of a paeoniflorin-sodium alginate-gelatin

skin scaffold for the treatment of diabetic wound: An in vivo study in a rat model. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2022;151(113165, doi:10.1016/j.biopha.2022.113165

39.   Malik EM, Müller CE. Anthraquinones As Pharmacological Tools and Drugs. Med Res Rev 2016;36(4):705-48, doi:10.1002/med.21391

40.   Cui Y, Chen LJ, Huang T, et al. The pharmacology, toxicology and therapeutic potential of anthraquinone derivative emodin. Chinese journal of natural medicines 2020;18(6):425-435, doi:10.1016/s1875-5364(20)30050-9

41.   Park JG, Kim SC, Kim YH, et al. Anti-Inflammatory and Antinociceptive Activities of Anthraquinone-2-Carboxylic Acid. Mediators of inflammation 2016;2016(1903849, doi:10.1155/2016/1903849

42.   Yen G-C, Duh P-D, Chuang D-Y. Antioxidant activity of anthraquinones and anthrone. Food Chemistry 2000;70(4):437-441, doi:https://doi.org/10.1016/S0308-8146(00)00108-4

43.   Cicero AF, Baggioni A. Berberine and Its Role in Chronic Disease. Advances in experimental medicine and biology 2016;928(27-45, doi:10.1007/978-3-319-41334-1_2

44.   Kang S, Li Z, Yin Z, et al. The antibacterial mechanism of berberine against Actinobacillus pleuropneumoniae. Natural product research 2015;29(23):2203-6, doi:10.1080/14786419.2014.1001388

45.   Dhamgaye S, Devaux F, Vandeputte P, et al. Molecular mechanisms of action of herbal antifungal alkaloid berberine, in Candida albicans. PloS one 2014;9(8):e104554, doi:10.1371/journal.pone.0104554

46.   Cao F, Xia W, Dai S, et al. Berberine: An inspiring resource for the treatment of colorectal diseases. Biomed Pharmacother 2023;167(115571, doi:10.1016/j.biopha.2023.115571

47.   Kawano M, Takagi R, Kaneko A, et al. Berberine is a dopamine D1- and D2-like receptor antagonist and ameliorates experimentally induced colitis by suppressing innate and adaptive immune responses. J Neuroimmunol 2015;289(43-55, doi:10.1016/j.jneuroim.2015.10.001

48.   Zhang YQ, Zhang M, Wang ZL, et al. Advances in plant-derived C-glycosides: Phytochemistry, bioactivities, and biotechnological production. Biotechnology advances 2022;60(108030, doi:10.1016/j.biotechadv.2022.108030

49.   Liu H, Lv P, Zhu Y, et al. Salidroside promotes peripheral nerve regeneration based on tissue engineering strategy using Schwann cells and PLGA: in vitro and in vivo. Scientific reports 2017;7(39869, doi:10.1038/srep39869

50.   Wang Y, Su Y, Lai W, et al. Salidroside Restores an Anti-inflammatory Endothelial Phenotype by Selectively Inhibiting Endothelial Complement After Oxidative Stress. Inflammation 2020;43(1):310-325, doi:10.1007/s10753-019-01121-y

51.   Lai WF, Rogach AL. Hydrogel-Based Materials for Delivery of Herbal Medicines. ACS Appl Mater Interfaces 2017;9(13):11309-11320, doi:10.1021/acsami.6b16120

52.   Chu C, Wang Y, Wang Y, et al. Evaluation of epigallocatechin-3-gallate (EGCG) modified collagen in guided bone regeneration (GBR) surgery and modulation of macrophage phenotype. Mater Sci Eng C Mater Biol Appl 2019;99(73-82, doi:10.1016/j.msec.2019.01.083

53.   Shen P, Chen Y, Luo S, et al. Applications of biomaterials for immunosuppression in tissue repair and regeneration. Acta Biomater 2021;126(31-44, doi:10.1016/j.actbio.2021.03.019

54.   Whitaker R, Hernaez-Estrada B, Hernandez RM, et al. Immunomodulatory Biomaterials for Tissue Repair. Chem Rev 2021;121(18):11305-11335, doi:10.1021/acs.chemrev.0c00895

55.   Schuhladen K, Roether JA, Boccaccini AR. Bioactive glasses meet phytotherapeutics: The potential of natural herbal medicines to extend the functionality of bioactive glasses. Biomaterials 2019;217(119288, doi:10.1016/j.biomaterials.2019.119288

56. Udalamaththa VL, Jayasinghe CD, Udagama PV. Potential role of herbal remedies in stem cell therapy: proliferation and differentiation of human mesenchymal stromal cells. Stem Cell Res Ther 2016;7(1):110, doi:10.1186/s13287-016-0366-4

57. Tarassoli SP, Jessop ZM, Al-Sabah A, et al. Skin tissue engineering using 3D bioprinting: An evolving research field. Journal of plastic, reconstructive & aesthetic surgery : JPRAS 2018;71(5):615-623, doi:10.1016/j.bjps.2017.12.006

58. Kim BS, Kwon YW, Kong JS, et al. 3D cell printing of in vitro stabilized skin model and in vivo pre-vascularized skin patch using tissue-specific extracellular matrix bioink: A step towards advanced skin tissue engineering. Biomaterials 2018;168(38-53, doi:10.1016/j.biomaterials.2018.03.040

59. Venkatasubbu GD, Anusuya T. Investigation on Curcumin nanocomposite for wound dressing. International Journal of Biological Macromolecules 2017;98(366-378, doi:10.1016/j.ijbiomac.2017.02.002

60. He Y, Yue Y, Zheng X, et al. Curcumin, Inflammation, and Chronic Diseases: How Are They Linked? Molecules 2015;20(5):9183-9213, doi:10.3390/molecules20059183

61. Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of advanced research 2015;6(2):105-21, doi:10.1016/j.jare.2013.07.006

62. Wang H, Xu Z, Zhao M, et al. Advances of hydrogel dressings in diabetic wounds. Biomater Sci 2021;9(5):1530-1546, doi:10.1039/d0bm01747g

63. Su Y, Zhang B, Sun R, et al. PLGA-based biodegradable microspheres in drug delivery: recent advances in research and application. Drug Deliv 2021;28(1):1397-1418, doi:10.1080/10717544.2021.1938756

64. Ghezzi M, Pescina S, Padula C, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J Control Release 2021;332(312-336, doi:10.1016/j.jconrel.2021.02.031

65. Mitchell MJ, Billingsley MM, Haley RM, et al. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov 2021;20(2):101-124, doi:10.1038/s41573-020-0090-8

66. Wan S, Sun Y, Qi X, et al. Improved bioavailability of poorly water-soluble drug curcumin in cellulose acetate solid dispersion. AAPS PharmSciTech 2012;13(1):159-66, doi:10.1208/s12249-011-9732-9

67. Dutt Y, Pandey RP, Dutt M, et al. Therapeutic applications of nanobiotechnology. J Nanobiotechnology 2023;21(1):148, doi:10.1186/s12951-023-01909-z

68. Gautam S, Dinda AK, Mishra NC. Fabrication and characterization of PCL/gelatin composite nanofibrous scaffold for tissue engineering applications by electrospinning method. Mater Sci Eng C Mater Biol Appl 2013;33(3):1228-35, doi:10.1016/j.msec.2012.12.015

69. Mutlu G, Calamak S, Ulubayram K, et al. Curcumin-loaded electrospun PHBV nanofibers as potential wound-dressing material. Journal of Drug Delivery Science and Technology 2018;43(185-193, doi:https://doi.org/10.1016/j.jddst.2017.09.017

70. Rajab TK, O'Malley TJ, Tchantchaleishvili V. Decellularized scaffolds for tissue engineering: Current status and future perspective. Artif Organs 2020;44(10):1031-1043, doi:10.1111/aor.13701

71. Fereshteh Z. 7 - Freeze-drying technologies for 3D scaffold engineering. In: Functional 3D Tissue Engineering Scaffolds. (Deng Y, Kuiper J. eds.) Woodhead Publishing: 2018; pp. 151-174.

72. Ren SY, Liu YS, Zhu GJ, et al. Strategies and challenges in the treatment of chronic venous leg ulcers. World journal of clinical cases 2020;8(21):5070-5085, doi:10.12998/wjcc.v8.i21.5070

73. Bhardwaj N, Chouhan D, Mandal BB. Tissue Engineered Skin and Wound Healing: Current Strategies and Future Directions. Current pharmaceutical design 2017;23(24):3455-3482, doi:10.2174/1381612823666170526094606

74. Kaur G, Narayanan G, Garg D, et al. Biomaterials-Based Regenerative Strategies for

Skin Tissue Wound Healing. ACS Appl Bio Mater 2022;5(5):2069-2106, doi:10.1021/acsabm.2c00035

75.   Kant V, Gopal A, Pathak NN, et al. Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats. International immunopharmacology 2014;20(2):322-30, doi:10.1016/j.intimp.2014.03.009

76.   Wang Y, Tang Q, Duan P, et al. Curcumin as a therapeutic agent for blocking NF-κB activation in ulcerative colitis. Immunopharmacology and immunotoxicology 2018;40(6):476-482, doi:10.1080/08923973.2018.1469145

77.   Akbik D, Ghadiri M, Chrzanowski W, et al. Curcumin as a wound healing agent. Life sciences 2014;116(1):1-7, doi:10.1016/j.lfs.2014.08.016

78.   Gong Y, Wang P, Cao R, et al. Exudate Absorbing and Antimicrobial Hydrogel Integrated with Multifunctional Curcumin-Loaded Magnesium Polyphenol Network for Facilitating Burn Wound Healing. ACS Nano 2023, doi:10.1021/acsnano.3c04556

79.   Kumbhar S, Khairate R, Bhatia M, et al. Evaluation of curcumin-loaded chitosan nanoparticles for wound healing activity. Admet dmpk 2023;11(4):601-613, doi:10.5599/admet.1897

80.   Shakiba M, Sheikhi M, Pahnavar Z, et al. Development of an antibacterial and antioxidative nanofibrous membrane using curcumin-loaded halloysite nanotubes for smart wound healing: In vitro and in vivo studies. Int J Pharm 2023;642(123207, doi:10.1016/j.ijpharm.2023.123207

81.   Liu J, Chen Z, Wang J, et al. Encapsulation of Curcumin Nanoparticles with MMP9-Responsive and Thermos-Sensitive Hydrogel Improves Diabetic Wound Healing. ACS Appl Mater Interfaces 2018;10(19):16315-16326, doi:10.1021/acsami.8b03868

82.   Zhang X, Feng J, Feng W, et al. Glycosaminoglycan-Based Hydrogel Delivery System Regulates the Wound Microenvironment to Rescue Chronic Wound Healing. ACS Appl Mater Interfaces 2022;14(28):31737-31750, doi:10.1021/acsami.2c08593

83.   Kamar SS, Abdel-Kader DH, Rashed LA. Beneficial effect of Curcumin Nanoparticles-Hydrogel on excisional skin wound healing in type-I diabetic rat: Histological and immunohistochemical studies. Ann Anat 2019;222(94-102, doi:10.1016/j.aanat.2018.11.005

84.   Hu B, Gao M, Boakye-Yiadom KO, et al. An intrinsically bioactive hydrogel with on-demand drug release behaviors for diabetic wound healing. Bioact Mater 2021;6(12):4592-4606, doi:10.1016/j.bioactmat.2021.04.040

85.   Khamrai M, Banerjee SL, Paul S, et al. Curcumin entrapped gelatin/ionically modified bacterial cellulose based self-healable hydrogel film: An eco-friendly sustainable synthesis method of wound healing patch. Int J Biol Macromol 2019;122(940-953, doi:10.1016/j.ijbiomac.2018.10.196

86.   Yang BY, Hu CH, Huang WC, et al. Effects of Bilayer Nanofibrous Scaffolds Containing Curcumin/Lithospermi Radix Extract on Wound Healing in Streptozotocin-Induced Diabetic Rats. Polymers (Basel) 2019;11(11), doi:10.3390/polym11111745

87.   Liu C, Zhu Y, Lun X, et al. Effects of wound dressing based on the combination of silver@curcumin nanoparticles and electrospun chitosan nanofibers on wound healing. Bioengineered 2022;13(2):4328-4339, doi:10.1080/21655979.2022.2031415

88.   Tong WY, bin Abdullah AYK, binti Rozman NAS, et al. Antimicrobial wound dressing film utilizing cellulose nanocrystal as drug delivery system for curcumin. Cellulose 2017;25(1):631-638, doi:10.1007/s10570-017-1562-9

89.   Singh H, Purohit SD, Bhaskar R, et al. Curcumin in decellularized goat small intestine submucosa for wound healing and skin tissue engineering. J Biomed Mater Res B Appl Biomater 2022;110(1):210-219, doi:10.1002/jbm.b.34903

90.   Singh H, Bashir SM, Purohit SD, et al. Nanoceria laden decellularized extracellular matrix-based curcumin releasing nanoemulgel system for full-thickness wound healing.

Biomater Adv 2022;137(212806, doi:10.1016/j.bioadv.2022.212806

91. Agarwal Y, Rajinikanth PS, Ranjan S, et al. Curcumin loaded polycaprolactone-/polyvinyl alcohol-silk fibroin based electrospun nanofibrous mat for rapid healing of diabetic wound: An in-vitro and in-vivo studies. International Journal of Biological Macromolecules 2021;176(376-386, doi:10.1016/j.ijbiomac.2021.02.025

92. Ranjbar-Mohammadi M, Bahrami SH. Electrospun curcumin loaded poly(epsilon-caprolactone)/gum tragacanth nanofibers for biomedical application. Int J Biol Macromol 2016;84(448-56, doi:10.1016/j.ijbiomac.2015.12.024

93. Jirofti N, Golandi M, Movaffagh J, et al. Improvement of the Wound-Healing Process by Curcumin-Loaded Chitosan/Collagen Blend Electrospun Nanofibers: In Vitro and In Vivo Studies. ACS Biomater Sci Eng 2021;7(8):3886-3897, doi:10.1021/acsbiomaterials.1c00131

94. Dong G, Liu H, Yu X, et al. Antimicrobial and anti-biofilm activity of tannic acid against Staphylococcus aureus. Natural product research 2018;32(18):2225-2228, doi:10.1080/14786419.2017.1366485

95. Samoilova Z, Tyulenev A, Muzyka N, et al. Tannic and gallic acids alter redox-parameters of the medium and modulate biofilm formation. AIMS microbiology 2019;5(4):379-392, doi:10.3934/microbiol.2019.4.379

96. Jing W, Xiaolan C, Yu C, et al. Pharmacological effects and mechanisms of tannic acid. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2022;154(113561, doi:10.1016/j.biopha.2022.113561

97. Jafari H, Ghaffari-Bohlouli P, Niknezhad SV, et al. Tannic acid: a versatile polyphenol for design of biomedical hydrogels. J Mater Chem B 2022;10(31):5873-5912, doi:10.1039/d2tb01056a

98. Natarajan V, Krithica N, Madhan B, et al. Preparation and properties of tannic acid cross-linked collagen scaffold and its application in wound healing. J Biomed Mater Res B Appl Biomater 2013;101(4):560-7, doi:10.1002/jbm.b.32856

99. Li N, Yang X, Liu W, et al. Tannic Acid Cross-linked Polysaccharide-Based Multifunctional Hemostatic Microparticles for the Regulation of Rapid Wound Healing. Macromol Biosci 2018;18(11):e1800209, doi:10.1002/mabi.201800209

100. Kaczmarek B, Wekwejt M, Nadolna K, et al. The mechanical properties and bactericidal degradation effectiveness of tannic acid-based thin films for wound care. J Mech Behav Biomed Mater 2020;110(103916, doi:10.1016/j.jmbbm.2020.103916

101. Yang Y, Zhao X, Yu J, et al. Bioactive skin-mimicking hydrogel band-aids for diabetic wound healing and infectious skin incision treatment. Bioact Mater 2021;6(11):3962-3975, doi:10.1016/j.bioactmat.2021.04.007

102. Zhou C, Zou Y, Xu R, et al. Metal-phenolic self-assembly shielded probiotics in hydrogel reinforced wound healing with antibiotic treatment. Mater Horiz 2023;10(8):3114-3123, doi:10.1039/d3mh00033h

103. Li D, Li J, Wang S, et al. Dually Crosslinked Copper-Poly(tannic acid) Nanoparticles with Microenvironment-Responsiveness for Infected Wound Treatment. Adv Healthc Mater 2023;12(17):e2203063, doi:10.1002/adhm.202203063

104. Zhou J, Wu Y, Zhang X, et al. Enzyme Catalyzed Hydrogel as Versatile Bioadhesive for Tissue Wound Hemostasis, Bonding, and Continuous Repair. Biomacromolecules 2021;22(4):1346-1356, doi:10.1021/acs.biomac.0c01329

105. Preman NK, E SS, Prabhu A, et al. Bioresponsive supramolecular hydrogels for hemostasis, infection control and accelerated dermal wound healing. J Mater Chem B 2020;8(37):8585-8598, doi:10.1039/d0tb01468k

106. Deng H, Yu Z, Chen S, et al. Facile and eco-friendly fabrication of polysaccharides-based nanocomposite hydrogel for photothermal treatment of wound infection. Carbohydr Polym 2020;230(115565, doi:10.1016/j.carbpol.2019.115565

107. Albright V, Xu M, Palanisamy A, et al. Micelle-Coated, Hierarchically Structured

Nanofibers with Dual-Release Capability for Accelerated Wound Healing and Infection Control. Adv Healthc Mater 2018;7(11):e1800132, doi:10.1002/adhm.201800132

108.   Al Zahrani NA, El-Shishtawy RM, Asiri AM. Recent developments of gallic acid derivatives and their hybrids in medicinal chemistry: A review. European journal of medicinal chemistry 2020;204(112609, doi:10.1016/j.ejmech.2020.112609

109.   Lin Y, Luo T, Weng A, et al. Gallic Acid Alleviates Gouty Arthritis by Inhibiting NLRP3 Inflammasome Activation and Pyroptosis Through Enhancing Nrf2 Signaling. Frontiers in immunology 2020;11(580593, doi:10.3389/fimmu.2020.580593

110.   Ferk F, Kundi M, Brath H, et al. Gallic Acid Improves Health-Associated Biochemical Parameters and Prevents Oxidative Damage of DNA in Type 2 Diabetes Patients: Results of a Placebo-Controlled Pilot Study. Molecular nutrition & food research 2018;62(4), doi:10.1002/mnfr.201700482

111.   Sun C, Zeng X, Zheng S, et al. Bio-adhesive catechol-modified chitosan wound healing hydrogel dressings through glow discharge plasma technique. Chemical Engineering Journal 2022;427(doi:10.1016/j.cej.2021.130843

112.   Park SG, Li MX, Cho WK, et al. Thermosensitive gallic acid-conjugated hexanoyl glycol chitosan as a novel wound healing biomaterial. Carbohydr Polym 2021;260(117808, doi:10.1016/j.carbpol.2021.117808

113.   Zhang Y, Wang Y, Chen L, et al. An injectable antibacterial chitosan-based cryogel with high absorbency and rapid shape recovery for noncompressible hemorrhage and wound healing. Biomaterials 2022;285(doi:10.1016/j.biomaterials.2022.121546

114.   Kaparekar PS, Pathmanapan S, Anandasadagopan SK. Polymeric scaffold of Gallic acid loaded chitosan nanoparticles infused with collagen-fibrin for wound dressing application.   Int   J   Biol   Macromol   2020;165(Pt   A):930-947, doi:10.1016/j.ijbiomac.2020.09.212

115.   Li Y, Yao J, Han C, et al. Quercetin, Inflammation and Immunity. Nutrients 2016;8(3):167, doi:10.3390/nu8030167

116.   Yang D, Wang T, Long M, et al. Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. Oxidative medicine and cellular longevity 2020;2020(8825387, doi:10.1155/2020/8825387

117.   Vedakumari WS, Ayaz N, Karthick AS, et al. Quercetin impregnated chitosan-fibrin composite scaffolds as potential wound dressing materials - Fabrication, characterization and in vivo analysis. Eur J Pharm Sci 2017;97(106-112, doi:10.1016/j.ejps.2016.11.012

118.   Wang L, Dong J, Zhao Z, et al. Quarternized chitosan/quercetin/polyacrylamide semi-interpenetrating network hydrogel with recoverability, toughness and antibacterial properties for wound healing. Int J Biol Macromol 2023;228(48-58, doi:10.1016/j.ijbiomac.2022.12.086

119.   Zhang Z, Dai Q, Zhang Y, et al. Design of a Multifunctional Biomaterial Inspired by Ancient Chinese Medicine for Hair Regeneration in Burned Skin. ACS Appl Mater Interfaces 2020;12(11):12489-12499, doi:10.1021/acsami.9b22769

120.   Zhou YX, Zhang H, Peng C. Puerarin: a review of pharmacological effects. Phytotherapy research : PTR 2014;28(7):961-75, doi:10.1002/ptr.5083

121.   Chang X, Zhang T, Liu D, et al. Puerarin Attenuates LPS-Induced Inflammatory Responses and Oxidative Stress Injury in Human Umbilical Vein Endothelial Cells through Mitochondrial   Quality   Control.   Oxidative   medicine   and   cellular   longevity 2021;2021(6659240, doi:10.1155/2021/6659240

122.   Wang ZK, Chen RR, Li JH, et al. Puerarin protects against myocardial ischemia/reperfusion injury by inhibiting inflammation and the NLRP3 inflammasome: The role of the SIRT1/NF-κB pathway. International immunopharmacology 2020;89(Pt B):107086, doi:10.1016/j.intimp.2020.107086

123.   Zeng X, Chen B, Wang L, et al. Chitosan@Puerarin hydrogel for accelerated wound healing in diabetic subjects by miR-29ab1 mediated inflammatory axis suppression. Bioact

Mater 2023;19(653-665, doi:10.1016/j.bioactmat.2022.04.032

124.   Ou Q, Zhang S, Fu C, et al. More natural more better: triple natural anti-oxidant puerarin/ferulic acid/polydopamine incorporated hydrogel for wound healing. J Nanobiotechnology 2021;19(1):237, doi:10.1186/s12951-021-00973-7

125.   Zhang S, Ou Q, Xin P, et al. Polydopamine/puerarin nanoparticle-incorporated hybrid hydrogels for enhanced wound healing. Biomater Sci 2019;7(10):4230-4236, doi:10.1039/c9bm00991d

126.   Chen B, Zhang H, Qiu J, et al. Mechanical Force Induced Self-Assembly of Chinese Herbal Hydrogel with Synergistic Effects of Antibacterial Activity and Immune Regulation for Wound Healing. Small 2022;18(21):e2201766, doi:10.1002/smll.202201766

127.   Warowicka A, Nawrot R, Goździcka-Józefiak A. Antiviral activity of berberine. Archives of virology 2020;165(9):1935-1945, doi:10.1007/s00705-020-04706-3

128.   Li S, Wang Y, Wang S, et al. In situ gelling hydrogel loaded with berberine liposome for the treatment of biofilm-infected wounds. Front Bioeng Biotechnol 2023;11(1189010, doi:10.3389/fbioe.2023.1189010

129.   Hu H, Zhong D, Li W, et al. Microalgae-based bioactive hydrogel loaded with quorum sensing inhibitor promotes infected wound healing. Nano Today 2022;42(doi:10.1016/j.nantod.2021.101368

130.   Zhang P, He L, Zhang J, et al. Preparation of novel berberine nano-colloids for improving wound healing of diabetic rats by acting Sirt1/NF-kappaB pathway. Colloids Surf B Biointerfaces 2020;187(110647, doi:10.1016/j.colsurfb.2019.110647

131.   Sh Ahmed A, Taher M, Mandal UK, et al. Pharmacological properties of Centella asiatica hydrogel in accelerating wound healing in rabbits. BMC complementary and alternative medicine 2019;19(1):213, doi:10.1186/s12906-019-2625-2

132.   Han Y, Jiang Y, Li Y, et al. An aligned porous electrospun fibrous scaffold with embedded asiatic acid for accelerating diabetic wound healing. J Mater Chem B 2019;7(40):6125-6138, doi:10.1039/c9tb01327j

133.   Chen X, Peng LH, Shan YH, et al. Astragaloside IV-loaded nanoparticle-enriched hydrogel induces wound healing and anti-scar activity through topical delivery. International journal of pharmaceutics 2013;447(1-2):171-81, doi:10.1016/j.ijpharm.2013.02.054

134.   Gao SQ, Chang C, Li JJ, et al. Co-delivery of deferoxamine and hydroxysafflor yellow A to accelerate diabetic wound healing via enhanced angiogenesis. Drug Deliv 2018;25(1):1779-1789, doi:10.1080/10717544.2018.1513608

135.   Yang H, Song L, Sun B, et al. Modulation of macrophages by a paeoniflorin-loaded hyaluronic acid-based hydrogel promotes diabetic wound healing. Mater Today Bio 2021;12(100139, doi:10.1016/j.mtbio.2021.100139

136.   Guo C, Wu Y, Li W, et al. Development of a Microenvironment-Responsive Hydrogel Promoting Chronically Infected Diabetic Wound Healing through Sequential Hemostatic, Antibacterial, and Angiogenic Activities. ACS Appl Mater Interfaces 2022;14(27):30480-30492, doi:10.1021/acsami.2c02725

137.   Zhou G, Zhu J, Jin L, et al. Salvianolic-Acid-B-Loaded HA Self-Healing Hydrogel Promotes Diabetic Wound Healing through Promotion of Anti-Inflammation and Angiogenesis. Int J Mol Sci 2023;24(7), doi:10.3390/ijms24076844

138.   Cao C, Yang N, Zhao Y, et al. Biodegradable hydrogel with thermo-response and hemostatic effect for photothermal enhanced anti-infective therapy. Nano Today 2021;39(doi:10.1016/j.nantod.2021.101165

139.   Lu Y, Zhang W, Wang J, et al. Recent advances in cell sheet technology for bone and cartilage regeneration: from preparation to application. International journal of oral science 2019;11(2):17, doi:10.1038/s41368-019-0050-5

140.   Sun H, Liu W, Zhou G, et al. Tissue engineering of cartilage, tendon and bone. Frontiers of medicine 2011;5(1):61-9, doi:10.1007/s11684-011-0122-1

141. James AW, LaChaud G, Shen J, et al. A Review of the Clinical Side Effects of Bone Morphogenetic Protein-2. Tissue engineering Part B, Reviews 2016;22(4):284-97, doi:10.1089/ten.TEB.2015.0357

142. Gao Z-R, Feng Y-Z, Zhao Y-Q, et al. Traditional Chinese medicine promotes bone regeneration in bone tissue engineering. Chinese medicine 2022;17(1):86, doi:10.1186/s13020-022-00640-5

143. Wong RW, Rabie AB. Traditional Chinese medicines and bone formation--a review. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2006;64(5):828-37, doi:10.1016/j.joms.2006.01.017

144. Zhu Y, Ye L, Cai X, et al. Icariin-Loaded Hydrogel Regulates Bone Marrow Mesenchymal Stem Cell Chondrogenic Differentiation and Promotes Cartilage Repair in Osteoarthritis. Frontiers in bioengineering and biotechnology 2022;10(755260, doi:10.3389/fbioe.2022.755260

145. Yang J, Liu Y, He L, et al. Icariin conjugated hyaluronic acid/collagen hydrogel for osteochondral interface restoration. Acta biomaterialia 2018;74(156-167, doi:10.1016/j.actbio.2018.05.005

146. Liu Y, Yang J, Luo Z, et al. Development of an injectable thiolated icariin functionalized collagen/hyaluronic hydrogel to promote cartilage formation in vitro and in vivo. J Mater Chem B 2019;7(17):2845-2854, doi:10.1039/c9tb00211a

147. Zhou M, Guo M, Shi X, et al. Synergistically Promoting Bone Regeneration by Icariin-Incorporated Porous Microcarriers and Decellularized Extracellular Matrix Derived From Bone Marrow Mesenchymal Stem Cells. Frontiers in bioengineering and biotechnology 2022;10(824025, doi:10.3389/fbioe.2022.824025

148. Jin Y, Koh RH, Kim SH, et al. Injectable anti-inflammatory hyaluronic acid hydrogel for osteoarthritic cartilage repair. Mater Sci Eng C Mater Biol Appl 2020;115(111096, doi:10.1016/j.msec.2020.111096

149. Wang W, Liu Y, Yang C, et al. Delivery of Salvianolic Acid B for Efficient Osteogenesis and Angiogenesis from Silk Fibroin Combined with Graphene Oxide. ACS Biomater Sci Eng 2020;6(6):3539-3549, doi:10.1021/acsbiomaterials.0c00558

150. Chen ST, Zhu L, Wen W, et al. Fabrication and Evaluation of 3D Printed Poly(L-lactide) Scaffold Functionalized with Quercetin-Polydopamine for Bone Tissue Engineering. ACS Biomater Sci Eng 2019;5(5):2506-2518, doi:10.1021/acsbiomaterials.9b00254

151. Yap SP, Shen P, Li J, et al. Molecular and pharmacodynamic properties of estrogenic extracts from the traditional Chinese medicinal herb, Epimedium. Journal of ethnopharmacology 2007;113(2):218-24, doi:10.1016/j.jep.2007.05.029

152. Wang ZC, Sun HJ, Li KH, et al. Icariin promotes directed chondrogenic differentiation of bone marrow mesenchymal stem cells but not hypertrophy in vitro. Experimental and therapeutic medicine 2014;8(5):1528-1534, doi:10.3892/etm.2014.1950

153. Wang Z, Li K, Sun H, et al. Icariin promotes stable chondrogenic differentiation of bone marrow mesenchymal stem cells in self-assembling peptide nanofiber hydrogel scaffolds. Molecular medicine reports 2018;17(6):8237-8243, doi:10.3892/mmr.2018.8913

154. Lei H, Zhou Z, Liu L, et al. Icariin-loaded 3D-printed porous Ti6Al4V reconstruction rods for the treatment of necrotic femoral heads. Acta Biomater 2023;169(625-640, doi:10.1016/j.actbio.2023.07.057

155. Hu YM, Cao SJ, Chen JD, et al. Biomimetic fabrication of icariin loaded nano hydroxyapatite reinforced bioactive porous scaffolds for bone regeneration. Chemical Engineering Journal 2020;394(13, doi:10.1016/j.cej.2020.124895

156. Lai Y, Cao H, Wang X, et al. Porous composite scaffold incorporating osteogenic phytomolecule icariin for promoting skeletal regeneration in challenging osteonecrotic bone in rabbits. Biomaterials 2018;153(1-13, doi:10.1016/j.biomaterials.2017.10.025

157. Chen P, Xia C, Mo J, et al. Interpenetrating polymer network scaffold of sodium

hyaluronate and sodium alginate combined with berberine for osteochondral defect regeneration. Mater Sci Eng C Mater Biol Appl 2018;91(190-200, doi:10.1016/j.msec.2018.05.034

158.   Ma L, Yu Y, Liu H, et al. Berberine-releasing electrospun scaffold induces osteogenic differentiation of DPSCs and accelerates bone repair. Scientific reports 2021;11(1):1027, doi:10.1038/s41598-020-79734-9

159.   Zhang Y, Wang T, Li J, et al. Bilayer Membrane Composed of Mineralized Collagen and Chitosan Cast Film Coated With Berberine-Loaded PCL/PVP Electrospun Nanofiber Promotes Bone Regeneration. Frontiers in bioengineering and biotechnology 2021;9(684335, doi:10.3389/fbioe.2021.684335

160.   Chen L, Tian M, Yang J, et al. Berberine-Encapsulated Poly(lactic-co-glycolic acid)-Hydroxyapatite (PLGA/HA) Microspheres Synergistically Promote Bone Regeneration with DOPA-IGF-1 via the IGF-1R/PI3K/AKT/mTOR Pathway. Int J Mol Sci 2023;24(20), doi:10.3390/ijms242015403

161.   Eliaz N, Metoki N. Calcium Phosphate Bioceramics: A Review of Their History, Structure, Properties, Coating Technologies and Biomedical Applications. Materials (Basel, Switzerland) 2017;10(4), doi:10.3390/ma10040334

162.   Hu C, Wu LN, Zhou CC, et al. Berberine/Ag nanoparticle embedded biomimetic calcium phosphate scaffolds for enhancing antibacterial function. Nanotechnol Rev 2020;9(1):568-579, doi:10.1515/ntrev-2020-0046

163.   Sun H, Hu C, Zhou CC, et al. 3D printing of calcium phosphate scaffolds with controlled release o antibacterial functions for jaw bone repair. Materials & Design 2020;189(13, doi:10.1016/j.matdes.2020.108540

164.   Steinmann J, Buer J, Pietschmann T, et al. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. Br J Pharmacol 2013;168(5):1059-73, doi:10.1111/bph.12009

165.   Liu J, Lu Y, Liu J, et al. Influence of epigallocatechin-3-gallate in promoting proliferation and osteogenic differentiation of human periodontal ligament cells. BMC oral health 2019;19(1):73, doi:10.1186/s12903-019-0768-7

166.   Wang D, Wang Y, Xu S, et al. Epigallocatechin-3-gallate Protects against Hydrogen Peroxide-Induced Inhibition of Osteogenic Differentiation of Human Bone Marrow-Derived Mesenchymal Stem Cells. Stem cells international 2016;2016(7532798, doi:10.1155/2016/7532798

167.   Ahmed S. Green tea polyphenol epigallocatechin 3-gallate in arthritis: progress and promise. Arthritis Res Ther 2010;12(2):208, doi:10.1186/ar2982

168.   Chu C, Deng J, Man Y, et al. Evaluation of nanohydroxyapaptite (nano-HA) coated epigallocatechin-3-gallate (EGCG) cross-linked collagen membranes. Mater Sci Eng C Mater Biol Appl 2017;78(258-264, doi:10.1016/j.msec.2017.04.069

169.   Gao B, Honda Y, Yamada Y, et al. Utility of Thermal Cross-Linking in Stabilizing Hydrogels with Beta-Tricalcium Phosphate and/or Epigallocatechin Gallate for Use in Bone Regeneration Therapy. Polymers (Basel) 2021;14(1), doi:10.3390/polym14010040

170.   Malaguarnera L. Influence of Resveratrol on the Immune Response. Nutrients 2019;11(5), doi:10.3390/nu11050946

171.   Ornstrup MJ, Harsløf T, Sørensen L, et al. Resveratrol Increases Osteoblast Differentiation In Vitro Independently of Inflammation. Calcified Tissue International 2016;99(2):155-163, doi:10.1007/s00223-016-0130-x

172.   Yu F, Li M, Yuan Z, et al. Mechanism research on a bioactive resveratrol- PLA-gelatin porous nano-scaffold in promoting the repair of cartilage defect. Int J Nanomedicine 2018;13(7845-7858, doi:10.2147/ijn.S181855

173.   Wang CC, Wang CH, Chen HC, et al. Combination of resveratrol-containing collagen with adipose stem cells for craniofacial tissue-engineering applications. International wound

journal 2018;15(4):660-672, doi:10.1111/iwj.12910

174. Li B, Wang M, Liu Y, et al. Independent effects of structural optimization and resveratrol functionalization on extracellular matrix scaffolds for bone regeneration. Colloids Surf B Biointerfaces 2022;212(112370, doi:10.1016/j.colsurfb.2022.112370

175. Lavrador P, Gaspar VM, Mano JF. Bioinspired bone therapies using naringin: applications and advances. Drug Discov Today 2018;23(6):1293-1304, doi:10.1016/j.drudis.2018.05.012

176. Yang X, Almassri HNS, Zhang Q, et al. Electrosprayed naringin-loaded microsphere/SAIB hybrid depots enhance bone formation in a mouse calvarial defect model. Drug Deliv 2019;26(1):137-146, doi:10.1080/10717544.2019.1568620

177. Zhao ZH, Ma XL, Zhao B, et al. Naringin-inlaid silk fibroin/hydroxyapatite scaffold enhances human umbilical cord-derived mesenchymal stem cell-based bone regeneration. Cell proliferation 2021;54(7):e13043, doi:10.1111/cpr.13043

178. Wu J, Miao G, Zheng Z, et al. 3D printing mesoporous bioactive glass/sodium alginate/gelatin sustained release scaffolds for bone repair. Journal of biomaterials applications 2019;33(6):755-765, doi:10.1177/0885328218810269

179. Ji C, Bi L, Li J, et al. Salvianolic Acid B-Loaded Chitosan/hydroxyapatite Scaffolds Promotes The Repair Of Segmental Bone Defect By Angiogenesis And Osteogenesis. Int J Nanomedicine 2019;14(8271-8284, doi:10.2147/ijn.S219105

180. Sistanipour E, Meshkini A, Oveisi H. Catechin-conjugated mesoporous hydroxyapatite nanoparticle: A novel nano-antioxidant with enhanced osteogenic property. Colloids Surf B Biointerfaces 2018;169(329-339, doi:10.1016/j.colsurfb.2018.05.046

181. Chen W, Li Y, Huang Y, et al. Quercetin modified electrospun PHBV fibrous scaffold enhances cartilage regeneration. Journal of materials science Materials in medicine 2021;32(8):92, doi:10.1007/s10856-021-06565-z

182. Yu W, Zhu Y, Li H, et al. Injectable Quercetin-Loaded Hydrogel with Cartilage-Protection and Immunomodulatory Properties for Articular Cartilage Repair. ACS applied bio materials 2020;3(2):761-771, doi:10.1021/acsabm.9b00673

183. Asgari N, Bagheri F, Eslaminejad MB, et al. Dual functional construct containing kartogenin releasing microtissues and curcumin for cartilage regeneration. Stem cell research & therapy 2020;11(1):289, doi:10.1186/s13287-020-01797-2

184. Oh Y, Ahn CB, Marasinghe M, et al. Insertion of gallic acid onto chitosan promotes the differentiation of osteoblasts from murine bone marrow-derived mesenchymal stem cells. Int J Biol Macromol 2021;183(1410-1418, doi:10.1016/j.ijbiomac.2021.05.122

185. Shi G, Yang C, Wang Q, et al. Traditional Chinese Medicine Compound-Loaded Materials in Bone Regeneration. Frontiers in bioengineering and biotechnology 2022;10(851561, doi:10.3389/fbioe.2022.851561

186. George J, Hsu CC, Nguyen LTB, et al. Neural tissue engineering with structured hydrogels in CNS models and therapies. Biotechnology advances 2020;42(107370, doi:10.1016/j.biotechadv.2019.03.009

187. Burns TC, Quinones-Hinojosa A. Regenerative medicine for neurological diseases-will regenerative neurosurgery deliver? BMJ (Clinical research ed) 2021;373(n955, doi:10.1136/bmj.n955

188. Willerth SM, Sakiyama-Elbert SE. Approaches to neural tissue engineering using scaffolds for drug delivery. Advanced drug delivery reviews 2007;59(4-5):325-38, doi:10.1016/j.addr.2007.03.014

189. Attari F, Ghadiri T, Hashemi M. Combination of curcumin with autologous transplantation of adult neural stem/progenitor cells leads to more efficient repair of damaged cerebral tissue of rat. Experimental physiology 2020;105(9):1610-1622, doi:10.1113/ep088697

190. Elkhenany H, Bonilla P, Giraldo E, et al. A Hyaluronic Acid Demilune Scaffold and

Polypyrrole-Coated Fibers Carrying Embedded Human Neural Precursor Cells and Curcumin for Surface Capping of Spinal Cord Injuries. Biomedicines 2021;9(12), doi:10.3390/biomedicines9121928

191. Luo J, Shi X, Li L, et al. An injectable and self-healing hydrogel with controlled release of curcumin to repair spinal cord injury. Bioact Mater 2021;6(12):4816-4829, doi:10.1016/j.bioactmat.2021.05.022

192. Jahromi HK, Farzin A, Hasanzadeh E, et al. Enhanced sciatic nerve regeneration by poly-L-lactic acid/multi-wall carbon nanotube neural guidance conduit containing Schwann cells and curcumin encapsulated chitosan nanoparticles in rat. Mater Sci Eng C Mater Biol Appl 2020;109(110564, doi:10.1016/j.msec.2019.110564

193. Chen S, Jiang H, Wu X, et al. Therapeutic Effects of Quercetin on Inflammation, Obesity, and Type 2 Diabetes. Mediators of inflammation 2016;2016(9340637, doi:10.1155/2016/9340637

194. Huang C, Fu C, Qi ZP, et al. Localised delivery of quercetin by thermo-sensitive PLGA-PEG-PLGA hydrogels for the treatment of brachial plexus avulsion. Artificial cells, nanomedicine, and biotechnology 2020;48(1):1010-1021, doi:10.1080/21691401.2020.1770265

195. Zhang B, Wang Y, Li H, et al. Neuroprotective effects of salidroside through PI3K/Akt pathway activation in Alzheimer's disease models. Drug design, development and therapy 2016;10(1335-43, doi:10.2147/dddt.S99958

196. Xin M, Olson EN, Bassel-Duby R. Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair. Nature reviews Molecular cell biology 2013;14(8):529-41, doi:10.1038/nrm3619

197. Wu T, Cui C, Huang Y, et al. Coadministration of an Adhesive Conductive Hydrogel Patch and an Injectable Hydrogel to Treat Myocardial Infarction. ACS Appl Mater Interfaces 2020;12(2):2039-2048, doi:10.1021/acsami.9b17907

198. Qian L, Huang Y, Spencer CI, et al. In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes. Nature 2012;485(7400):593-8, doi:10.1038/nature11044

199. Shao-Mei W, Li-Fang Y, Li-Hong W. Traditional Chinese medicine enhances myocardial metabolism during heart failure. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2022;146(112538, doi:10.1016/j.biopha.2021.112538

200. Huang T, Liu Y, Zhang C. Pharmacokinetics and Bioavailability Enhancement of Baicalin: A Review. European journal of drug metabolism and pharmacokinetics 2019;44(2):159-168, doi:10.1007/s13318-018-0509-3

201. Kong F, Luan Y, Zhang ZH, et al. Baicalin protects the myocardium from reperfusion-induced damage in isolated rat hearts via the antioxidant and paracrine effect. Experimental and therapeutic medicine 2014;7(1):254-259, doi:10.3892/etm.2013.1369

202. Zhang S, Wang J, Pan J. Baicalin-loaded PEGylated lipid nanoparticles: characterization, pharmacokinetics, and protective effects on acute myocardial ischemia in rats. Drug delivery 2016;23(9):3696-3703, doi:10.1080/10717544.2016.1223218

203. Wang J, Zhang S, Di L. Acute myocardial infarction therapy: in vitro and in vivo evaluation of atrial natriuretic peptide and triphenylphosphonium dual ligands modified, baicalin-loaded nanoparticulate system. Drug delivery 2021;28(1):2198-2204, doi:10.1080/10717544.2021.1989086

204. Chen R, Zhu C, Xu L, et al. An injectable peptide hydrogel with excellent self-healing ability to continuously release salvianolic acid B for myocardial infarction. Biomaterials 2021;274(120855, doi:10.1016/j.biomaterials.2021.120855

205. Chen JR, Han XX, Deng J, et al. An injectable hydrogel based on phenylboronic acid hyperbranched macromer encapsulating gold nanorods and Astragaloside IV nanodrug for myocardial infarction. Chemical Engineering Journal 2021;413(15,

doi:10.1016/j.cej.2020.127423

206.   Liao X, Song X, Li J, et al. An injectable co-assembled hydrogel blocks reactive oxygen species and inflammation cycle resisting myocardial ischemia-reperfusion injury. Acta biomaterialia 2022;149(82-95, doi:10.1016/j.actbio.2022.06.039

207.   Fan C, Shi J, Zhuang Y, et al. Myocardial-Infarction-Responsive Smart Hydrogels Targeting Matrix Metalloproteinase for On-Demand Growth Factor Delivery. Advanced materials (Deerfield Beach, Fla) 2019;31(40):e1902900, doi:10.1002/adma.201902900

208.   Wu T, Liu W. Functional hydrogels for the treatment of myocardial infarction. NPG Asia Materials 2022;14(1):9, doi:10.1038/s41427-021-00330-y

209.   Liu Y, Zhang X, Wu T, et al. Chinese herb-crosslinked hydrogel bearing rBMSCs-laden polyzwitterion microgels: Self-adaptive manipulation of micromilieu and stemness maintenance for restoring infarcted myocardium. Nano Today 2021;41(101306, doi:https://doi.org/10.1016/j.nantod.2021.101306

210.   Yang J, Wei K, Wang Y, et al. Construction of a small-caliber tissue-engineered blood vessel using icariin-loaded β-cyclodextrin sulfate for in situ anticoagulation and endothelialization. Science China Life sciences 2018;61(10):1178-1188, doi:10.1007/s11427-018-9348-9

211.   Wang H, Zhang Y, Xia T, et al. Synergistic promotion of blood vessel regeneration by astragaloside IV and ferulic acid from electrospun fibrous mats. Molecular pharmaceutics 2013;10(6):2394-403, doi:10.1021/mp400031y

212.   Kuang H, Wang Y, Hu J, et al. A Method for Preparation of an Internal Layer of Artificial Vascular Graft Co-Modified with Salvianolic Acid B and Heparin. ACS applied materials & interfaces 2018;10(23):19365-19372, doi:10.1021/acsami.8b02602

213.   Lin S, Cui L, Chen G, et al. PLGA/β-TCP composite scaffold incorporating salvianolic acid B promotes bone fusion by angiogenesis and osteogenesis in a rat spinal fusion model. Biomaterials 2019;196(109-121, doi:10.1016/j.biomaterials.2018.04.004