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Review article

Developing Chinese herbal-based functional biomaterials for tissue engineering

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A R T I C L E I N F O

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A B S T R A C T

The role of traditional Chinese medicine (TCM) in treating diseases is receiving increasing attention. Chinese herbal medicine is an important part of TCM with various applications and the active ingredients extracted from Chinese herbal medicines have physiological and pathological effects. Tissue engineering combines cell biology and materials science to construct tissues or organs *in vitro* or *in vivo*. TCM has been proposed by the World Health Organization as an effective treatment modality. In recent years, the potential use of TCM in tissue engineering has been demonstrated. In this review, the classification and efficacy of TCM active ingredients and delivery systems are discussed based on the TCM theory. We also summarized the current application status and broad prospects of Chinese herbal active ingredients in different specialized biomaterials in the field of tissue engineering. This review provides novel insights into the integration of TCM and modern Western medicine through the application of Chinese medicine in tissue engineering and regenerative medicine.

1. Introduction

With the rapid development of modern technology and the integration of traditional Chinese medicine (TCM), current studies on Chinese herbal medicine have led to substantial achievements in biological and clinical research. Significant advancements have been made in the realm of Chinese herbal medicine research, encompassing various aspects such as processing techniques, dosage forms, pharmacological properties, toxicological considerations, and clinical applications. The active ingredients in herbs directly affect the therapeutic outcome of medicines. The active ingredients of herbal medicines are generally classified into flavonoids, alkaloids, terpenoids, and polyphenols, and their main effects include anti-inflammatory, antibacterial, antioxidant, and antitumor functions, as well as the regulation of growth factors, promotion of vascular regeneration, and regulation of stem cell proliferation and differentiation.

Tissue engineering (TE) is an interdisciplinary field that integrates engineering, materials, and medical sciences to develop biological patterns for the repair, replacement, preservation, or enhancement of tissues and organs [1]. Certain components of Chinese

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herbal medicines have functions similar to growth factors and corresponding pharmacological effects, which are important for promoting cell proliferation as well as repair and regeneration of tissues or organs. Moreover, the physicochemical properties of Chinese medicines are relatively stable, so their application in tissue engineering has increasingly attracted extensive attention from researchers at home and abroad. Current barriers to TE include the lack of appropriate biomaterials, ineffective seed cell growth, lack of techniques for adaptation to physiological structures, and instability of growth factors [2]. Nowadays, Chinese medicine has been shown to play a vital role in the prevention and management of diseases such as cardiovascular disease, cancer, and diabetes, and has therefore been widely used in TE research. For example, Icariin-induced made from herbal extracts has good osteoconductive and osteoinductive activities, which can effectively fill bone defects and promote early osteogenesis [3]. Kaempferol can promote the proliferation of human periodontal membrane cells, which provides a new method of value-added expansion *in vitro* for seed cells for periodontal tissue engineering [4]. All of these findings bode well for the application of natural and traditional Chinese medicines in the field of tissue engineering. In addition, Chinese medicines have anti-inflammatory, angiogenesis-promoting, anticoagulant, and stem cell proliferation and differentiation effects in tissue engineering.

This review provides an overview of the potential therapeutic capabilities of herbal medicine combined with tissue engineering. The chemical structures, sources, efficacy, and mechanisms of active ingredients in Chinese medicine are also described. Finally, the applications and prospects of TCM in TE are presented, providing directions for further development of novel TCM.

2. Traditional Chinese medicine

2.1. *Bioactive substances of Chinese herbal medicine*

Chinese herbal medicine is one of the oldest healing methods used in the treatment of different diseases and health-associated conditions in China [5,6]. Herbal medicine is becoming increasingly popular owing to its holistic and systemic approach, particularly for the prevention and treatment of chronic diseases [7]. The active ingredients of Chinese herbal medicine are extracted from different herbs, which have biological functions and therapeutic properties. More than 2000 years ago, the *Shennong Ben Cao Jing* (Classic of the Divine Husbandman's Materia Medica) recorded the use of Chinese herbs in the treatment of diseases [8]. Nowadays, herbal medicine plays a pivotal role in the prevention and management of cardiovascular diseases, cancer, diabetes, and other diseases [9]. Artemisinin-based combination therapies have been widely used to treat malaria over the past 20 years, and the "Chinese grass" has saved millions of lives around the world [10]. Therefore, further understanding of the biological functions of herbal medicines can expand their application.

The classification of Chinese herbal medicines is both complex and diverse. From ancient texts and pharmacopoeias, such as *Shennong's Herbal Classic*, *Compendium of Materia Medica*, and *Shanghan Zabing Lun*, to the latest Chinese Pharmacopoeia, there are still differences in the classification criteria of Chinese herbal medicine. The active ingredients of herbal medicines can be categorized into alkaloids, terpenoids, flavonoids, and volatile oils **(Table 1)**.

2.2. *Efficacy of effective active ingredients in Chinese medicine*

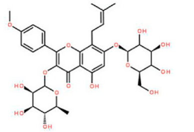
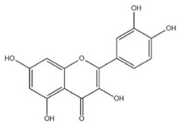
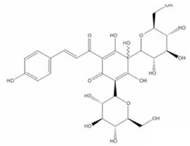
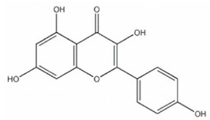
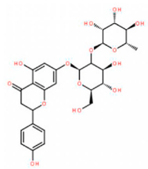
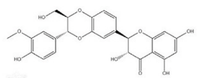
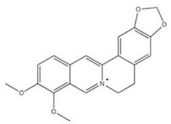
2.2.1. *Antibacterial and anti-inflammatory*

Herbs have antibacterial and anti-inflammatory properties. Chinese herbal medicine has a long history in the prevention and treatment of infectious diseases. Compared with contemporary antibacterial drugs, Chinese herbal medicine has a wide range of sources and a reduced incidence of adverse reactions. Furthermore, in the context of prolonged clinical utilization, no obvious drug resistance of pathogens has been observed [11]. For instance, the Coptis extract berberine exhibits noteworthy antibacterial properties, demonstrating inhibitory effects on a range of bacteria including *Shigella*, *Mycobacterium tuberculosis*, *Pneumococcus*, *Salmonella typhi*, and *Diphtheria* [12]. Quercetin produces bactericidal effects and reduces bacterial adhesion by more than 70% [13]. Over the past few years, there has been a growing trend in integrating traditional Chinese medicine extracts with biomaterials, showcasing their remarkable antibacterial efficacy. For example, 10 g/mL of zinc silymarin complex has shown significant antibacterial effects against *Escherichia coli* and *Staphylococcus aureus*, which minimized the risk of implant bacterial infection [14]. The Chinese herbal hydrogel was prepared by self-assembling chitosan (CS) and puerarin (PUE), resulting in an antibacterial rate that surpassed 95% (Fig. 1A) [15]. The therapeutic effect of traditional Chinese medicine regulates the immune system of the body to a certain extent, ultimately playing a therapeutic role. Ginsenoside Rb1 can inhibit the expression of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 [16]**.** Based on the available reports, it has been observed that the multifunctional nanomaterial aggregated of ginsenoside Rb1 with man-nose-modified azocalix [4]arene (ManAC4A) exhibits both macrophage induction function and the capability to eliminate reactive oxygen species (ROS) [17] (Fig. 1B).

2.2.2. *Wound healing*

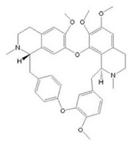
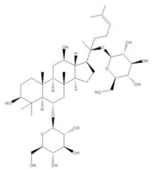
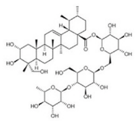
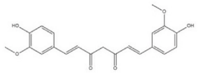
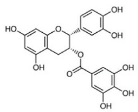
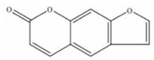
Several herbal drugs, such as *Centella asiatica*, birch bark, calendula, aloe vera, and turmeric have been extensively studied and demonstrated to be clinically effective, promoting wound healing (Fig. 1C). *Centella asiatica* promotes the proliferation of fibroblasts, increases the synthesis of collagen, and inhibits inflammation, thus promoting wound healing [18]. Owing to its excellent wound-healing properties, researchers have developed various wound dressings containing *Centella asiatica*, all of which have shown excellent wound-healing activity, suggesting their potential use as wound-healing agents [19,20]. *Calendula officinalis* can accelerate the proliferation and migration of fibroblasts and can promote angiogenesis and collagen deposition [21]. By regulating inflammation and increasing wound contraction and epithelialization, *Aloe vera* has been found to exert excellent wound-healing effects with

Table 1
Bioactive substances of traditional Chinese herbal medicine.

Category	Composition	Chemical structure formula	Origin	Main role	References
Flavonoids	Icariin		*Epimedium brevicornum* Maxim	bone regeneration, treat fractures	[104]
	Quercetin		*Fagopyrum esculentum* Moench	antioxidant, free radical scavenging, metal ion chelating	[105]
	hydroxysafflor yellow A		*Carthamus tinctorius* L.	promotes angiogenesis, inhibits platelet-activating factor	[106]
	Kaempferol		*Kaempferia galanga* L.	osteoclast bone resorption inhibition, anti-inflammatory, antioxidant	[107,108]
	Naringin		*Citrus maxima* (Burm.) Merr.	anti-inflammatory, antiviral, anticancer, analgesic, hypotensive, improves local microcirculation, treats cardiovascular disease	[109]
	Silymarin		*Silybum marianum* (L.) Gaertn.	removal of reactive oxygen species, liver protection, antitumor	[110]
Alkaloid Compounds	Berberine		Coptis chinensis Franch.	antibacterial	[111]

(*continued on next page*)

Table 1 (*continued*)

Category	Composition	Chemical structure formula	Origin	Main role	References
	(+)-Tetrandrine		*Stephania tetrandra* S. Moore	inhibits platelet aggregation caused by collagen, thrombin, etc.	[112]
terpenoid	Ginsenoside Rg1		*Panax ginseng* C. A. Meyer	cell proliferation and differentiation, antiapoptosis and anti-inflammation	[113]
	Asiaticoside		*Centella asiatica* (L.) Urban	antioxidant, antifibrotic, promotes wound healing, analgesic, antitumor	[114]
Polyphenol	Curcumin		*Curcuma longa* L.	antioxidant, anti-inflammatory, anticancer	[115]
	Epigallocatechin gallate, EGCG		Green Tea	antioxidant, anti-inflammatory	[116]
Benprotinin	Psoralen		*Psoralea corylifolia* Linn.	anticancer, hemostatic, promotes bone healing	[117]

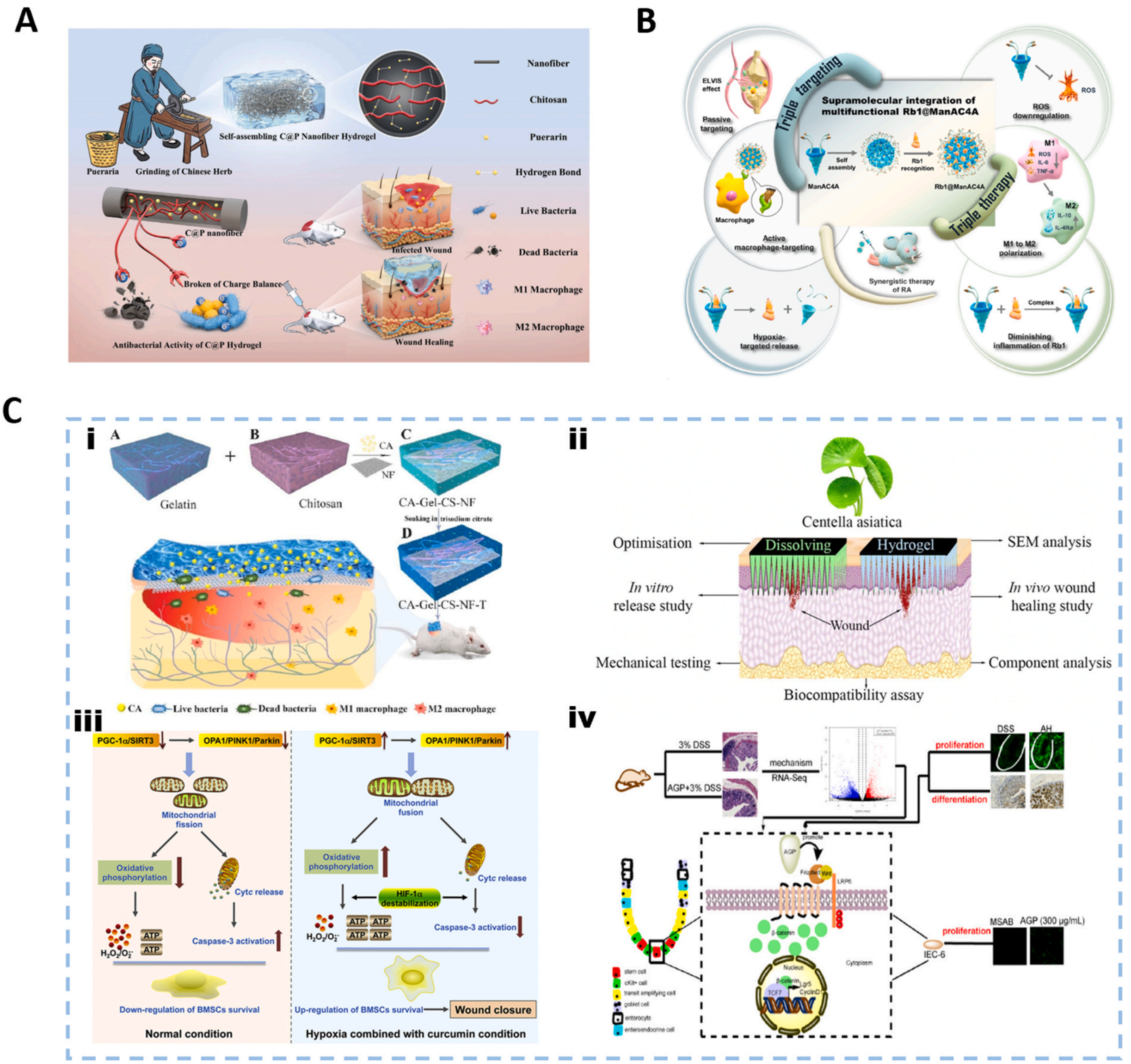


Fig. 1. The efficacy of the active ingredients of Chinese medicine. (A) The Chinese herbal medicine hydrogel of chitosan and puerarin has antibacterial activity. (B)The multifunctional nanomaterial of ginsenoside Rb1 exhibits macrophage induction function and the ability to clear reactive oxygen species (ROS). (C) Effects of proangiogenic phytochemicals in wound healing. Reprinted with permission from Ref. [15,17].

negligible toxicity [22]. Glucomannan, the principal constituent of *Aloe vera*, elicits fibroblast proliferation, thereby enhancing collagen synthesis and secretion [23]. Curcumin, the primary bioactive compound found in turmeric, has demonstrated the ability to expedite epithelial reformation, enhance neovascularization, and promote the migration of diverse cell types, such as dermal myofibroblasts and fibroblasts to the site of injury [24,25].

2.2.3. Osteogenesis

After the use of Epimedium, new bone formation can be observed at the site of the lesion, which is attributed to the upregulation of osteogenesis-related factors such as text-related transcription factor 2 (RUNX2), alkaline phosphatase (ALP), collagen (COL-I), and osteoblastin (OPN) [26]. Various herbal medicines, such as hydroxy saffron yellow A, kaempferol, naringin, quercetin, silymarin, safranin, ginsenoside, curcumin, and epigallocatechin gallate exert similar effects. Naringenin exerts positive effects on osteoblasts, such as upregulating the expression of bone morphogenetic protein 2 (BMP-2), osterix (OSX), OPN, COL-I, OCN, and increasing the calcium content, as well as inhibiting tartrate-resistant acid phosphatase (TRAP) [27]. The BMP family plays a crucial role in various biological processes associated with osteogenic differentiation, encompassing the preservation of bone homeostasis and the facilitation of bone regeneration. Several studies have demonstrated the mechanisms through which TCM promotes bone regeneration [28]. Intracellular calcium levels are enhanced through the activation of phospholipase C by Ca-polyP particles loaded with baicalin and

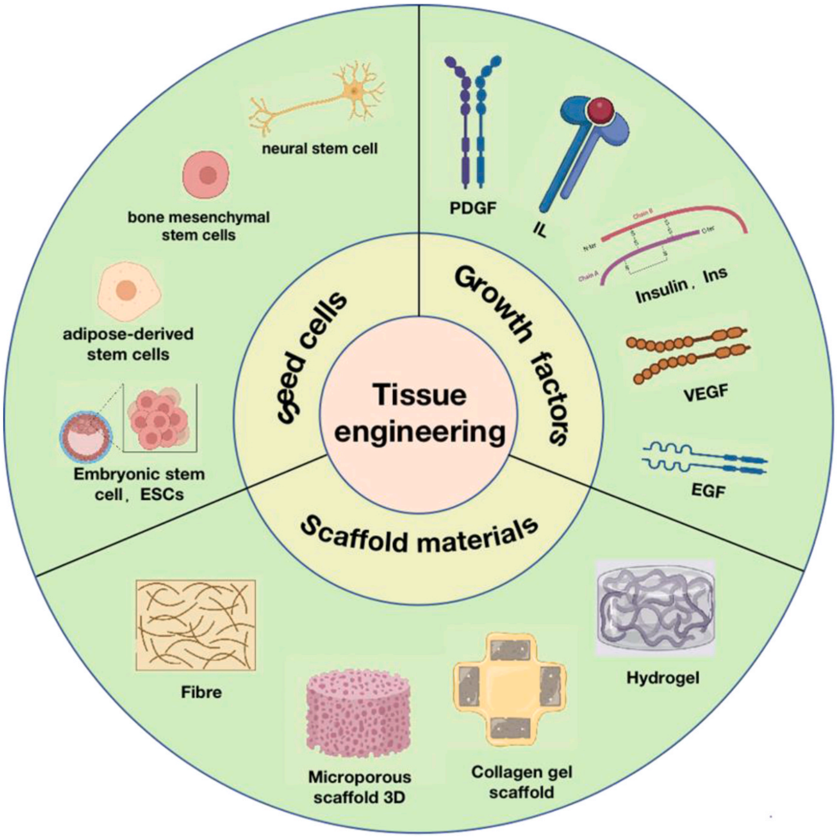


Fig. 2. Elements of tissue engineering (TE): seed cells, scaffold material, and growth factors.

scutellarin. Additionally, both flavonoids upregulate the expression of plasma membrane Ca^{2+}-ATPase (PMCA) and alkaline phosphatase (ALP), which facilitate bone mineralization [29].

Moreover, the Zn-silymarin complex exhibited favorable outcomes in promoting osteoblast differentiation through the regulation of the miR-590/Smad-7 signaling pathway [30]. Furthermore, anthocyanins have the capability to function as crosslinking agents, thereby enhancing the osteogenic process through the upregulation of RUNX2, OCN, OPN, and ALP expression [31].

3. TCM in tissue regeneration

The three elements of TE are cells, biomaterials, and the *in vivo* microenvironment (Fig. 2). TE has been performed for decades, with epidermal cell cultures and composite skin for the treatment of large burns being among the earliest examples of TE approaches [32,33]. Efforts have been made to develop tissue regeneration engineering techniques for cartilage, skin, bone, joints, tendons, blood vessels, nerves, and organs. Herbal active ingredients have osteogenic, vascular regeneration-promoting, anti-inflammatory, and antibacterial effects. Some studies have applied herbal active ingredients in different areas of tissue engineering. In this section, we present the application of TCM in tissue regeneration.

3.1. Bone and cartilage TE

Bone remodeling and regeneration are ongoing and dynamic physiological processes that are governed by two cellular mechanisms, namely bone formation and bone resorption [34]. The loss of bone tissue can potentially transpire as a consequence of accidents, trauma, cancer, or congenital malformations [35]. Despite bone remodeling and regeneration being continuous processes throughout life, the inherent capacity of bone tissue for self-repair is constrained, leading to the inevitable occurrence of post-surgical side effects [36]. Particularly, the presence of bone defects, especially those of considerable magnitude, significantly impairs the functionality of the affected region and adversely impacts the patient's overall quality of life [37]. Currently, autologous bone transplantation is regarded as the prevailing method for clinical bone transplantation and reconstruction [38]. Nevertheless, it is imperative to thoroughly assess the potential hazards associated with donor site lesions, the scarcity of graft availability, and the delayed formation of bone. In order to surmount these inherent obstacles, bone tissue engineering (BTE) is employed to create a microenvironment conducive to cellular activity, thereby facilitating defect repair and tissue regeneration. Currently, BTE has been utilized in the management of extensive bone tissue loss, encompassing cases of traumatic tumors, bone cancer tumor resection, congenital

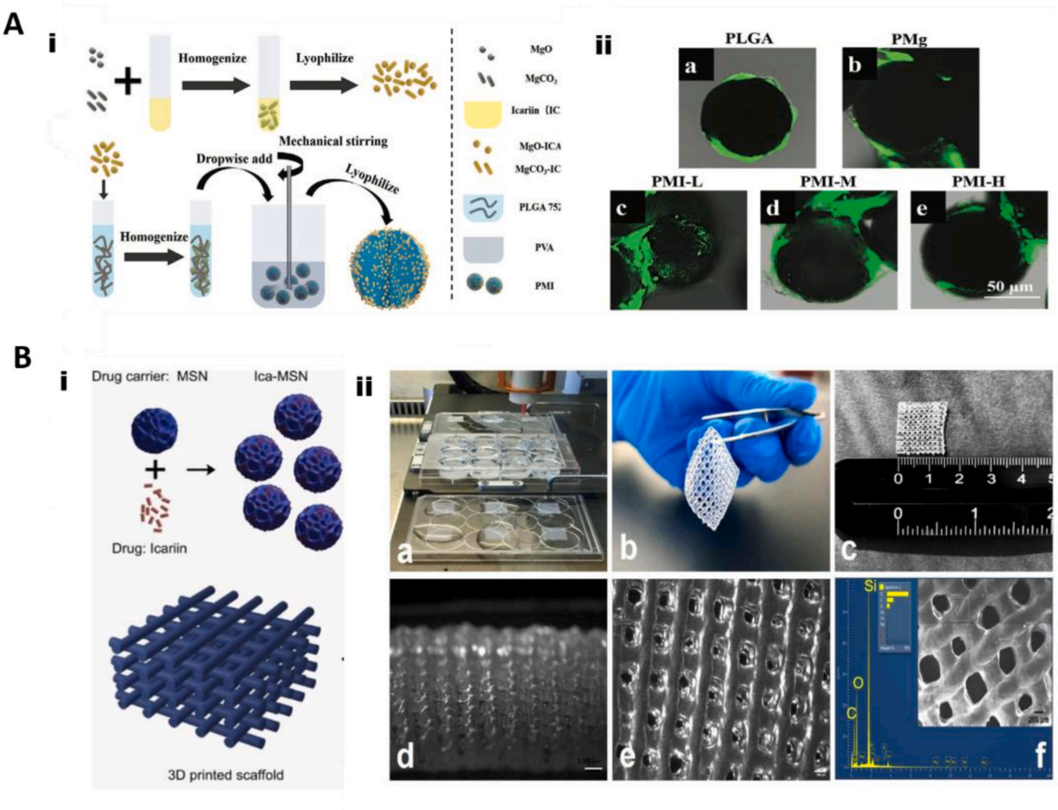


Fig. 3. Active ingredients of Chinese medicine for bone tissue engineering (BTE). (A) 3D printed TE scaffold. **(B)** Epimedium for BTE. Reprinted with permission from Ref. [47,50].

malformations, and infected bone tissue debridement. Desirable attributes of BTE encompass non-immunogenicity, biocompatibility, controllability, ready accessibility, mechanical properties akin to natural tissue materials, as well as structure, configuration, and pore size conducive to cell survival and activity [39]. As such, the emergence and development of BTE have provided a new method for bone regeneration.

The integration of TCM with bone transplantation has demonstrated distinctive benefits in the context of bone regeneration [40]. Different types of TCM promote bone formation through a variety of mechanisms and targets, such as regulating cell proliferation, osteogenesis and mineralization, cartilage formation, angiogenesis, or through anti-inflammatory, antioxidant, and antibacterial effects [41,42]. Natural Chinese medicine has been used for the treatment of various types of orthopedic diseases, with their local application directly affecting injured tissues and improving bone healing. One of the modes of action of these drugs is to increase osteoblast formation. According to previous studies, in addition to promoting osteogenesis and reducing the imbalance of osteoclast activity, TCM has been suggested to regulate bone anabolism, thereby improving bone density and its biomechanical properties, and reducing the degradation of bone microstructure. Here, we describe several common TCM active ingredients used in BTE that promote bone healing.

3.1.1. *Icariin*

Icariin has various therapeutic effects, including anticancer activity, immune regulation, and protective effects on various systems in the body. Notably, numerous studies have reported the efficacy of icariin in promoting bone tissue regeneration and preventing osteoporosis [43]. Moreover, icariin influences the regulation of multiple signaling pathways, such as those involved in anti-osteoporosis, osteogenesis, antiosteoclast formation, cartilage formation, angiogenesis, and antiinflammation [44]. While many synthetic bone substitutes exhibit high bone conductivity, they lack the ability to induce bone growth. Historically, the supplementation of scaffolds with growth factors such as BMP-2 has been employed to increase bone inductivity. However, the considerable costs and rapid degradation of these factors have presented significant challenges. The osteoinductive potential of icariin on osteoblasts was first demonstrated as early as 2008, making it a promising alternative [45].

A previous study has reported that a scaffold loaded with icariin is well suited for local delivery of icariin as a means of repairing bone defects. Icariin exhibits potential benefits for scaffold structure. The loaded icariin bioactive glass scaffold exhibits stronger mineralization effects [46]. A recent study developed a microsphere scaffold for dual controlled release of Chinese herbal medicine (i.e., icariin, collagen-induced arthritis (ICA)) and bioactive substances (i.e., Mg^{2+}), exhibiting superior bone formation induction ability

[47] (Fig. 3A). A separate study demonstrated that Icariin has the ability to stimulate both ERα (a non-genomic estrogen receptor) and Akt (a serine/threonine-specific protein kinase) through the enhanced rapid induction of insulin-like growth factor I (IGF-1) signaling in osteoblastic cells, thereby promoting osteogenesis [48]. Another study provides evidence that Icariin has the ability to both promote and inhibit the differentiation of bone marrow mesenchymal stem (BM-MS) cells into osteogenic and adipogenic lineages, respectively. This effect is achieved through the activation of the Wnt/β-catenin pathway, which is mediated by microRNA 23a [49]. The field of TE has witnessed an increased interest in the application of 3D printing technology. Its ability to provide precise and controlled microstructure within bone repair areas is particularly noteworthy. As such, 3D printing has emerged as a promising technology in TE research and development. For instance, combining different biomaterials together through 3D printing can effectively enhance the loading of icariin and enhance the inducing effect of loaded drugs on bone formation [50] (Fig. 3B).

3.1.2. Tetrandrine

Tetrandrine, derived from the Chinese medicinal plant *Stephania tetrandra*, has demonstrated potent antiviral properties against the Ebola virus [51]. Tetrandrine blocks the translocation of NF-κB-p65 and nuclear factor (NFATc1), which activates T-cells by reducing the activation of spleen tyrosine kinase, thereby inhibiting the generation of osteoclasts and reducing the bone destruction associated with CIA [52,53]. Tetrandrine effectively suppresses the formation of osteoclasts induced by RANK-l by impeding the signaling pathways of NF-κB, Ca^{2+}, PI3K/AKT, and MAPKs [54,55]. Tetrandrine has garnered significant attention in the realm of orthopedic biomaterials due to its diverse effects on bone tissues. Notably, the incorporation of tetrandrine at minimal concentrations within polylactic acid membranes promotes the proliferation of chondrocytes adhered to the drug carrier materials, bolster the functionality of chondrocytes, and amplify the expression of genes linked to cellular functions [56].

Furthermore, the use of tetrandrine-loaded membranes has demonstrated a notable decrease in the inflammatory response of macrophages. This was evident in implanted rats, where the tetrandrine-loaded membrane group exhibited significantly lower levels of inflammatory reaction compared to the normal polylactic acid membrane group [57]. A previous study has developed a

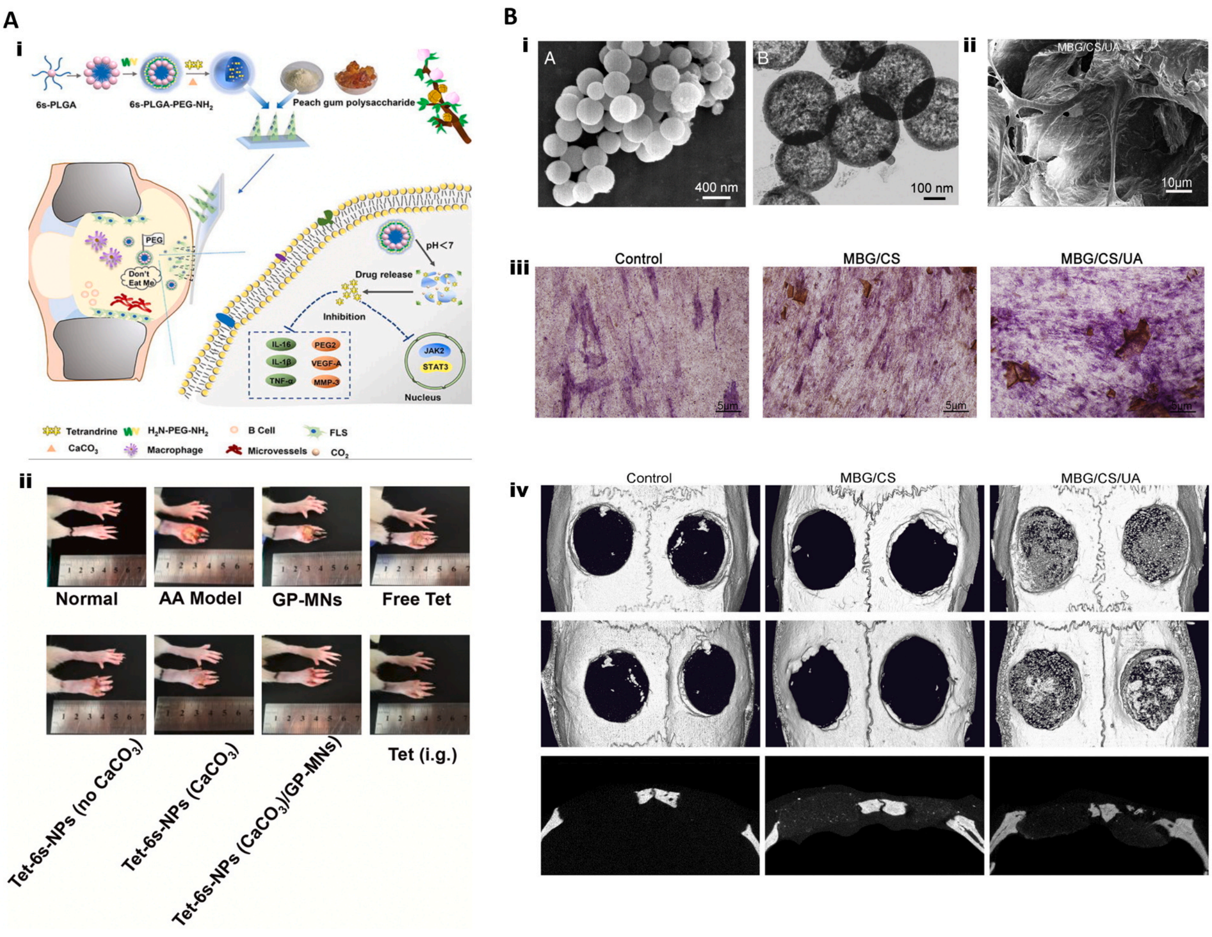


Fig. 4. Tetrandrine, Ursolic acid and bone tissue engineering (BTE). (A) A Schematic illustration showing the design and fabrication of the nanoparticles. The nanoparticles are formed by PEGylated star-shaped PLGA and calcium carbonate, which are loaded with tetrandrine. **(B)** SEM images of hBMSCs cultured on MBG/CS and MBG/CS/UA scaffolds. Micro-CT images of a calvarial defect repair model at 3 months post-surgery for the control, MBG/CS, and MBG/CS/UA groups. Reprinted with permission from Ref. [58,62].

nanoparticle loaded with tetrandrine that uses an integrated delivery strategy to increase the synovial uptake of tetrandrine (Fig. 4A) [58]. This multifunctional transdermal carrier loaded with tetrandrine manufactured by nanotechnology is a promising therapeutic approach to prevent local inflammation and improve arthritis.

3.1.3. Ursolic acid

Ursolic acid (UA) is a triterpene compound that exists in various natural plants and has various biological effects, such as sedative, anti-inflammatory, antibacterial, antidiabetic, antiulcer, and hypoglycemic functions [59]. The application of UA in a rat model of osteoporosis successfully mitigated the changes in serum alkaline phosphatase, osteocalcin, urine deoxypyridinoline, serum phosphorus, urine calcium, and urine phosphorus induced by retinoic acid, while concurrently exhibiting a significant improvement in bone density [60]. Additionally, UA exerts inhibitory effects on the proliferation and metastasis of osteosarcoma cells through the suppression of the epidermal growth factor receptor (EGFR) signaling pathway, a biomarker for osteosarcoma [61]. A novel porous scaffold composed of mesoporous bioglass and chitosan, incorporating UA (MBG/CS/UA), has been fabricated with the aim of augmenting bone regeneration. The corresponding structure of MBG microspheres and the chemical connection with UA drugs provided the stent with controllable drug release performance. The administration of the UA drug via the scaffold resulted in a substantial augmentation of alkaline phosphatase activity, as well as an upregulation in the expression of genes associated with osteoblast differentiation, namely type I collagen, run-related transcription factor 2, and osteoblast-related proteins. In addition, micro-CT images and histomorphology examination showed that the MBG/CS/UA scaffold improved the formation of new bone. Therefore, the MBG/CS/UA porous scaffold can be used as a new BTE material [62] (Fig. 4B). Although few studies have been conducted, the potential of using UA in combination with orthopedic biomaterials has gradually emerged.

3.1.4. Others

Cresol, primarily derived from locust trees, is a flavonoid renowned for its notable antioxidant, antifungal, and osteogenic attributes. Nevertheless, its utilization is constrained by its inadequate solubility and bioavailability. The incorporation of kaempferol into nanoparticles has demonstrated enhanced bioavailability [63,64]. A previous study showed that TiO_2 implantation and immobilization of kaempferol might be an effective tool for efficient bone regeneration in rats [65]. Furthermore, multiple studies have demonstrated that the active constituents found in TCM can fortify and augment the composition of biological substances, albeit lacking the capacity to directly elicit therapeutic outcomes. For example, procyanidins, primarily derived from grapes, serve as collagen crosslinking agents that have been employed in the restoration and prevention of dentin matrix degradation. This is achieved through the augmentation of collagen scaffolds' physical attributes and the stimulation of human periodontal ligament cell (hPDLC) proliferation [66,67].

3.2. Skin tissue engineering

The skin is the largest organ of the human body that reduces mechanical stimulation, prevents water evaporation, microbial invasion, and ultraviolet ray penetration, as well as regulates sensation, temperature, and various other bodily functions. However, once the skin is seriously injured, such as in burns and extensive wounds, it is difficult to heal itself, thereby hindering clinical treatment [68]. Natural active ingredients contained in herbal plants have immunomodulatory activity, control inflammatory responses, and influence coagulation, inflammation, epithelialization, collagen formation and wound contraction. Therefore, the incorporation of medicinal plant components in natural/synthetic polymers to make novel wound dressings is a method of skin wound care. The active components of these plants impart antimicrobial, anti-inflammatory and antioxidant properties to the dressings, which contribute to wound contraction, angiogenesis and epithelialization [69].

3.2.1. Flavonoids

In ancient China, the application of herbal formulas significantly enhanced wound healing, and one such formula, which contains four herbs, namely, *Lycopodium*, *Lotus seed*, thyme, and the pollen placenta, has been reported to promote and enhance wound healing [70,71]. These four herbs possess a diverse range of flavonoids and trace metal ions. Some flavonoids are known to chelate metal ions; consequently, the biological activity of these metal ion chelates of flavonoids may be higher than that of nonchelated flavonoids. In particular, three of these above-mentioned four herbs contain quercetin (Qu), a widely known flavonoid that promotes wound healing and stimulates the differentiation of related cells in damaged skin tissues [72]. Several scholars have suggested and developed composite electrospun membranes incorporating a quercetin copper chelate. To create a novel wound dressing for the treatment of skin burns, copper silicate bioceramic ($CaCuSi_4O_{10}$) was introduced into Polycaprolactone (PCL)/gelatin electrospun fibers. This innovative approach demonstrated significant efficacy in facilitating the expedited healing of burned skin and the regeneration of hair follicle tissue. By examining ancient Chinese medicine prescriptions and identifying shared components, it is possible to devise novel bioactive materials for tissue regeneration [73]. A study suggested that quercetin facilitates the proliferation of Epidermal Stem Cells (EpSCs) by activating the β-catenin/c-Myc/cyclinA2 signaling pathway via estrogen receptor (ER) mediation, which potentially expediting the process of skin wound healing [74]. This endeavor has the potential to broaden the scope of Chinese medicine in the field of regenerative medicine.

3.2.2. Aloe

Aloe gel encompasses a diverse array of glycoproteins capable of mitigating inflammation and alleviating discomfort, thereby expediting the recuperation process. Additionally, it contains polysaccharides that foster skin regeneration and proliferation and possesses the versatility to address both external and internal wounds [75]. Aloe gel exhibits dual effects on wound healing, as it not only enhances collagen synthesis and promotes wound closure through collagen structural modification and increased crosslinking between fibers, but also contains essential components such as vitamin C, vitamin E, and amino acids that contribute significantly to metabolic acceleration during the healing process. Vitamin C specifically stimulates collagen production and prevents fiber degradation, while vitamin E, known for its potent antioxidant properties, actively participates in wound healing [76,77]. A previous study used nanofibers to prepare plane-fiber scaffolds containing aloe gel [78] and observed that the scaffold gel enhanced and expedited the complete wound healing process by diminishing the inflammatory phase (resulting in a decrease in the quantity of multinuclear immune cells) and promoting fibroblast maturation, tissue proliferation, collagen synthesis, and epithelial cell regeneration. Aloe has been found to have a significant down-regulating effect on the expression of pro-inflammatory cytokines, such as IL-1β, thereby inducing anti-inflammatory effects [79]. This leads to a notable reduction in the duration of inflammation and the levels of malondialdehyde (MDA), tumor necrosis factor α (TNF-α), and IL-1β. Additionally, Aloe vera has been shown to significantly increase the expression of VEGF, insulin-like growth factor 1 (IGF-1), glucose transporter 1 (GLUT-1), and fibroblast growth factor 2 (FGF-2), which promotes cell proliferation, collagen synthesis, and angiogenesis [80].

3.3. Vascular tissue engineering

Tissue engineering provides a new avenue for vascular repair from a regenerative perspective. Tissue engineered blood vessels (TEBV) use tissue engineering methods to grow vascular seed cells (endothelial cells, smooth muscle cells) on natural or synthetic material scaffolds in order to construct tissue engineered blood vessels that are close to living blood vessels in terms of morphology and function. The synergistic integration of tissue manufacturing and stem cell engineering has introduced a novel approach to autologous vascular engineering, enabling the replication of both the mechanical characteristics and biological functionalities of native blood vessels [81]. In this context, icariin holds promising potential for the treatment of cardiovascular diseases. Furthermore, β-cyclodextrin sulfate, a hollow molecule exhibiting favorable biocompatibility and anticoagulant properties, has been reported to exhibit a sustained release effect on icariin. A previous study has investigated whether icariin-loaded sulfuric acid β-cyclodextrin promotes endothelialization of TEBV [82]. The authors showed that icariin significantly promoted the proliferation and migration of endothelial progenitor cells; concomitantly, icariin promoted the migration of rat vascular endothelial cells (RAVECs). Interestingly, icariin-loaded sulfuric acid β-cyclodextrin achieved the anticoagulation and rapid endothelialization of TEBV and ensured its long-term patency. The subsequent release of icariin promoted the migration of endothelial cells at the anastomotic site and the proliferation and migration of endothelial progenitor cells, thus accelerating the endothelialization of TEBV, ultimately realizing its long-term patency. A small diameter vascular scaffold combined with purslane flavonoids (PTFs) biomimetic fiber arrangement has been developed to provide contact guidance and growth control for human vascular smooth muscle cells (HVSMC), and the results showed that PTFs significantly inhibited intimal hyperplasia and atherosclerotic stenosis formation [83]. The promotion of vascular initiation and growth is a crucial factor in the successful attainment of therapeutic vascularization and functional tissue regeneration. Astragalus and Angelica are frequently employed as blood tonic herbs. In a previous investigation, electrospun fiber scaffolds were utilized to incorporate astragaloside IV (AT), the primary active constituent of Astragalus, and ferulic acid (FA), the primary component of Angelica, in order to facilitate a plentiful and sustained release of biokines necessary for the establishment and maturation of blood vessels. The localized and sustained co-delivery of AT and FA resulted in a significant enhancement of cell viability and secretion [84].

3.4. Nervous system tissue engineering

Repair of neurological damage due to diseases and accidents has always been an important clinical research problem. Unfortunately, following severe debilitating diseases such as spinal cord injury and traumatic brain injury, the nervous system is unable to repair damaged areas, and the central nervous system in particular has a very limited ability to regenerate in damaged areas [85]. In the case of minor injuries, the peripheral nervous system can rehabilitate itself under appropriate circumstances, and its inherent regenerative capacity provides post-injury nerve repair offers the possibility. End-to-end surgical reattachment of injured nerve ends and autologous nerve grafting are now standard techniques for repairing damaged peripheral nerves [86]. However, end-to-end surgical reattachment is not suitable for large gaps; autologous nerve grafting carries the risk of causing damage to the donor region and limited donor tissue. Tissue engineering offers the possibility of fabricating tissue substitutes that mimic the structural and physiological properties of tissues by combining principles and methods from cell biology, engineering, and materials science [87]. Due to its unique repair properties, neural tissue engineering has attracted much attention in the field of neural tissue repair and control of neuronal cell behavior (e.g., proliferation, differentiation, neutrophilic growth, and neural gap bridging) [88,89]. Some traditional Chinese medicines and their active ingredients can regulate stem cell activity and promote neuronal repair, and have been gradually applied in the field of neural tissue engineering in recent years.

3.4.1. Ginsenoside Rg1

Ginsenoside Rg1 is an active ingredient isolated from *Panax notoginseng* saponins (PNS), which can significantly reduce the volume of cerebral infarction caused by cerebral ischemia/reperfusion and alleviate neurological dysfunction [90]. Several scholars have postulated that the mechanism of this neuroprotective effect of ginsenoside Rg1 could potentially be attributed to its antioxidant, anti-inflammatory, and antiapoptotic properties, which facilitate the restoration of the blood-brain barrier and hinder excessive calcium accumulation [91]. Previous research has substantiated the participation of ginsenoside Rg1 in the regulation of stem cell activity. More specifically, experimental evidence has indicated that ginsenoside Rg1 augments the expression of neural cell adhesion molecule (NCAM) and synaptophysin-1 (SYN-1), thereby promoting enhanced proliferation and neural phenotype differentiation of adipose-derived stem cells in both human and murine models [92,93]. Moreover, the administration of Rg1 exhibited a positive influence on the proliferation and differentiation of endogenous NSCs in rats afflicted with Alzheimer's disease (AD), concurrently promoting the functional expression and maturation of human NSCs [94]. The administration of ginsenoside Rg1 to mice with middle cerebral artery occlusion (MCAO) resulted in a reduction of disorders in amino acid and fat metabolism, leading to improvements in neurological deficits and cerebral infarction. Nonetheless, there were minor distinctions observed between the treatment involving ginsenoside Rg1 alone and the combination therapy incorporating NSC transplantation [95]. There is a plethora of evidence suggesting that the ginsenoside metabolite 20(S)-protopanaxadiol plays a substantial role in promoting the transformation of neural stem cells (NSCs) from a proliferative state to a differentiating state. This transformation is accomplished through the initiation of autophagy and the halting of the cell cycle [96].

3.4.2. Astragaloside IV

Astragaloside IV (AST), a purified compound extracted from the root of Astragalus, has gained widespread usage in China for treating organ diseases [97]. A systematic review suggested that the primary beneficial effect of AST on neurological disorders was its antiedema effect achieved by reducing the infiltration of lymphocytes and the number of dopaminergic neurons [98]. Low-dose AST promoted the proliferation of NSCs, whereas high-dose did not affect the cells. Moreover, low-dose AST promoted the differentiation of NSCs *in vitro* [99]. Ni et al. have investigated the role of AST after stroke using an MCAO rat model and showed that treatment with AST reduced the cerebral infarction volume of rats and promoted the proliferation, migration, differentiation, and maturation of neurons in the hippocampus by enhancing the BDNF TrkB signaling pathway [100]. In their investigation of the MCAO model, Sun et al. discovered that AST exerts regulatory control over the apoptosis and proliferation of NSCs by modulating the Wnt/β-Catenin and Akt/gsk-3β pathways [101].

3.5. Periodontal tissue engineering

Periodontal diseases are the leading cause of deterioration in the health of the gingiva and supporting tissues, often resulting in tooth loss among adults, which can significantly impact the overall health and quality of life of patients. Extensive research efforts aimed at developing innovative methods to enhance tooth attachment or rebuild periodontal support tissue for the treatment of periodontal disease are currently underway. Although some progress has been made in treating periodontal defects, existing methods require further refinement. In this regard, periodontal TE has emerged as a promising approach for the clinical treatment of periodontal disease. The selection of a suitable support is crucial, and Shuanghuangbu, a TCM, has been recognized as a growth factor [102], showing promise in enhancing patient outcomes. To investigate its impact on cell proliferation, shuanghuangbu scaffold extract was introduced to periodontal ligament cells. The resulting scaffold exhibited a spongy structure with considerable porosity and adequate thickness. By adjusting the quantity and size of the pore-forming agent particles, the porosity and pore diameter of the scaffold could be effectively regulated. Interestingly, the shuanghuangbu scaffold extract enhanced the proliferation and osteogenic differentiation of human periodontal ligament fibroblasts (PDLCs) [103]. The reconstruction of periodontal tissues is very complex and requires that the newborn dentin and periodontal fibers have an organized structure. Currently, there remain several challenges with periodontal TE, and it is believed that through the combination of TCM and TE, regenerative periodontal tissues can be developed.

4. Conclusion

This review summarized the various types of active ingredients in TCM and their main efficacies. Among these, BTE has currently made significant research progress. TE scaffolds containing active ingredients of Chinese medicine are widely used in combination with 3D printing technology. TCM includes a wide range of herbal medicines or herbal extracts for the treatment of diseases; however, despite the fervent research on TCM in recent years, there remain challenges in promoting the internationalization of Chinese medicine such as (1) limited resources of TCM: the increasing demand for TCM has decreased the abundance of natural sources of TCM and a gradual increase in artificial cultivation. However, there are many problems associated with artificial planting, such as excessive use of pesticides and fertilizers, soil pollution, long planting periods, and collection time against scientific laws. Consequently, the efficacy of source medicinal materials is reduced, and their quality and safety cannot be guaranteed. For example, the Chinese herb *Panax notoginseng* has strict growth conditions and environmental requirements, and, more importantly, faces crop rotation obstacles. Continuously planting *Panax pseudoginseng* on a piece of land will lead to necrosis and wilting, side-effects that will be difficult to eliminate even at cultivation intervals of 10–20 years. This has led to a series of crises that threaten the cultivation of *Panax pseudoginseng*. (2) Development of research technology of TCM: research on TCM has aimed to separate and extract the main active ingredients in TCM using modern science technology and methods to investigate their roles, potential applications, and long-term clinical efficacy. Currently, an increasing number of studies are devoted to the combination of TCM and advanced drug-loading systems, such as nanoparticles; however, the development of technologies, such as extraction, purification, and nanotechnology applications of active components of TCM requires further strengthening.

Nevertheless, there are several herbal extracts, the clinical efficacy of which has been internationally recognized and commercialized, such as the use of artemisinin for the treatment of malaria. However, due to the limitations of modern technology and the differences between Chinese and Western concepts, intensive studies remain warranted prior to the application of Chinese herbal medicine concomitantly with modern Western medicine. Despite the significant potential applications of Chinese herbal medicine in TE and biomaterials science, only a few studies have confirmed the application of its active ingredients in enhancing the effects of TE biomaterials.

We believe that with the continuous progress of modern technology and the delineation of the advantages of herbal medicine, the goal of complementing modern medicine with TCM will be achieved. Scientific progress and technological developments will enable the recognition and broad use of Chinese herbal medicine in the field of TE.

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CRediT authorship contribution statement

Wenhui Ge: Writing – original draft. **Yijun Gao:** Supervision, Conceptualization. **Liming He:** Data curation. **Zhisheng Jiang:** Data curation. **Yiyu Zeng:** Writing – review & editing, Conceptualization. **Yi Yu:** Writing – review & editing, Conceptualization. **Xiaoyan Xie:** Supervision, Funding acquisition. **Fang Zhou:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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