

Review

Application of Composite Biomaterials from Chinese Herbal Medicine in the Field of Bone Tissue Engineering

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Abstract: Research into bone tissue engineering is increasing with advances in biomaterials. Natural products of plant origin have exciting therapeutic effects through multiple targets. The purpose of this article is to review the outstanding performance of herbal-derived natural products in bone tissue engineering. We have categorized herbal-derived natural products that exert different effects in bone tissue engineering into osteogenic, vascular, chondrogenic, anti-inflammatory and antibacterial. Natural products of plant origin are readily available and can be combined with biomaterials as bioactive molecules to complement each other and provide additional opportunities for bone tissue engineering. Finally, we discuss the challenges and opportunities for the development of plant composite biomaterials for bone tissue engineering and highlight emerging strategies in this field.

Keywords: Chinese herbal medicine; biomaterials; bone tissue engineering; modernization of Chinese herbal medicine

1. Introduction

The use of biomaterials has a long history, with rapid developments in materials science, cell biology and other disciplines facilitating the versatile applications of biomaterials. At the same time, the use of biomaterials has increased due to the needs of the medical field, particularly in orthopedics. Biomaterials are a class of special functional materials, natural or synthetic, used to contact and interact with living systems and to diagnose and treat, replace and repair or induce regeneration of cells, tissues and organs. These materials from synthetic, natural or combined sources are not drugs per se; they bind directly to the biological organism, respond to biological signals and interact with the immune system and endogenous cells to stimulate regeneration [1]. When used in the human body, biomaterials must be biocompatible, biodegradable, mechanically stable and malleable.

Bone defects caused by bone and joint trauma, degenerative diseases, bone tumors and osteomyelitis are very common. The ideal approach is to allow the bone to repair itself through tissue regeneration functions, but bone defects above a certain threshold will not heal on their own [2]. Treating large defects requires harvesting fresh, living bone from the iliac crest, which is associated with significant pain and morbidity [3]. To address this problem, 3D printing and electric-field-assisted techniques have been used to process biomaterials such as polymers, ceramics, metals and composites into a form suitable for bone tissue engineering. Bone tissue engineering is used to develop biological substitutes that restore, maintain or improve tissue function and is divided into in vitro tissue engineering and in situ tissue regeneration [4]. In vitro tissue engineering requires large numbers of immunologically acceptable cells to assemble synthetic scaffolds, resulting in practical applications limited by high costs and complex requirements. These limitations have inspired the use of in situ tissue regeneration, which relies on the body's ability to regenerate itself by implanting biomaterials to direct endogenous progenitor or stem cells to the site of injury to aid in the healing of damaged tissue. In this process, biomaterials



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provide a structural scaffold that facilitates the attachment and migration of host stem and progenitor cells and drives their differentiation into tissue-specific cell types [1].

Traditional Chinese medicine refers to substances used for prevention, treatment and diagnosis of diseases and rehabilitation of health care under the guidance of the theory of traditional Chinese medicine. Traditional Chinese medicine includes herbal medicine, animal medicine and mineral medicine. For thousands of years, herbal medicines have been tested on humans, and some of them have been shown to treat a variety of diseases. In addition to single natural compounds, these proven herbs can also be used in combination [5]. Compounding refers to the combination of various herbs in specific proportions. *Scutellaria* Decoction (Huang Qin Tang) is a classic compound formula in the book *Treatise on Cold Pathogenic and Miscellaneous Diseases* by Zhang Zhongjing, a famous Chinese physician. It is now named YIV-906 [6]. Seven early clinical trials have been completed under the U.S. Food and Drug Administration orphan drug designation for hepatocellular carcinoma of the liver and pancreatic cancer. Artemisinin, a natural product extracted from the herb *Artemisia annua*, is currently the most effective and important means of treating malaria, and its other pharmacological effects are gradually being discovered and applied in research [7].

Using various chromatographic separation techniques and various spectroscopic methods, herbs can be extracted and isolated, and their chemical structures can be determined. Those extracted compounds for which the efficacy has been determined can be used as part of a biomaterial for the manufacture of scaffolds. A variety of natural product complexes derived from herbs have been proposed and have shown exciting therapeutic effects [8].

In this paper, we will illustrate the advantages of herbal natural product composite biomaterials in bone tissue engineering. To better understand the potential of herbal natural products in bone tissue engineering, we reviewed some natural products that have been used in bone tissue engineering and classified them according to their different functions. Then, we discuss the opportunities and challenges of natural product composite biomaterials in modern scientific research.

2. The Advantages of Chinese Herbal Composite Biomaterials

2.1. Chinese Herbs Improve the Physiological Effects of Composite Biomaterials

There are some toxic ingredients in Chinese medicine, such as Xiong Huang, Arsenicum and Croton, which can be toxic to humans if used in the wrong dose or method. When used correctly, herbal medicines take advantage of the unique benefits of natural substances, their stable healing effects and their abundant supply. Without the need to introduce other biomolecules and cells, herbal composite biomaterials with different functions can provide additional biological properties to better guide the functional recovery of damaged sites. Due to the lack of cellular components, more effective herbal composite biomaterials face fewer regulatory hurdles, greatly reduce costs and improve practicality by avoiding the use of biological factors [9].

When biomaterials are implanted into biological systems, proteins are first adsorbed onto the surface of the biomaterials, which then promote and control the adhesion of cells and the subsequent cellular events [10]. Therefore, the manipulation of the behavior of interface proteins is a starting point for the improvement in the surface design of various medical implants. The multi-target therapeutic effects of Chinese herbal medicine determine the selective adsorption of proteins or prevent the binding of non-target proteins. Chinese herbal medicine composite biomaterials can provide a variety of personalized designs for bone tissue engineering.

2.2. Biomaterials Address Chinese Herbal Medicine Shortcomings

However, the benefits of herbal medicines are not without shortcomings. Many herbal medicines have significant efficacy, but unfortunately, the low bioavailability of the drugs often limits their usefulness. Some scientists have attempted to improve the bioavailability of herbal medicines by nano-sizing them, using nanotechnology to process the active

ingredients of herbal medicines on a nanoscale particle size. However, simply changing the physical size of herbal medicines does not significantly improve their solubility, which is a limitation of herbal medicine nano-sizing [11].

Therefore, to achieve the purpose of Chinese herbal medicine delivery, the strategy of constructing Chinese medicine nanosystems using nanomaterials as carriers is increasingly being adopted. In addition to nanomaterials, a large number of different types of materials and combinations of materials have been found to be promising candidates for applications in bone tissue engineering. Among them, many materials have also been combined with Chinese herbal medicines, which have confirmed the role of Chinese herbal medicines in enhancing bone repair in bone tissue engineering. The composition, structure and properties of materials interact with each other and influence the physicochemical properties of the material [12]. These composite biomaterials facilitate the slow release of botanicals. They also improve solubility and increase stability.

3. Bioactive Functions of Chinese Herbs in the Field of Bone Tissue Engineering

Many studies have demonstrated the benefits of the aforementioned botanical natural product complex biomaterials. We have classified natural products into osteogenic, angiogenic, chondrogenic, anti-inflammatory, targeting and antibacterial according to their different effects in bone tissue engineering. It is important to note that natural products of plant origin have a multi-targeted mechanism of action, such as cucurbitacin B, which has both osteogenic and pro-angiogenic effects, so the following description will show that natural products with different classifications can have the same effects. Furthermore, to better illustrate the unique appeal of this multi-targeted natural product therapy, we have chosen representative examples, as shown in Figure 1.

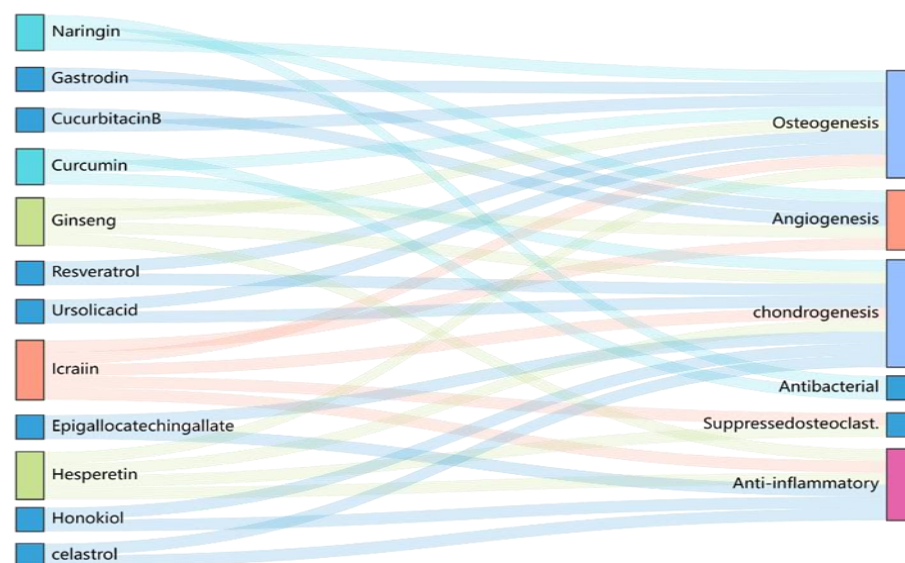


Figure 1. Chinese herbs with two effects or more in bone tissue engineering.

3.1. Osteogenesis

Steroid-associated osteonecrosis is an orthopedic side effect of steroid treatment that can lead to joint collapse and subsequent joint replacement [13]. Inspired by the superior therapeutic effects of Chinese herbs on bone diseases, herbs with osteogenic effects are beginning to be considered for incorporation into biomaterials [14].

Icaritin, a chemically stable dehydrated *Epimedium*, was incorporated into the FDA-approved biomaterials polylactic acid–glycolic acid (PLGA) and tricalcium phosphate (TCP) to create a PLGA/TCP/icaritin (PTI) composite porous scaffold was implanted in model rabbits with bone defects using cryogenic 3D printing [15]. The sustained release of the herb icaritin from the composite scaffold significantly induced new bone formation in

the defects. HPLC results showed that icaritin was released slowly over 12 weeks and in the end, a total of 79.93 μg of icaritin was released from the PLGA–TCP–icaritin scaffold into the SBF. In addition, the PTI scaffold exhibited better biodegradability and biocompatibility compared to the PT scaffold. In addition to *in vivo* experiments, *in vitro* experiments also showed that both P/T and P/T/I scaffolds could recruit BMSCs, but higher expression of the migration-related gene VCAM1 was found only in the PTI group *in vitro*. It is suggested that an important reason for P/T/I recruiting more than P/T is the introduction of icaritin, which can promote BMSC migration by increasing the expression of migration-associated genes [16]. Although some flavonoids have been shown to modulate the coupled processes of angiogenesis and osteogenesis during bone repair, some studies have shown that icaritin has no direct effect on promoting angiogenesis *in vitro*. However, as the mechanisms and regulation of the two processes of osteogenesis and angiogenesis are very different, the lack of direct action on the target of angiogenesis leads to its inability to promote angiogenesis *in vitro*, despite the ability of icaritin to modulate osteogenesis. [17]. Inspired by similar molecular structures that have the same function, a new plant-based composite bioscaffold has been developed, in which icaritin is able to provide structural and mechanical support and promote bone regeneration. *In vivo* studies showed that the PLGA/TCP/icaritin (PTI) scaffold enhanced the mechanical properties of new bone tissue and improved angiogenesis within the implanted region compared to PLGA/TCP (PT) scaffold in a SAON rabbit model. Sections of undecalcified femoral condyles from animals treated in the PT and PTI groups were mechanically tested with a mechanical testing machine. The compressive strength and modulus at yield significantly declined in the PT scaffold without icaritin incorporation, with degradation over time *in vitro*. Potential osteoblastic mechanisms were investigated *in vitro* using MC3T3-E1 cells and it was found that the *Epimedium* could promote the growth of MC3T3-E1 cells into the PTI scaffold and regulate osteoblast differentiation [18]. In conclusion, it has been demonstrated that *Epimedium* and its metabolites are potential bioactive molecules for use in bone tissue engineering [19].

In addition to *dehydro-icaritin* and *icaritin*, cucurbitacin B (CuB) is also a promising candidate compound for bone tissue engineering. The linear release of CuB from porous PLGA/ β -TCP/CuB composite scaffolds without affecting the pH enhanced bone regeneration *in vivo* in a rat calvarial critical-sized bone defect model. The PT/CuB scaffold released CuB into the degradation medium, which significantly promoted osteogenesis and angiogenesis *in vitro*, indicating that the CuB released from the PT/CuB scaffold remained biologically active. It is suggested that CuB released *in vivo* regulates the expression of osteogenic- and angiogenic-related gene proteins in the body. These results highlight the potential use of CuB as a therapeutic agent and strongly support its use as a component of a composite scaffold for bone repair [20]. Epigallocatechin gallate (EGCG) integrated with gelatin implanted into the bone defect of rats inhibited MMP2 and MMP9 better than gelatin without EGCG, and thus had a stronger bone forming capacity. Chemical modification of EGCG on gelatin (vEGCG-GS) reduced MMP expression to levels similar to the unimplanted group after 1 week [21].

3.2. Angiogenesis

Angiogenesis plays a key role in bone regeneration. In bone tissue engineering, the multi-target action characteristics of Chinese herbal medicines make it possible to simultaneously enhance angiogenesis and bone regeneration. The aforementioned cucurbitacin B, a tetracyclic terpene derived from the *Cucurbitaceae* plant, has such a function. By incorporating CuB into a porous PLGA/ β -TCP scaffold, the angiogenesis was enhanced, in addition to promoting osteogenesis. *In vitro* experiments showed that CuB stimulated angiogenic signaling by upregulating VEGFR2- and VEGFR-related signaling pathways. Tyr 996 autophosphorylation of VEGFR2 was largely activated by CuB exposure [20].

Puerarin is the main active constituent of the Chinese herb *Pueraria lobata*. Various dosage forms of puerarin are clinically available for the treatment of angina pectoris and hypertension. Some studies have shown that puerarin has a preventive effect on bone loss.

In one study, puerarin was incorporated into a PLGA/TCP (PT) scaffold, and the resulting PLGA/TCP/puerarin (PTP) scaffold not only inherited all the advantages of the PT scaffold in terms of mechanical stress and biodegradation, but also released puerarin stably and continuously. The mechanical properties of the scaffolds were tested and measured by a static and dynamic material testing machine. The compressive strength of the PTP scaffold was 1.08 ± 0.05 MPa, which was significantly higher ($p < 0.05$) than that of the PT scaffold (0.95 ± 0.04 MPa). During the degradation process, PTP scaffolds showed greater stability. They retained their porous structure for at least 10 weeks. Mechanistic studies have shown that puerarin-rich PTP scaffolds stimulate the secretion of VEGF and BMP-2 in peri-implant tissues to induce vascular infiltration and recruitment of repair cells, enabling the coupling of angiogenesis and osteogenesis [22]. Resveratrol (Res), a non-flavonoid polyphenolic compound, and angiotensin-2 (ANG2) were prepared as PEGDA/TCS hydrogels. BMSCs were cultured in PEGDA/TCS scaffolds and transplanted into a large tibia defect. The results showed that the density and size of new vessels in the bone defect were significantly increased by ANG2 and Res at 8 weeks post-operation. In addition, Res reduces ANG2- and hypoxia-induced apoptosis by increasing autophagy in endothelial cells, thereby maintaining endothelial cell growth and proliferation and upregulating CD31 expression in bone defect areas [23].

3.3. Chondrogenesis

The articular surface of the knee joint has a hard, shiny coating called articular cartilage. Unlike the vast majority of other tissues, cartilage is essentially avascular and low in cellularity in nature [24]. As a result, cartilage lacks the ability to repair itself due to a lack of sufficient nutrients and proper progenitor cells. However, if cartilage defects are left untreated, the joints progressively and irreversibly deteriorate, leading to osteoarthritis and ultimately disability. Mimicking the unique biological functions of articular cartilage and osteochondral interface tissue remains a challenge [24]. The major bioactive flavonoid of the *Epimedium* plant, icariin, has broad applications in improving scaffolds as a constant and non-immunogenic material, and it also stimulates cell growth, chondrocyte differentiation and differentiation of embryonic stem cells into cardiomyocytes. In addition, fusing or chemically cross-linking icariin into hydrogel scaffolds can enhance collagen matrix and proteoglycan secretion in bone and cartilage tissue [25].

Hesperidin is a flavanone glycoside widely found in citrus fruits with antioxidant and anti-inflammatory properties. It has been shown that loading hesperidin into nanoparticles (HGdPDW) leads to the low cytotoxicity and chondrogenic binding capacity of HGdPDW in a mouse model of osteoarthritis, confirmed by bimodal magnetic resonance imaging (MRI)/interactive video information system (IVIS) imaging. After intra-articular injection (IA) of OA model mice for 12 h, the cartilage signal was found to be much stronger after GdPDW treatment than those of PBS and GdP treatments. HGdPDW treatment increased the knee cartilage thickness, preserved proteoglycans and collagen and reduced progressive articular cartilage degeneration in vivo. It also significantly improved the OARSI scores in anterior cruciate ligament transection (ACLT) OA mice [26].

Andrographolide (AG), the major plant extract of *Andrographis paniculata*, is safe and effective for pain relief in patients with osteoarthritis. A study validated the anti-inflammatory and chondroprotective properties of AG-bound mesoporous silica nanoparticles (AG-MSN) using a rat model of osteoarthritis. CCK8 assessment and Safranin O staining showed that AG-MSN promotes chondrocyte proliferation and inhibits the loss of GAG (a major component of chondrocyte ECM) [27]. Curcumin is a diketone compound extracted from the rhizome of the ginger family with hypolipidemic, antitumor, anti-inflammatory, choleric and antioxidant activities. A curcumin–silk protein composite scaffold was constructed to serve as a clinical alternative for cartilage defects [28]. The results showed that chondrocytes cultured in the curcumin/silk scaffold had adequate cell viability and cell phenotype. Subcutaneous areas of thymus-free nude mice confirmed the biocompatibility and cartilage matrix formation of the curcumin/silk scaffold.

3.4. Anti-Inflammatory

Osteoarthritis (OA) is a common joint disease that causes inflammation of the joints. Dexamethasone sodium phosphate (DEX-P) is a synthetic corticosteroid that has been widely used in the treatment of OA because it reduces inflammation and ECM loss in cartilage. In clinical practice, DEX-P is injected locally into the joint cavity to deliver the drug to the site of action and minimize side effects. However, a major challenge with locally injected soluble drugs such as DEX-P is their rapid clearance, which requires frequent administration of the therapeutic drug (e.g., once daily for 3–6 weeks). Therefore, the development of a controlled release vehicle capable of delivering therapeutic drugs specifically to inflamed tissue is highly desirable [29].

Cordycepin was the first nucleoside antibiotic isolated from a fungus. It has a variety of pharmacological effects, including antibacterial, anti-inflammatory, antiviral, antitumor and immunomodulatory activities. Cordycepin has been shown to be an inhibitor of the expressions of ADAMTS-5 and MMP13 in IL-1 β -induced osteoarthritis, thereby preventing inflammation. A synergistic therapeutic effect of chitosan-microsphere-coated cordycepin (CM-cordycepin) and a photo-cross-linked hyaluronic acid methacrylate (HAMA) hydrogel to promote chondrocyte autophagy was proposed, which was injected into the joints of mice in a controlled manner to support the long-term release of cordycepin. All of the CM-encapsulated cordycepin was released within 72 h in PBS. In addition, about 50% of the CM-encapsulated cordycepin was released at a relatively stable rate during the first 24 h, after which the release rate slowed down [30].

The inflammatory microenvironment and the lack of stem cell differentiation factors at the lesion site are the main reasons for the poor healing response after rotator cuff reconstruction. A composite hydrogel of anti-inflammatory curcumin and osteogenic magnesium ions was synthesized to overcome the challenge of combining efficient loading with controlled release. The composite hydrogel mediated the sustained in situ release of curcumin and Mg²⁺, effectively promoting rotator cuff tendon-to-bone healing through anti-inflammatory- and differentiation-promoting effects [31].

3.5. Antibacterial

Total joint replacement has a certain likelihood of early periprosthetic joint infection (PJI), in which bacteria can damage cells and cause bone destruction [32].

With antimicrobial therapy alone, lipopolysaccharide (LPS)-induced inflammation can cause bone destruction due to the release of inflammatory cytokines from M1. By combining Geraniol and LPS, macrophages tend to differentiate into M2 rather than M1, which can inhibit inflammatory bone destruction. In addition, the composite could promote the differentiation of rBMSCs, thereby accelerating bone formation. In a study, a nanowire-like composite material called P@C was prepared by combining chitosan and geranoside through a solid-phase reaction, which could accurately mimic the biological functions of natural antimicrobial peptides (AMPs). Chitosan acts as a bacterial membrane puncturing agent and puerarin acts as an LPS targeting agent. They synergistically disrupt the bacterial membrane structure and inhibit its rebuilding, which imparts good antibacterial properties to P@C. In addition, P@C has good bone immunomodulatory capacity due to its LPS elimination and macrophage differentiation modulating ability. In vivo results showed that P@C could inhibit LPS-induced bone destruction in rats. P@C exhibited superior bone regeneration in rats infected with *E. coli* due to its combined functions of superior antibacterial properties and LPS elimination and immunomodulatory abilities. P@C may well mimic the function of AMPs, providing a novel and effective approach for the clinical treatment of PJI [33].

Most artificial skeletons focus mainly on osteogenic activity and ignore the importance of antimicrobial activity. It is important to develop artificial skeletons with excellent antimicrobial, anti-inflammatory and osteogenic activities at the same time. A hydrogel composite of curcumin (Cur) and phytic acid (PA) was loaded onto delignified white wood to form a woody hydrogel composite membrane. In addition to its bone-strengthening

properties, Cur has antimicrobial properties. PA has also been shown to have antibacterial and antioxidant properties. The synergistic effect of the two drugs resulted in a wood hydrogel composite film with significant antimicrobial activity. The possible mechanism behind this improved antimicrobial function is that the presence of Cur inhibits biofilm formation, allowing the PA to come into direct contact with the bacterial surface. Interestingly, when compared to the composite membranes of wood-derived hydrogels loaded with no drugs and those loaded with Cur or PA alone, the composite membranes loaded with Cur and PA were significantly more capable of inhibiting the growth and inflammatory response of bacilli and promoting the adhesion, proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells [34].

4. Discussion

Chinese herbal medicines have unique structures, numerous modification sites and rich sources. For the development of new therapies to treat many diseases, it is a treasure trove. Research combining herbs and biomaterials for bone tissue engineering has shown exciting results. Chinese herbs can provide osteogenesis, vascularization, chondrogenesis, anti-inflammatory and antibacterial effects in bone tissue engineering. With the development of genomics and metabolomics, research on Chinese herbal medicine has increasingly turned to high-throughput screening of the molecular effects of herbs/ingredients. Metabolomics has evolved from the concept of metabolic profiling and aims to qualitatively and quantitatively analyze all the metabolites present in an organism at a given time and under a given set of conditions. This approach ultimately allows the indirect monitoring of gene functions and the biochemical status of an organism. A combination of metabolomics and genomics can be used to optimize a biosynthetic pathway to selectively produce biologically active secondary metabolites [35]. The mechanism of action of herbal medicine to enhance the therapeutic effect of bone tissue engineering will become clearer in the future.

In addition, the active ingredients in Chinese medicines can form nanoscale particles by self-assembly, thus improving their efficacy and bioavailability. This method is similar to nanotechnology, which allows drugs to be more easily absorbed and utilized by the body by controlling particle size, shape, surface properties, etc. Some non-functional compounds can also be utilized, as they can act as “carriers” of the active ingredient to form nanoscale particles. Inspired by the milling therapy of traditional Chinese medicine, a mechanical force was introduced to facilitate the collision of active molecules of chitosan (CS) and puerarin (PUE) and accelerate their self-assembly, thereby creating herbal-based hydrogels [12]. The fat-soluble active ingredients in *Salvia miltiorrhiza* and the amphiphilic active ingredients in licorice can construct nanomicelles through a self-assembly strategy, and these drug-only nanomicelles have better biodegradability, biological compatibility and safety, contributing to their clinical application value [36].

Most of the current composites used for bone tissue engineering use active compounds of herbal origin with precise efficacy and structural stability. However, under the guidance of TCM compound theory, Chinese herbal compounds are the main components of TCM clinical medicine [37]. At present, the core connotation of TCM compound theory has not been fully revealed through the research on the material basis of TCM compounds. For example, a prescription containing *Tetradium ruticarpum*, ginseng, ginger and jujube is used to treat headaches and gagging. However, the multiple components and prescribed ratios of such compound formulas limit its combination with biological materials, and the efficacy of many herbs would be greatly reduced without such herbal monomers. In addition, the active ingredients of many compound formulations have not been identified. There is an urgent need to develop the active ingredients of these herbs to be exploited as a potential library of active molecules for biomaterials.

Although natural products of herbal origin have the advantage of multi-targeted action, this does not mean that they cannot be used in combination. On the contrary, herbs with different effects can be incorporated into bone tissue engineering as needed. To prevent infection and loosening of implants after joint replacement, polyetheretherketone

(PEEK) is embedded with osteogenic osthole and antibacterial berberine. This makes it an orthopedic material with antibacterial and osteogenic activities. The implant has been shown to promote osteogenesis and prevent endogenous infection *in vivo* in rat intrafemoral implantation studies [38].

The fate of the material and its performance after implantation is determined by the ability to control the protein adsorption process by promoting the selective binding of desired proteins or preventing the binding of undesired proteins [10]. Despite the excellent efficacy and safety profile, few natural products have well-defined targets. To better design biomaterials, chemical biology and various histological techniques are needed to explore the active ingredients in natural products as well as the target proteins of the active ingredients.

Excitingly, the modernization of Chinese herbal medicine is receiving increasing attention. With the advent of next-generation sequencing technologies, more and more TCM research is focusing on the use of high-throughput technologies to identify the molecular effects of active herb components [39]. Based on these gene expression profiles, systematic data mining and analyses of the mechanisms of action of herbal medicines and developing database resources can provide a theoretical basis for using herbal medicines to treat various diseases and conditions [40].

5. Outlook

Rapid developments in the fields of chemical biology and mass spectrometry are helping to identify active ingredient structures and targets in herbal medicines. The precise targets of herbal medicines help in the comprehensive design of biomaterials for bone tissue engineering, which promises a vast library of bioactive molecules. With the introduction of 4D printing technology [41], smart materials are also being developed. Herbs may also be candidates for smart materials if the self-assembling mechanism of action of herbs is elucidated [42]. Certain herbal plants have low levels of natural active molecules, such as artemisinin and paclitaxel, which are difficult to isolate and extract. They also have complex structures that are difficult to synthesize chemically. The emerging field of synthetic biology has great potential to address pressing material challenges [43]. Not only can it provide a more efficient and stable method for the production of the active ingredients of herbal medicines, but it can also further modify their structures and enhance their utilization [44]. At the same time, herbs can be used as chemical cues for synthetic biology in the preparation of responsive dynamic biomaterials to provide (spatial) temporal control of biomaterial properties [43]. Research on herbal modernization, such as through the use of big data and machine learning, has also contributed to the understanding of herbal exploration for better integration in herbal medicine and biomaterials. A total of 12,933 targets and 28,212 diseases have been linked to 7263 herbs and 49,258 components in the HERB database, and six relationships between them have been identified [45]. Machine learning correlates the molecular properties of herbs with TCM meridians and may provide new insights into understanding the meridian theory in TCM [46].

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