Hydrogel-Based Materials for Delivery of Herbal Medicines

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ABSTRACT: Herbal medicine, as an integral component of oriental medicine, has assimilated into the lives of Asian people for millennia. The therapeutic efficiency of herbal extracts and ingredients has, however, been limited by various factors, including the lack of targeting capacity and poor bioavailability. Hydrogels are hydrophilic polymer networks that can imbibe a substantial amount of fluids. They are biocompatible, and may enable sustained drug release. Hydrogels, therefore, have attracted widespread studies in pharmaceutical formulation. This article first reviews the latest progress in the development of hydrogel-based materials as carriers of herbal medicines, followed by a discussion of the relationships between hydrogel properties and carrier performance. Finally, the promising potential of using hydrogels to combine medicinal herbs with synthetic drugs in one single treatment will be highlighted as an avenue for future research.

KEYWORDS: hydrogels, oriental medicine, drug delivery, herb, sustained release

1. INTRODUCTION

Herbal medicine is an integral component of oriental medicine. Attributed to the prospect of drug discovery from medicinal herbs, the therapeutic potential of herbal medicine has begun to be recognized globally. One example of drugs discovered from herbal medicines is Kanglaite, which is an investigational anticancer drug extracted from Semen coicis. The injectable form of Kanglaite has been approved in China for treating cancers. Another example is ephedrine. It is a sympathomimetic amine isolated from Ephedra vulgaris. This drug has been commonly used as a cardiac stimulant, a bronchodilator, and a hypoglycaemic agent.2 From vision enhancement with barbarum fruits to cancer treatments,3 herbal medicine has assimilated into the lives of Asian people for millennia. Despite this, the therapeutic efficiency of herbal medicines has been hindered by various factors, including the lack of targeting capacity and poor bioavailability. Furthermore, because of the variations in structures and physicochemical properties of different bioactives in herbal medicines, the efficiency of absorption and cellular internalization of those bioactives, which are integral parts of the herbal treatment, may vary greatly, reducing the treatment efficacy.

To solve these problems, one possible strategy is to adopt a carrier to facilitate the delivery of herbal bioactives. As a matter of fact, various materials (including lipids and hydrogels) have already been developed over the years for drug delivery purposes.4–10 While there is an upsurge of reviews summarizing the applications of these materials in the delivery of synthetic drugs, the possible use of these materials in formulating herbal medicines has rarely been put to formal discussions in the literature. This article attempts to fill this gap by highlighting the possible incorporation of current drug delivery technologies, with a special focus on hydrogels, into herbal treatment, and examining how the properties of hydrogels can be tailored to enhance the delivery efficiency of herbal medicines.

2. STRENGTHS OF HYDROGELS FOR DELIVERY OF HERBAL MEDICINES

Hydrogels are swellable networks that can absorb a substantial amount of fluids. Their major constituents are polymers, which can be natural or synthetic in origin. One important natural polymer for hydrogel synthesis is alginic acid (Alg). It is an anionic polysaccharide consisting of (1→4)-linked β-D-mannuronic acid and α-L-guluronic acid.11–13 Upon gelation with simple divalent ions (e.g., Ca2+), Alg can form matrices for beads, gels, microparticles, and nanospheres.18,19 Another example of natural polymers is collagen, which is a major constituent of the extracellular matrix of the connective tissue. Collagen has high mechanical strength.20 It has been used to fabricate hydrogels for tissue engineering21 and corneal applications.22 Other common examples of natural polymers for hydrogel synthesis are chitosan (CS),23 gelatin,24 agarose,25 and hyaluronic acids.26 Apart from natural polymers, advances in materials science have led to the development of diverse synthetic polymers for hydrogel formation, including poly(N-vinylpyrrolidone) (PVP),27 poly(2-hydroxyethyl methacrylate)
used to treat herpes simplex,\textsuperscript{51} chronic sinusitis,\textsuperscript{52} and nasal polyps.\textsuperscript{52} It has also been reported to have anticancer,\textsuperscript{53} antioxidant,\textsuperscript{54} and adjuvant activities. A hydrogel patch containing the two extracts has been fabricated by Lim et al.,\textsuperscript{49} who have prepared a hydrogel patch containing two herbal medicines for treatment of atopic dermatitis (AD). The first extract is from \textit{Ulmus davidiana} var. japonica (UD), which is a deciduous broad-leaved tree commonly found in oriental countries. Its root bark and stem have been found to be therapeutic to mastitis, cancers, inflammation, edema, and rheumatoid arthritis.\textsuperscript{60} The second one is from \textit{Houttuynia cordata} Thumb. The extract has been used to treat herpes simplex,\textsuperscript{43} chronic sinusitis,\textsuperscript{52} and nasal polyps.\textsuperscript{52} It has also been reported to have anticancer,\textsuperscript{53} antioxidant,\textsuperscript{54} and adjuvant activities.\textsuperscript{55} A hydrogel patch containing the two extracts has been fabricated by "freezing and thawing" and 60Co $\gamma$-ray irradiation.\textsuperscript{49} Because of the moisturizing effects and the activity of the extracts on atopic wounds, mice treated with the patch have effectively recovered from edema led by contact dermatitis (Figure 2),\textsuperscript{16} and have suffered from less itchiness caused by AD.\textsuperscript{49} In addition, the patch can be attached to or detached from the skin easily.\textsuperscript{49} This makes clinical applications of the patch more viable.

The promising potential of using hydrogels to deliver herbal medicines has been further supported by a recent study,\textsuperscript{56} in which a solid lipid nanoparticle (SLN)-enriched hydrogel has been reported for topical delivery of astragaloside IV, which is a major constituent of \textit{Astragalus membranaceus}. The hydrogel has enabled sustained release of astragaloside IV, and has enhanced the migration and proliferation of keratinocytes \textit{in vitro}.\textsuperscript{56} In a full-skin excision rat model, the hydrogel has demonstrated to increase the wound closure rate. It has also facilitated angiogenesis and collagen deposition (Figure 3).\textsuperscript{56} These have rendered the hydrogel-based system viable for use as a wound management product. As a matter of fact, over the years, the possible use of hydrogels loaded with herbal medicines has already been exploited in diverse areas, from product development to disease treatment (Table 2).\textsuperscript{46,57--69} For the latter, the clinical potential has been evidenced in clinical trials. A good example has been provided by a randomized, double-blind, placebo-controlled clinical trial.

### Table 1a. Some of the Delivery Systems Exploited in the Literature for Delivery of Herbal Medicines: Phytosomes and Liposomes

<table>
<thead>
<tr>
<th>Delivery System</th>
<th>Description</th>
<th>Strengths</th>
<th>Limitations</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phytosomes</td>
<td>Phytosomes are usually prepared by complexation between phosphatidylcholine inclusion and polyphenolic phytoconstituents.</td>
<td>• comparably safe and biocompatible • can be produced in different sizes, thereby enabling encapsulation of molecules with diverse size ranges</td>
<td>• poor storage stability • laborious production procedures</td>
<td>Liposomes have been adopted to enhance the inhibitory effect of diospyrin, a bisnaphthoquione from the milk thistle plant (\textit{Silybum marianum}); compared to conventional administration, the liposomes have enabled enhanced bioavailability and liver protection effects.</td>
</tr>
<tr>
<td>Liposomes</td>
<td>Liposomes are constituted by hydrophilic and hydrophobic molecules.</td>
<td>• can be produced in different sizes, thereby enabling encapsulation of molecules with diverse size ranges</td>
<td>• poor encapsulation efficiency • laborious production procedures</td>
<td>Liposomes have been applied to enhance the inhibitory effect of diospyrin, a bisnaphthoquinone from the milk thistle plant (\textit{Silybum marianum}); compared to conventional administration, the liposomes have enabled enhanced bioavailability and liver protection effects.</td>
</tr>
<tr>
<td>Delivery System</td>
<td>Description</td>
<td>Strengths</td>
<td>Limitations</td>
<td>Use</td>
</tr>
<tr>
<td>-----------------</td>
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<tr>
<td>Polymeric nanoparticles and microparticles</td>
<td>Polymeric nanoparticles and microparticles generally have spherical morphologies, though generation of non-spherical particles has been reported; during the loading process, the agent to be delivered can be encapsulated inside, or can adsorb on the particle surface.</td>
<td>• Can offer controlled and sustained release of the encapsulated molecules</td>
<td>• Particle-particle aggregation may occur, limiting the storage stability.</td>
<td>PLA nanoparticles have been reported to improve the solubility, permeability and stability of quercitrin, which is an antioxidant isolated from Albizzia chinensis.</td>
</tr>
<tr>
<td>Emulsions</td>
<td>Emulsions generally are biphasic systems in which one phase is dispersed in the other phase in the form of minute droplets; some emulsions may have more than two phases.</td>
<td>• Comparatively easy in production</td>
<td>• Poor storage stability.</td>
<td>Quercetin has been formulated as a water-in-oil microemulsion to enhance its skin penetration.</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Hydrogels are hydrophilic polymer networks that can imbibe a substantial amount of fluids.</td>
<td>• Biocompatible, and comparatively low in toxicity</td>
<td>• Difficult to encapsulate hydrophobic molecules, or to be simultaneously loaded with molecules with varying degrees of hydrophilicity.</td>
<td>The Sanqi bone paste, which is a formulation containing herbal medicines such as Notoginseng Radix et Rhizoma (Sanqi) and Dipsaci Radix, has been incorporated into a hydrogel; compared to the conventional bone paste, the generated hydrogel patch has exhibited enhanced transdermal properties, and has allowed for more sustained release of the herbal bioactives.</td>
</tr>
</tbody>
</table>

"PLA = poly-D,L-lactide."
conducted with ambulatory patients. In the study, the extract of the *Mimosa tenuiflora* cortex, which is a popular remedy utilized in Mexico to treat skin lesions, has been incorporated into a hydrogel (which has been prepared using Carbopol 940, PEG 200, and triethanol amine) for the treatment of venous leg ulceration (VLU) disease. The size of the ulcer in patients treated with the extract-loaded hydrogel has been significantly reduced (Figure 4), while those treated with the hydrogel alone have exhibited no significant improvement. Based on the evidence above, it is clear that delivery of herbal medicines using hydrogels holds promise for clinical applications.

### 3. PREPARATION OF HYDROGELS FOR DELIVERY OF HERBAL MEDICINES

Many first-generation hydrogels are principally chemical hydrogels. Some of them have been fabricated by cross-linking hydrophilic polymers such as poly(vinyl alcohol) (PVA) and PEG. Others have been formed via polymerization of water-soluble monomers in the presence of a cross-linker. A representative example of the latter case is the poly(acrylamide) hydrogel, which has been exploited initially for physical entrapment of cells and enzymes and later for use as soft tissue fillers. Notwithstanding the track record of applying chemical hydrogels to drug delivery, using chemical hydrogels as carriers of herbal medicines might not be favorable. This is because loading of the herbal medicines is usually performed by simply mixing the medicines with hydrogel constituents before cross-linking occurs. Herbal medicines usually contain multiple components and, hence, a variety of functional groups. Side reactions with the herbal components can be minimized.

Compared to chemical hydrogels, physical hydrogels may have lower long-term stability and mechanical strength; however, covalent cross-linkers are not required for their formation. Side reactions with the herbal components can be minimized. This has been demonstrated using the crude leaf extract of *Hemigraphis alternata*. The extract has previously been reported to have anti-inflammatory effects and has facilitated wound contraction and epithelialisation in the carrageenan-induced paw edema mouse model. Upon loading into a hydrogel, the extract has maintained its hemostatic and antibacterial activities. This, together with the effects of the extract-loaded hydrogel in facilitating platelet activation, dermal fibroblast attachment, and blood clotting, has made the hydrogel-based system potentially useful for future wound care.

To obtain physical hydrogels, various methods have been reported. One method is ionic gelation.
Table 2. Some of the Applications of Hydrogels Loaded with Herbal Medicines

<table>
<thead>
<tr>
<th>Area of Application</th>
<th>Principal of Application</th>
<th>Polymer Constituent(s)</th>
<th>Form of Hydrogel</th>
<th>Method of Fabrication</th>
<th>Agent to be Delivered</th>
<th>Herb(s) Involved</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Cutaneous Anomalies</td>
<td>be applied topically to skin to deliver herbal medicines to the site of interest</td>
<td>Poloxamer 407, CMC</td>
<td>Bulk</td>
<td>Poloxamer 407 has been added into a CMC solution in an ice bath under constant magnetic stirring</td>
<td>Herbal extract</td>
<td>Paeonia suffruticosa Andrews</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbopol 940</td>
<td>Bulk</td>
<td>Carbopol 940 has been dispersed in water at room temperature, followed by neutralization with triethanolamine</td>
<td>Herbal extract</td>
<td>Ipomoea pes-tigridis</td>
<td>58</td>
</tr>
<tr>
<td>Tissue Engineering</td>
<td>be loaded with herbal medicines that are thought to facilitate tissue regeneration, and be applied to the affected area</td>
<td>Alg</td>
<td>Bulk</td>
<td>Alg has undergone ionic gelation with Ca²⁺</td>
<td>Active ingredient</td>
<td>Liver-soothing herbs</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CS</td>
<td>Bulk</td>
<td>The CS solution has been mixed with a solution of ammonium hydrogen phosphate salt at 4 °C</td>
<td>Herbal extract</td>
<td>Cissus quadrangularis</td>
<td>60</td>
</tr>
<tr>
<td>Wound Healing</td>
<td>be adopted to deliver herbal medicines to the wound to facilitate the wound healing process</td>
<td>CS, PVP, PNIPAm</td>
<td>Film</td>
<td>Solutions of CS and PVP have been mixed, followed by the addition of the PNIPAm solution; the mixed solution has then been dried to form a film</td>
<td>Herbal extract</td>
<td>Salix alba leaves</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pluronic F-127</td>
<td>Bulk</td>
<td>Gel formation has been induced by elevation of temperature</td>
<td>Herbal extract</td>
<td>Terminalia arjuna bark</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pluronic F-127</td>
<td>Bulk</td>
<td>Gel formation has been induced by elevation of temperature</td>
<td>Herbal extract</td>
<td>Terminalia arjuna bark for tannins</td>
<td>62</td>
</tr>
<tr>
<td>Development of Cosmeceutical Products</td>
<td>be adopted to develop skin care products containing herbal extracts or ingredients</td>
<td>Carbopol 934, Carbopol 940, Carbopol 941, Xanthan gum</td>
<td>Bulk</td>
<td>The polymers have been dispersed in water, followed by neutralization with NaOH; the hydrogel has been incorporated with nanoparticles before use</td>
<td>Herbal ingredient</td>
<td>Rhodiola rosea for salidroside, and peonies for paeonol</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbomer</td>
<td>Bulk</td>
<td>The polymer has been dispersed in water, followed by neutralization with triethanolamine</td>
<td>Herbal extract</td>
<td>Imperata cylindrical</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbopol Ultrace 20</td>
<td>Bulk</td>
<td>The polymer has been dispersed in water, followed by neutralization with NaOH; the hydrogel has been incorporated with a nanosuspension before use</td>
<td>Herbal extract</td>
<td>Achyranthes bidentata</td>
<td>65</td>
</tr>
<tr>
<td>Food Production</td>
<td>be utilized to encapsulate herbal components to improve the stability and functionality of those components in food products</td>
<td>Alg</td>
<td>Beads</td>
<td>Alg has undergone ionic gelation with Ca²⁺</td>
<td>Herbal extract</td>
<td>Pterospartum tridentatum</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ilex paraguariensis</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thymus serpyllum</td>
<td>68</td>
</tr>
<tr>
<td>Cancer Treatment</td>
<td>be adopted to release the herbal ingredient to the tumor site in a sustained manner</td>
<td>PECT</td>
<td>Bulk</td>
<td>PECT has been used to form a powder, in which the herbal active ingredient has been incorporated, via nanoprecipitation; the powder has subsequently been dispersed in saline to form a solution, which can form a gel by elevation of temperature</td>
<td>Active ingredient</td>
<td>Embelia ribes Burm for embelin</td>
<td>69</td>
</tr>
<tr>
<td>Bone Setting</td>
<td>be used to release the herbal bioactives to the affected site in a sustained manner to facilitate alleviation of the musculoskeletal injury</td>
<td>Viscomate NP7000, Carbopol 940, PVP, gelatin</td>
<td>Bulk</td>
<td>The polymers have been used to form different phases by being dissolved in their corresponding solvents; the phases have then been mixed at different time points to form the hydrogel patch</td>
<td>Herbal formulation</td>
<td>Panax notoginseng, Carthamus tinctorius L., and other herbs used in the Sanqi bone paste</td>
<td>46</td>
</tr>
</tbody>
</table>

Abbreviations: Alg, alginate; CMC, carboxymethylcellulose; CS, chitosan; PECT, poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ε-caprolactone-co-1,4,8-trioxa[4.6]spiro-9-undecanone); PNIPAm, poly(N-isopropylacrylamide); and PVP, poly(vinyl pyrolidone).
The hydrogel has enabled sustained release of embelin. Applications have been limited by its poor aqueous solubility. Active herbal ingredient, namely embelin, whose delivery into a liver at a low dosage of 0.5 mg per hepatocarcinoma-bearing mouse, the antitumor efficacy has been found to be comparable to a total dose of 6 mg of free embelin per mouse. This promising result has corroborated the possible role of physical hydrogels in boosting the efficacy of oriental herbal medicine.

4. MODULATION OF HYDROGEL PROPERTIES FOR DELIVERY OF HERBAL MEDICINES

When carriers of herbal medicines are developed, one of the factors to be considered is the loading efficiency, which is largely affected by the affinity of the herbal components to the hydrogel matrix. In oriental medicine, one regimen is generally consisted of multiple herbs. Therefore, multiple components must be delivered simultaneously in order for the treatment to be effective. This is technically challenging, because most of the delivery systems reported in the literature are mainly designed for use in single drug therapies. Setting this problem necessitates a hydrogel-based system that can carry herbal components with different degrees of hydrophilicity. Hydrogels, however, are hydrophilic in nature. If the loaded components are hydrophobic, the affinity of the components to the hydrogel matrix will generally be low. The components may simply diffuse out of the matrix before the loading process is complete, limiting the final loading yield.

One strategy to solve this problem is to first encapsulate the hydrophobic components into a system that shows a higher affinity to the hydrogel matrix, before the components are loaded into a hydrogel. This approach has been adopted in an in situ gel-forming system, which composes of curcumin-loaded micelles and a thermosensitive hydrogel. Curcumin is an active component of turmeric (the powdered rhizome of Curcuma longa L.). In China and some Asian countries, it has been used as a spice, and as a remedy to treat diverse inflammatory and chronic diseases. It has also been reported to be effective in wound repair upon oral and topical administration. Despite this, the clinical efficacy of curcumin has been limited partly by extensive first-pass metabolism. This problem might be alleviated by loading curcumin into hydrogels for more sustained release. Curcumin, however, has low aqueous solubility. Its affinity to the hydrogel matrix is low. To address this problem, curcumin has first been encapsulated in polymeric micelles. The encapsulated curcumin (Cur-M) has subsequently been loaded into a thermosensitive PEG−poly(ε-caprolactone)−PEG (PEG−PCL−PEG) hydrogel (Figure S5A) to form a system (viz. Cur-M-H) for use as a wound dressing. The system is a free-flowing sol under ambient conditions, but can be converted to a nonflowing gel at body temperature (Figure S5B). Compared to those treated with normal saline, wounds treated with Cur-M-H have exhibited negligible signs of inflammation and infection, and have not had any pathological fluid oozing out (Figure S5C). Histopathologic analysis has revealed that wounds treated with Cur−M−H have shown a higher degree of re-epithelialization, well-organized granulation tissues, and significant fibroblastic deposition, compared to those treated with Cur−M, normal saline, and the hydrogel containing blank micelles (Figure S5D). This study has demonstrated the feasibility of enhancing the efficiency of the loading process by first encapsulating a herbal ingredient in another system before hydrogel encapsulation.

To improve the loading efficiency, another method is to modulate hydrogel properties to increase the affinity of the hydrogel matrix to hydrophobic components. This has been hinted at in a previous study, in which an Alg-based hydrogel has been adopted to encapsulate a herbal extract of Piper sarmentosum. Hydrogels fabricated from Alg with a higher mannuronate/guluronate (M/G) ratio have been shown to have higher encapsulation efficiency. This suggests that engineering the chemical composition of polymers can be a strategy to facilitate the loading of herbal medicines into hydrogels. Although related efforts are still incipient, the theoretical plausibility of this strategy has already been demonstrated by Byrne and co-workers, who have used different functional monomers and template molecules to generate a hydrogel for loading molecules with varying degrees of hydrophilicity. A more recent study has also modified CS with hyromellose to generate hyromellose-graft-chitosan (HC) (Figure 6A). The copolymer has higher aqueous solubility than native CS and can form a hydrogel upon
complexation with carboxymethylcellulose (CMC) to physically entrap drug molecules (Figures 6B). In total four drug models (viz. mometasone furoate, methylene blue, tetracycline hydrochloride, and metronidazole) with different degrees of hydrophilicity have been tested. The drug encapsulation efficiency of the HC/CMC hydrogel has been found to be 1–2 times higher than that attainable by the hydrogel formed using CS (Figure 6C). This has pointed to the prospects of improving the loading of components with varying properties by optimizing the molecular design of a hydrogel-based system.

In addition to the loading efficiency, when a carrier is developed, another factor to be considered is the release sustainability. It can be controlled by changing the polymer composition to modulate the tortuosity and mesh size of the polymer network, diffusion, and the swelling property of a hydrogel. This has been illustrated by Patenaude and Hoare, who have functionalized natural polymers (such as CMC, dextran, and hyaluronic acid) and PNIPAM-based synthetic oligomers with hydrazide or aldehyde functional groups to generate a series of in situ gelation, hydrazone-cross-linked hydrogels (Figure 7). By changing the number and ratio of different reactive oligomers or polymer precursors, hydrogels with different swelling properties and degradation kinetic profiles have been generated. More recently, a composite hydrogel comprising both poloxamer 407 (P407) and CMC has been reported as a carrier of the Cortex Moutan (CM) extract for the treatment of AD. The high moisture content of the P407-based hydrogel has helped moisturizing the skin of AD patients. Upon the addition of CMC, the porous structure, the gelation transition

**Figure 5.** (A) Structural formula of PEG−PCL−PEG, which is used to form Cur−M−H. (B) Preparation and characterization of the Cur−M−H composite ((i) Cur−M−H at 10 °C (left) and 37 °C (right); (ii) dermal adhesiveness of the Cur−M−H composite). (C) Images of skin wounds treated with (i) normal saline, (ii) the hydrogel containing blank micelles, (iii) Cur−M, and (iv) Cur−M−H, on the 14th day of wound healing. (D) The hematoxylin and eosin stained sections of the granulation tissue in groups treated with (i) normal saline, (ii) the hydrogel containing blank micelles, (iii) Cur−M, and (iv) Cur−M−H, on the 14th day of wound healing. (Reproduced with permission from ref 84. Copyright 2013, Elsevier, Amsterdam.)
temperature, and the rheological property of the hydrogel have been further optimized. Changes in the concentrations of P407 and CMC have been shown to lead to changes in the bulk viscosity of the hydrogel-based system and, hence, the release profile of the extract.57 This has revealed the close relationship between the release sustainability and composition of a hydrogel.

Last, but not least, high biodegradability and low toxicity are important prerequisites to be met if a carrier is to be applied to a biological body, but this is particularly a problem in chemical hydrogels. This problem can be tackled by incorporating biodegradable chemical groups or polymer segments into the backbone of the polymer constituent, as demonstrated in an earlier study in which dextran has been copolymerized with lactic acid oligomers.35 The generated hydrogel has been reported to be fully degradable under physiological conditions.35 A similar strategy has also been adopted in a recent study,91 in which the toxicity of poly(ethyleneimine) (PEI) has been lowered by graft polymerization with polysorbate 20, generating hydrogel nanoparticles with a higher safety profile for biological applications.91 Over the years, substantial efforts have been devoted in the literature to generating polymers with low toxicity and high biodegradability. Many of these efforts have already been reviewed elsewhere.56−41 Readers are referred to those reviews for details.

5. PROSPECTS AND LIMITATIONS

Oriental medicine and Western medicine are two important systems in medical science. Oriental medicine views the human body as a microcosm consisting of both internal and external conditions, emphasizing the equipoise of "energies" in the five zang-viscera.90 It has the merit of being attentive to the root of the medical condition, but is perceived to be slower in action.91 On the other hand, Western medicine confronts the symptoms directly and, hence, has quicker effects, but the restoration of the internal balance has not been emphasized as much as that in oriental medicine.91 In the light of this, integrating herbal medicines with synthetic drugs from Western medicine may become a future approach in disease treatment. This potential has been presented in an earlier study on patients with idiopathic nephrotic syndrome.92 Compared to those treated with synthetic drugs (viz. prednisone and Cytoxan) alone, those treated with both synthetic drugs and herbal soups have been reported to have a higher remission rate, a lower adverse reaction rate, and a longer remission period. Similar promising effects have also been documented by Yao et al.,93 who have integrated herbal remedies (comprising herbs such as dandelion, giant knotweed, and barbed stullcap) with synthetic drugs (e.g., cyclosporine A, mycophenolate, prednisone, rapamycin, azathioprine, and tacrolimus) in the treatment of...
severe post-kidney-transplant lung infection. Among the 18 patients participated in the study, 15 of them have shown positive outcomes. This has been attributed to the effect of the herbal remedies in increasing the blood neutrophilic granulocyte phagocytic index and the blood plasma total complementary level in patients, thereby enhancing patients’ immune functions to fight against the infection.93

Despite the potential as depicted above, some herbal medicines and synthetic drugs may be incompatible with each other. Their combined use may jeopardize the efficacy of the treatment. This is exemplified by the herb Hypericum perforatum, which induces the expression of cytochrome P450 enzymes and P-glycoprotein, ultimately lowering the serum concentrations of synthetic drugs such as cyclosporine, indinavir, irinotecan, and nevirapine.94 Another study on pulmonary fibrosis rat models has also found that the health conditions of animals treated with a combined therapy consisting of azathioprine and Tripterygium wilfordii were worse than those treated with azathioprine alone.95 Therefore, herb−drug interactions must be taken into consideration when a combined therapy is administered. While further elucidation of the nature of those interactions is desired, if the incompatibility problem is caused by direct interactions between herbal medicines and synthetic drugs, this problem might be solved by advances in microfabrication technologies such as microfluidic electrospray, which has been adopted to generate multicompartment hydrogel beads for codelivery of incompatible agents.7 By using cadmium−telluride (CdTe) quantum dots (QDs) and PEI as a model pair, the beads have separated the incompatible agents in different compartments during the delivery process.7 Moreover, the composition of the compartments can be tuned using the polymer blending technique to attain different release profiles of the codelivered agents.7 The versatility provided by the beads is expected to bring new opportunities to the development of therapies that integrate both herbal medicines and synthetic drugs into one single system.

Finally, it is worth noting that the success of delivering herbal medicines using hydrogels may be more complicated than expected. Much more optimization may be required before success can be achieved. This is demonstrated in a clinical trial in which a hydrogel containing tepescohuite, which is the extract of the bark of Mimosa tenuiflora, has been studied for the treatment of VLU disease.96 The study has recruited 41 patients, who have topically applied the hydrogel on the ulcer on a daily basis. Histologic evaluation, however, has shown that the therapeutic effect of the extract-loaded hydrogel is not significantly different from that of the blank hydrogel. This reveals that successful incorporation of herbal medicines into hydrogels for clinical use may necessitate prior optimization and careful execution.

6. CONCLUDING REMARKS

Herbal medicine is an important part of oriental medicine that has been gaining recognition and popularity around the world. In this article, we have reviewed the latest advances in the development of hydrogel-based materials as carriers of herbal medicines, and have discussed the clinical challenges and potential for future research. As shown by the evidence presented, hydrogels are biocompatible materials that can be used as carriers to improve the efficacy of herbal treatments in both clinical and preclinical studies. This encouraging potential has been augmented by advances in microfabrication technologies, which enable hydrogel manipulation and make future integration of both herbal medicines and synthetic drugs into one single treatment technically feasible. In the forthcoming decade, rejuvenation and advancement of herbal medicine are expected to be facilitated continuously by advances in drug delivery technologies and materials science. What we are looking forward to is the emergence of more effective herbal treatments in the foreseeable future.
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Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to thank Marie C. Lin, Cheng-Shen Hu, and Yau-Foon Tsui for their help and support during the preparation of this manuscript.

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