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FULL PAPER

Synergistic effects of curcumin with other herbal compounds and chemical polymers in the preparation of wound dressings: A systematic review

Leila Amiri[a] |Sepideh Houshmand[b] |Hossein Kazemi[c] |Ghazal Moattari[d] |Mahsa Ouni[a,*]

[a]*Faculty of Chemistry, Islamic Azad University, Central Tehran Branch, Tehran, Iran*

[b]*Department of Horticultural Science, University of Tabriz of Agricultural Science, Tabriz, Iran*

[c]*Faculty of Chemistry, NaghsheJahan University, Isfahan, Iran*

[d]*Department of Genetics, Faculty of Basic Science, Shahrekord University, Shahrekord, Iran*

***Corresponding Author:**
Mahsa Ouni
Email: mahsaouni70@gmail.com
Tel.: +989143206158

Curcumin is among the herbal substances that are of high significance for many researchers as a wound dressing and a wound-healing substance. Curcumin's functioning can be substantially improved by its blending with other natural and industrial components. A systematic review was conducted by searching queries in reliable databases, including Scopus, Web of Sciences, and PubMed. The search results were screened by two researchers employing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) algorithm. A total of 320 studies were identified, of which 11 were chosen for evidence synthesis. According to the studies, the antimicrobial effect (in 8 studies), mechanical properties (in 7 studies), electrospinning (in 8 studies), and cytotoxicity (in 6 studies) in wound dressings were parameters significantly influenced by blending curcumin with other herbal components and chemical polymers. According to the evidence synthesis results, herbal compounds combined with curcumin improve and strengthen the wound healing property of curcumin.

KEYWORDS

Curcumin; herbal substances; wound dressing; wound healing; chemical polymer.

Introduction

Cutaneous wounds negatively impact the economic and hygienic systems worldwide [1]. Globally, it has been estimated that over one billion people suffer from acute and chronic wounds [2]. According to the literature, more than 5.7 million US citizens suffer from chronic wounds, which imposes an annual treatment cost exceeding $27.2 billion in 2027 [3]. Wound management and healing are believed to be the critical steps in lowering adverse health outcomes [4]. Fife *et al.* (2018) reported a wound healing frequency of around 40%, contrary to public reports suggesting wound healing in 90% of cases in the community [5]. The advances in wound healing have made significant gains. In recent years, research has widely explored some foods' biological and molecular impacts on wound healing.

Wound healing is an interactive process encompassing cellular and molecular events [6]. These include four main natural and overlapping stages: homeostasis, inflammation, proliferation, and regeneration [7]. Using wound dressings with biological effects promoting these stages results in the rapid and more efficient wound healing.

Following outstanding achievements in traditional medicine and herbal science, using herbal compounds to heal wounds has become a standard treatment worldwide, especially in countries with robust conventional medicine systems such as China and India [8,9]. An ideal wound dressing should possess excellent mechanical properties, high porosity, reasonable water vapor transmission rate (WVTR), high water absorption, antibacterial effects, and bacterial and fungal inhibition capacities [10-12].

In cases of non-healing wounds, nanofibers are used as wound dressings for healing purposes. One of the main wound-healing strategies is fabricating porous and biocompatible scaffolds using medicinal herbs, which serve as a proper matrix for tissue adhesion and growth [13]. These dressings can be made of synthetic and natural polymers. Generally, synthetic polymers possess superior mechanical properties. However, biopolymers are preferred to synthetic polymers due to their non-toxicity, bio-adherence, biocompatibility, biodegradability, and antimicrobial properties [14,15]. Curcumin has long been utilized for wound-healing purposes owing to its anti-inflammatory, antimicrobial, and antioxidant properties [16-18].

Curcumin's biocompatibility, non-toxicity, and biological properties have received significant attention from researchers [18, 19]. It has been approved by the US Food and Drug Administration (FDA) as a "generally recognized as safe" (GRAS) molecule [14, 20]. The poor water-solubility and low bioavailability of curcumin have restricted its use as a wound dressing. Researchers have combined curcumin with various other herbal compounds to tackle this limitation. This process is facilitated in the polymer presence [14]. Herbal compounds combined with curcumin can influence curcumin's wound-healing effects, such as mechanical, antioxidant, antibacterial properties, water vapor permeability, and so on [21-23]. This study provides a systematic review of the synergistic effects of curcumin with other herbal compounds in the preparation of wound dressings.

Method

A systematic review was conducted by searching the defined queries using a combination of keywords and creating a search strategy. This way, Scopus, Web of Sciences, and PubMed databases were employed. An example of the search strategy is given in Table 1. Studies were screened by two researchers independently using the PRISMA algorithm. This way, following extracting search results from databases and removing the duplicates, the articles were checked for their titles and abstracts. Researchers then shared the screening results. Conflicts were settled by discussing them by the two researchers. Afterward, the same researchers investigated the full text of the articles independently using the inclusion and exclusion criteria.

TABLE 1 An example of the search strategy

Database	Search Strategy	Results
PubMed	((Curcumin[Title/Abstract]) AND ("wound dressing"[Title/Abstract])) AND (toxicity[Title/Abstract] OR "Water absorption"[Title/Abstract] OR "water vapor permeability"[Title/Abstract] OR "Antibacterial" [Title/Abstract] OR electrospinning [Title/Abstract] OR "mechanical properties" [Title/Abstract] OR "antioxidant activity"[Title/Abstract] OR "cell viability" [Title/Abstract] OR hydrophobicity [Title/Abstract])	**60**

The inclusion criteria were the reports on blending curcumin with herbal substances in the preparation of wound dressings, reports of the results of at least one of the nine properties, and access to the full text of the articles. Studies using curcumin for wound healing or utilizing it on different polymer matrixes and those reporting on the synergistic effect of curcumin with the other non-herbal substances and extracts such as titanium dioxide were excluded from this study. The extraction table was initially designed based on the study objectives, and the data of two articles were then extracted as a pilot. Next, two researchers extracted data from articles after making the necessary corrections in the form. The extracted data included author affiliation, the publication year, the type of the utilized polymer, the herbal composition, and other characteristics including electrospinning, antibacterial effects, water absorption, WVPR, mechanical properties, cellular toxicity, antioxidant activity, cell viability, and hydrophobicity.

Results

A total of 320 articles were identified by searching, of which 117 duplicates were removed, and 203 articles were eventually chosen for screening. Firstly, the studies were checked for their title and abstract by two researchers independently using the PRISMA algorithm. A total of 180 articles were removed in this stage. Ultimately, 23 articles were selected for the full-text assessment (Figure 1). Concerning the inclusion criteria, 11 articles were chosen for qualitative synthesis, and relevant data were extracted. According to the studies, combining various herbal compounds with curcumin improves curcumin properties for use as a wound dressing. This effect is primarily manifested in improved mechanical properties (Table 2).

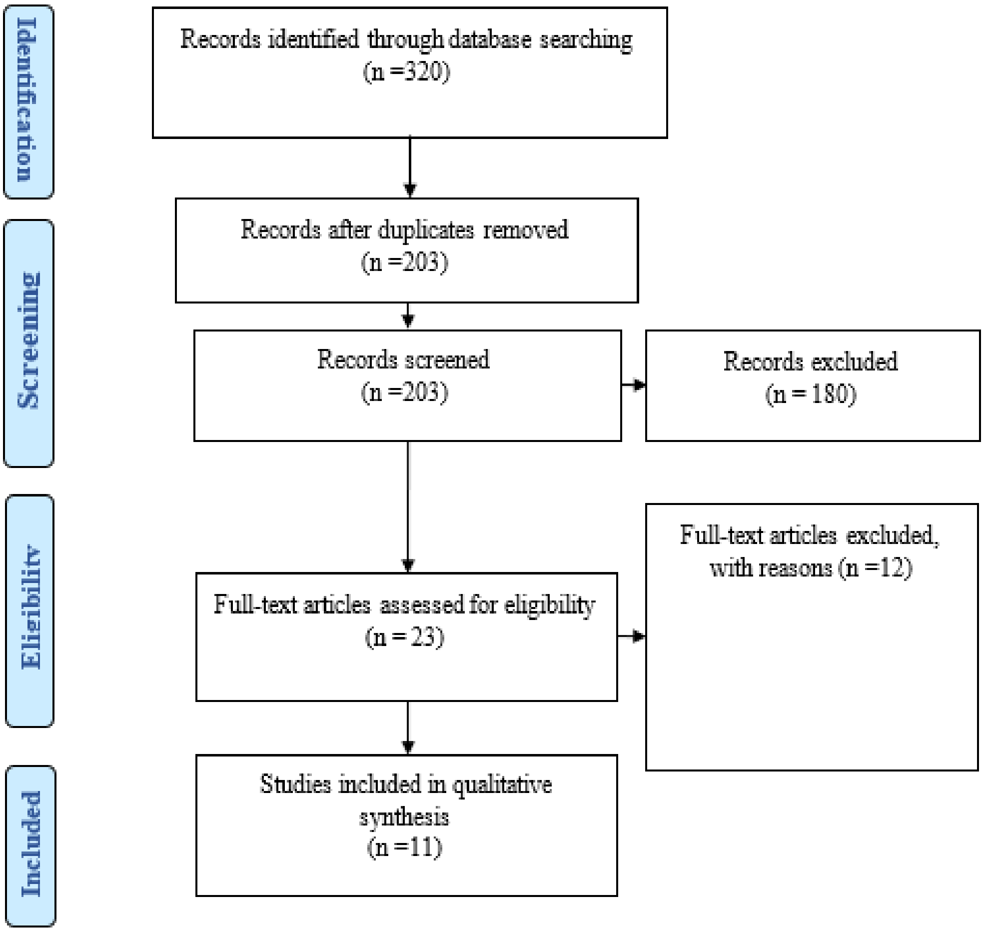

FIGURE 1 Searching and screening process

TABLE 2 Characteristics of articles included in the systematic review

No.	Author	Year	Chemical Polymer	Curcumin component	Electrospinning	Antibacterial	Water absorption	Water vapor permeability	Mechanical properties	Cellular toxicity	Antioxidant activity	Cell viability
1	Bhubhanil, S. *et al.* [24]	2021	Silver nanoparticle hydrogel	Guar gum/curcumin	-	60% higher antibacterial action	-	-	-	More than 80%	-	Improving
2	Comotto, M. *et al.* [25]	2019	Hydrogels alginate	Curcumin and t-resveratrol	-	Improving	-	-	Excellent	Non-toxic	-	Improving
3	Ehsani, A. *et al.* [26]	2021		Tragacanth and curcumin	-	-	-	-	Suitable	Decrease	-	Improving
4	Ezhilarasu, H. *et al.* [27]	2020	Polyvinyl alcohol	Curcumin-honey	695.1 nm	E. coli: 90%	1655%	~10 mg /cm² h			93%	
5	Fernández, J. *et al.* [28]	2021		Curcumin-honey	340 nm	More antibacterial actions	-	-	-	-	-	-
6	Gaydhane, M. K. *et al.* [29]	2019		Aloe vera and curcumin	360 to 770 nm	Improving	-	-	Good	Non-toxic	-	High cell viability
7	Ouni.M. *et al.* [13]	2019	Poly-caprolactone	Allicin, curcumin, piperine	200 nm	-	-	-	Tensile strengths (Elastic modulus of 5-9 MPa) Elongation at breaks higher than 25%		Enhancing the antioxidant activity of curcumin	-
8	Ranjbar-Mohammadi, M. Bahrami, S. H. [30]	2022		Curcumin/piperine/ellagic acid	172.18 nm	Staph:79% Acceptable f. enters:99/54% considerable	%337	11.55 mg/cm².h	Strength module (MPa): 0/924 Tensile strength (MPa): 0/205	79%	-	

								Elongation at break (%): 20.282			
9	Safdari, F. *et al.* [31]	2016	Tragacanth and curcumin	164 to 191 nm	Excellent	-	-	Suitable	-	-	-
10	Shahid, M. A. *et al.* [32]	2022	Curcumin-piperine-rutin Curcumin-piperine-eugenol	(1): 142/60 nm (2): 198/38 nm	Staph: 74%: (1) 75%: (2) f.enter: 99.47%: (1) 96.88% (2)	-	8.33–10.42 mg /cm^2 h	Good	Good	-	
11	Suteris, N. N. *et al.* [33]	2020	Curcumin-cellulose	152 nm	-	High water uptake	-	-	-	-	-

Discussion

According to the studies, combining herbal extracts and substances with curcumin using polymers as a matrix improves curcumin's healing properties as a wound dressing [13, 31,34]. Most studies have reported a 60% improvement in antibacterial, mechanical, and electrospinning properties of curcumin in wound healing when using it with other herbal substances [24-25,28-29].

The antibacterial effect of wound dressings is of paramount importance in wound healing. The results of this review revealed that incorporating curcumin with the other herbal compounds such as honey, piperine, and ellagic acid enhances the antibacterial effects [27-28,13,30,32]. Ouni *et al.* (2021) showed that blending piperine and curcumin leads to synergistic antibacterial effects and hinders the bacterial growth. Furthermore, a mixture of ellagic acid with curcumin improved the antimicrobial properties in felt samples [13]. Mahdi Saeed *et al.* (2017) designed and fabricated curcumin-loaded PCL/PVA multi-layer nanofibrous electrospun structures as an active wound dressing. Scaffolds containing 16% of curcumin were investigated for their antibacterial effects. Due to the presence of curcumin, scaffolds possessed high antibacterial properties [34].

In a study conducted in 2018, Thomas George *et al.* reported the positive impacts of curcumin, piperine, and ellagic acid on the recovery and relief of pancreatitis in mice [35]. The other studies have reported similar findings [6,20,36].

Moisture permeation in wound dressings is a critical factor to control and inspect, concerning the necessity to keep low water contents in open or wet wounds. The allowed and proper WVPR value for the standard wound dressing is reported to be around 8.33 to 42.10 mg/cm^2.h [34].

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Vitality and cytotoxicity are the two other critical indices in improving the performance of wound dressings. The evidence synthesis results revealed that combining curcumin with other herbal substances improves both the above properties. Ranjber *et al.* (2016) reported that mixing curcumin with tragacanth gum enhances cell proliferation and adhesion in wound dressing [30]. In another study, the piperine-loaded PLA-gelatin nanofibers improved the antibacterial properties and reduced the growth of cancer cells [37]. Furthermore, Sedghi *et al.* reported that loading graphene oxide (GO) and Zn-Curcumin complex (Zn-CUR) into coaxial electrospun nanofibers improves the toxic properties [38].

Conclusion

The evidence synthesis results showed that mixing herbal compounds with curcumin improves and strengthens curcumin's properties in wound healing. The antimicrobial, mechanical, and electrospinning properties of curcumin-based wound dressing scaffolds are further enhanced when using curcumin with the other herbal compounds. Using curcumin as a wound dressing with the other herbal substances can facilitate and optimize wound healing process.

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Abbreviations

CUR: Curcumin; FDA: Food and Drug Administration; GO: Graphene Oxide; GRAS: Generally Recognized as Safe; PCL: Polycaprolactone; PVA: Polyvinyl Alcohol; WVPR: Water Vapor Permeation Rate; WVTR: Water Vapor Transmission Rate.

Orcid:

Mahsa Ouni:
https://www.orcid.org/0000000225706478

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