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Review

Exploring recent developments to improve antioxidant, anti-inflammatory and antimicrobial efficacy of curcumin: A review of new trends and future perspectives

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ABSTRACT

Curcumin derivatives have been well-documented due to their natural antioxidant, antimicrobial and anti-inflammatory activities. Curcuminoids have also gained widespread recognition due to their wide range of other activities which include anti-infective, anti-mutagenic, anticancer, anti-coagulant, antiarthritic, and wound healing potential. Despite of having a wide range of activities, the inherent physicochemical characteristics (poor water solubility, low bioavailability, chemical instability, photodegradation, rapid metabolism and short half-life) of curcumin derivatives limit their pharmaceutical significance. Aiming to overcome these pharmaceutical issues and improving therapeutic efficacy of curcuminoids, newer strategies have been attempted in recent years. These advanced techniques include polymeric nanoparticles, nanocomposite hydrogels, nanovesicles, nanofibers, nanohybrid scaffolds, nanoconjugates, nanostructured lipid carriers (NLCs), nanoemulsion, polymeric micelles and polymeric blend films. Incorporation of curcumin in these delivery systems has shown improved solubility, transmembrane permeability, long-term stability, improved bioavailability, longer plasma half-life, target-specific delivery, and upgraded therapeutic efficacy. In this review, a range of *in vitro* and *in vivo* studies have been critically discussed to explore the pharmaceutical significance and therapeutic viability of the advanced delivery systems to improve antioxidant, anti-inflammatory and antimicrobial efficacies of curcumin and its derivatives.

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Abbreviations: NLCs, nanostructured lipid carriers; SLN, solid lipid nanoparticles; CUR, curcumin; CS, chitosan; NPs, nanoparticles; PEVs, penetration enhancer-containing vesicles; SNEDDS, self-nanoemulsifying drug delivery systems; MRSA, methicillin resistant *Staphylococcus aureus*; ESBL, extended spectrum β lactamase; PEG–PCL, poly(ethylene glycol)–poly(ε-caprolactone); PVA, polyvinyl alcohol; PLGA, poly (lactic-*co*-glycolic acid); MPO, myeloperoxidase; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; TMC, *N*-trimethyl chitosan; TPP, sodium tripolyphosphate; SLS, sodium lauryl sulfate; MPEG–PCL, methoxy poly(ethylene glycol)-b-poly(ε-caprolactone) copolymer; CS-OA hydrogel, CS/oxidized alginate hydrogel; NSAIDs, non-steroidal anti-inflammatory drugs; SC, stratum corneum; ROS, reactive oxygen species; TEM, transmission electron microscopy.

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1. Introduction

Curcuminoids (CUR) are naturally occurring low molecular weight polyphenolic constituents isolated from rhizome of turmeric *Curcuma longa* (family, Zinfiberaceae) [125]. The chemical structure of CUR is shown in Fig. 1. This natural versatile drug has gained widespread popularity due to its remarkable applicability in prophylaxis and treatment of a variety of inflammatory conditions [2,3,61]. Numerous studies have discovered the therapeutic potential of CUR and their derivatives in the treatment of wide range of chronic diseases including cardiovascular [23,52,114], neurodegenerative [11,70,71,76,80,87,102,116], autoimmune [12,22,151], pulmonary [17,98,132], metabolic [105,111], gastrointestinal [69,108,150] and psychotropic disorders [18,63]. In addition to its exceptional therapeutic activities against a wide range of chronic diseases, CUR derivatives are also known to accelerate wound healing in cutaneous [47,82,99,104], excisional [62,65,75,103,134] and chronic wounds [58,74,141]. Moreover, curcumin derivatives have also shown strong antioxidant and free radical scavenging activities [7,66,155,99]. CUR are also known for their anti-infectious [103,126] and anti-inflammatory [66,82,89] activities. In spite of its excellent pharmacological benefits, researchers are still facing difficulties related to its poor aqueous solubility [10], low oral bioavailability [29,79], chemical instability, inadequate absorption and transmembrane permeation, and rapid metabolism and elimination. CUR had poor absorption, scarce bioavailability and efficacy owing to its low water solubility; however, due to its lipophilic nature it has adequate transmembrane permeability [40,67]. Besides, photo-degradation is another challenge to effective CUR delivery [128]. This may restrict its applications on industrial scale as well as minimize its shelf-life. Rapid metabolism (*via* conjugation – glucuronidation and sulfation) and short half-life of CUR are crucial limitations in the delivery of CUR [59,107,143] and hence reduce its therapeutic significance. These limitations reduce pharmaceutical and therapeutic feasibility of CUR and its derivatives [2,3,10,152].

In recent decades, various strategies have been employed to overcome pharmaceutical issues related to the effective delivery of CUR which include micellar solubilization [88], cyclodextrin complexation [136], crystal modification (*e.g.* metastable polymorphs, salt or co-crystal formation, and amorphization), prodrug strategies and particle size reduction (micronization). However, none of the strategies has been completely successful in enhancing water solubility and oral bioavailability. Novel strategies are therefore required to address the pharmaceutical issues related to aqueous solubility, oral bioavailability, chemical instability, rapid metabolism and short half-life and to improve therapeutic efficacy and patient compliance. Recently, nanotechnology-based approaches have gained remarkable attention due to their potential in enhancing *in vitro* and *in vivo* activities of CUR [19,49,144]. In this article, we have critically reviewed the available evidence related to the pharmaceutical significance and therapeutic feasibility of advanced technologies in improving antioxidant, anti-inflammatory and antimicrobial activities of the CUR and its analogs.

2. New developments and improved therapeutic efficacy of CUR analogs

CUR and its derivatives have shown remarkable activities against a wide range of chronic diseases including cardiovascular, neurodegenerative, autoimmune, pulmonary, metabolic syndrome, psychotropic disorders, and chronic wound healing. However, pharmaceutical significance and therapeutic efficacy of CUR and its derivatives is limited due to their poor water solubility, low oral bioavailability, extensive first pass metabolism, short-half-life, chemical instability and photo-degradation. To overcome these pharmaceutical problems, new strategies are needed to be developed.

In recent years, researchers have focused on the development of nanotechnology-based delivery systems to overcome pharmaceutical issues related to the delivery of CUR. These novel strategies include polymeric NPs, liposomes, nanohybrid scaffolds, nanocomposite hydrogels, SLN, NLCs, nanofibers, CUR-loaded CS films and blends [90, 153] and polymeric micelles. These nanotechnology-based delivery systems have gained widespread recognition because of their promising potential and advantages over the conventional approaches such as, 1) they help avoid enzymatic degradation of the encapsulated cargo [131], 2) provide controlled release of therapeutic payloads, 3) enhance dissolution rate and permeability of the poorly water-soluble drugs, 4) prolong residence of drug in plasma and improve pharmacokinetic profile [4], 5) improve cellular uptake which make them a successful delivery tool for many bioactive molecules, and 6) optimize target-specific delivery of drugs and superior drug retention into the target tissues [54,55,56,57], and 7) reduce off-target effects by achieving target-specific delivery of the therapeutic payload [43]. We have critically reviewed literature and found a wide range of new delivery systems that have improved therapeutic efficacies of curcumin and its derivatives. For better understanding, we have classified these delivery systems as, 1) particulate formulations (which include microparticles and

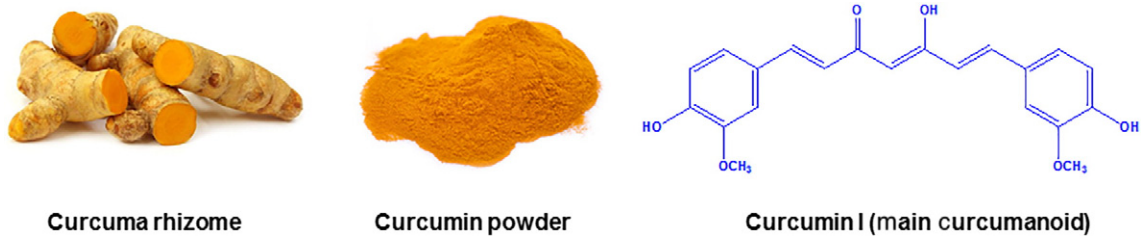

Fig. 1. *Curcuma* rhizome, commercial curcumin powder and chemical structure of curcumin.