Materials Science and Engineering C 77 (2017) 1316–1326

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Review

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

Zahid Hussain [a,*], Hnin Ei Thu [b], Muhammad Wahab Amjad [c], Fahad Hussain [d], Tarek A. Ahmed [e], Shahzeb Khan [f]

[a] Department of Pharmaceutics, Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Bandar Puncak Alam 42300, Selangor, Malaysia
[b] Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak 56000 Cheras, Kuala Lumpur, Malaysia
[c] College of Pharmacy, Northern Border University, Rafha, Saudi Arabia
[d] Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore, Raiwind Road 55150, Lahore, Pakistan
[e] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
[f] Department of Pharmacy, University of Malakand, Chakdara, Dir (L), KPK, Pakistan

ARTICLE INFO

Article history:
Received 17 October 2016
Accepted 24 March 2017
Available online 27 March 2017

Keywords:
Curcumin
Advanced delivery systems
Nanoparticles
Liposomes
Nanoconjugates
Improved antioxidant, anti-inflammatory and antimicrobial efficacies

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.

Contents

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.

* Corresponding author.
E-mail address: zahid3224@puncakalam.uitm.edu.my (Z. Hussain).

http://dx.doi.org/10.1016/j.msec.2017.03.226
0928-4931/

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.

nanoparticles), 2) scaffolds (or matrix)-based formulations (which include hydrogels, nanofibers, and foams), and 3) hybrid formulations (*e.g.*, particle embedded scaffolds or matrixes).

2.1. Particulate formulations

2.1.1. Nanoparticles (NPs)

Numerous studies have explored the pharmaceutical significance and therapeutic viability of the polymeric NPs for the delivery of a wide range of therapeutic agents and in the treatment of various skin inflammatory diseases [54,55,121].The success of polymeric NPs-based delivery system is attributed to their ultra-small size, high encapsulation efficiency, adequate surface potential, biodegradability and biocompatibility [126]. In addition, these delivery systems can prevent premature degradation of encapsulated drugs, provide controlled delivery, achieve target-oriented delivery of the drugs [54,55], and prevent systemic toxicity. These delivery systems have also been proposed to augment percutaneous delivery of the drugs without permanent damage to the stratum corneum [54,55]. Shao et al. [121] have recently written an excellent review article after critical evaluation of the literature and suggested that nanoencapsulation of a wide range of pharmacological moieties significantly improved their therapeutic feasibility in treating various skin inflammatory disorders.

Recently, Krausz et al. [6] evaluated the pharmaceutical significance, antioxidant and antimicrobial efficacies of CUR-encapsulated polymeric NPs. After the successful fabrication of CUR-loaded polymeric NPs, they tested these NPs for the mean particle size, zeta potential, *in vitro* release characteristics, cellular cytotoxicity, zebrafish cytotoxicity, and antibacterial activity against MRSA and *P. aeruginosa* [6]. Due to susceptibility of MRSA and *P. aeruginosa* infections in burn wounds, the activity of CUR-NPs against these species was evaluated *in vitro*. Results showed that CUR-NPs exhibit strong antibacterial activity against MRSA and *P. aeruginosa*. After 6 h incubation with CUR-NPs, MRSA displayed edema and damage with subsequent lysis and extrusion of contents after 24 h, in contrast to untreated MRSA with intact cellular structures, uniform cytoplasmic density, and well-defined cell wall [6]. The quantification of CFU showed that CUR-loaded NPs caused approx. 97% reduction in MRSA growth and around 60% reduction of *P. aeruginosa* growth which was significantly greater compared to both untreated control and control np ($p \leq 0.0001$).

To further investigate the mode of action of antimicrobial activity of CUR-NPs, MRSA incubated with CUR-NPs as well as with control NPs were studied over time using TEM (Fig. 2). Untreated MRSA (Fig. 2A) showed intact cellular architecture with uniform cytoplasmic density and highly contrasting cross wall. After 24 h, MRSA incubated with control NPs did not exhibit changes in cellular architecture compared to untreated control despite visible interaction with nanoparticles (Fig. 2B). In contrast, after 6 h treatment with CUR-NPs (Fig. 2C), the cells of MRSA which were in contact with particles displayed edema and distortion, with subsequent lysis and extrusion of contents after 24 h (Fig. 2D).

The delivery of CUR-loaded PLGA NPs has also shown promising potential in improving *in vitro* performance of CUR [73]. In this study, authors prepared CUR-loaded PLGA NPs by emulsification-solvent evaporation method [13,138]. Briefly, 50 mg of PLGA was dissolved in 2 mL dichloromethane and stirred to obtain a uniform PLGA solution. After a homogenous solution of PLGA was obtained, 5 mg of CUR was added and sonicated (at 70 W) for 30 s. The solution was then

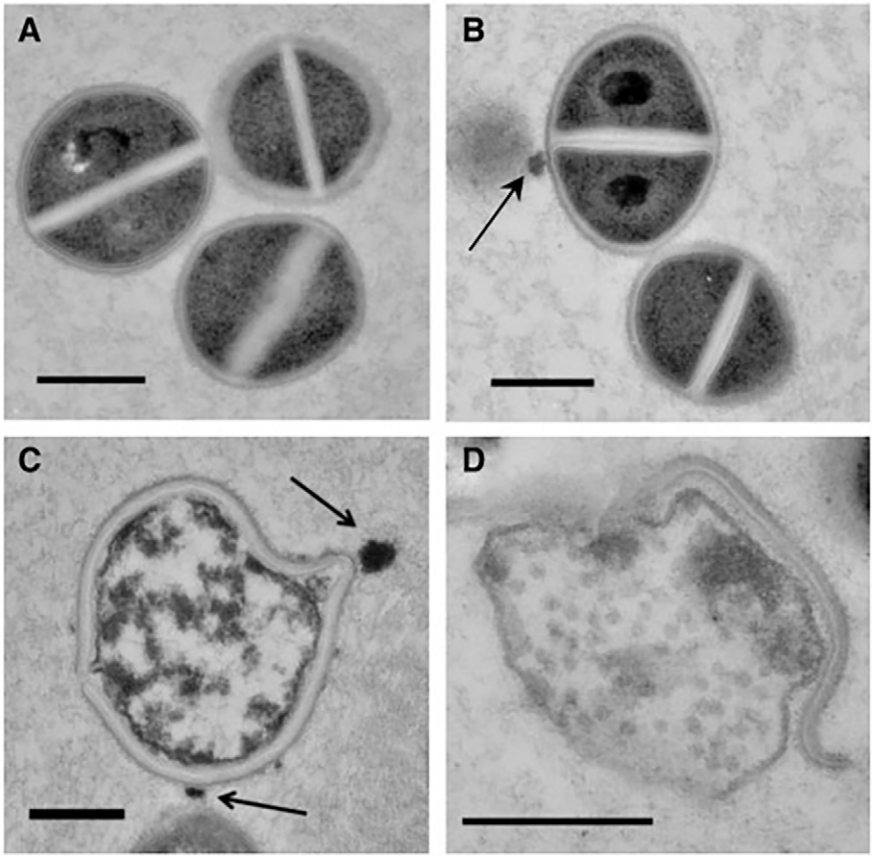

Fig. 2. CUR-NPs induced cellular damage to MRSA. High-power transmission electron microscopy demonstrated interaction of nanoparticles (arrows) with MRSA cells. (A) Untreated MRSA showed uniform cytoplasmic density and central cross wall surrounding a highly contrasting splitting system. (B) After 24 h, cells incubated with control NPs (5 mg/mL) did not exhibit changes in cellular morphology compared to untreated control. (C) After 6 h, cells incubated with CUR-NPs (5 mg/mL) exhibited distortion of cellular architecture and edema, followed by lysis and extrusion of cytoplasmic contents after 24 h (D). All scale bars = 500 nm [6].

emulsified with 10 mL of 1% (w/v) PVA solution and again sonicated for 1 min to generate the o/w emulsion. The CUR-loaded NP suspension was then washed twice in distilled water using centrifugation techniques. In order to evaluate successful fabrication, PLGA-CC NP were characterized for particle size, zeta potential, encapsulation efficiency, morphology, and *in vitro* release studies [73]. In addition, the tissue-associated MPO assay was performed to quantify the degree of inflammatory infiltration in the wounds. MPO is an enzyme that is found predominantly in the azurophilic granules of neutrophils and can be used as a quantitative index of inflammatory infiltration.

The findings demonstrated that the prepared PLGA-CC NP showed optimal physicochemical characteristics including smaller particle size (176.5 ± 7.0 nm), narrow distribution index (0.105 ± 0.025), acceptable zeta potential (−23.2 ± 3.8 mV), and greater encapsulation efficiency (89.2 ± 2.5%). On the other hand, *in vitro* release studies suggested biphasic release pattern with the initial burst release (approx. 40% of encapsulated CUR) within the first 24 h, followed by a sustained and gradual (approx. 75%) over a period of 8 days [138]. The assessment of anti-inflammatory activity of CUR revealed that on day 5 there was a significant increase in the activity of MPO in wound tissue of untreated and PLGA NP-treated mice due to inflammatory response. In contrast, CC and PLGA-CC NP-treated group showed significantly lower MPO activity. The MPO inhibition was much evident on day 10 in the case of PLGA-CC NP-treated mice as shown in Fig. 3 [73]. Furthermore, the authors also evaluated the significant downregulation of anti-oxidative enzymes like glutathione peroxidase (GPx) and NFκB which is a well-known transcription factor involved in cellular inflammatory responses. The results revealed that encapsulation of CUR in PLGA nanoparticles improve their anti-inflammatory efficacy.

2.1.2. Nanovesicles

Liposomes, spherical vesicles having at least one lipid bilayer, have widespread recognition as carriers or vehicle system for the administration of nutrients, pharmaceuticals and gene delivery [137]. Liposomes are versatile carriers having bilayer arrangement of hydrophilic core surrounded by hydrophobic membrane and thus are capable of carrying hydrophilic and hydrophobic drug cargo simultaneously. They are mainly composed of phospholipids, especially phosphatidylcholine, but may also include other lipids, such as egg phosphatidylethanolamine [137].

Liposomal systems have been numerously used to encapsulate a wide range of pharmaceutical moieties such as NSAIDs [39], immunoglobulins [41], growth factors [147], opioid analgesics [15], hyaluronic acid [93], superoxide dismutase [142], quercetin [21] and CUR [91], aiming to improve their antioxidant, antimicrobial and anti-inflammatory activities.

Recently, encapsulation of CUR in sodium hyaluronate immobilized vesicles (hyalurosomes) has been investigated and compared with conventional liposomes for *in vitro* and *in vivo* performance [91]. In this work, Manca and co-workers developed highly biocompatible nanovesicles by direct addition of polyanion sodium hyaluronate to the polyphenol CUR to fabricate polymer immobilized vesicles, so called hyalurosomes. CUR-loaded hyalurosomes were then characterized for particle size, zeta potential, encapsulation efficiency, stability, rheology, *in vitro* skin delivery, antioxidant activity, cellular toxicity, and anti-inflammatory activity [91].

The antioxidant activity of both curcumin ethanolic solution and vesicles was tested by measuring their ability to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH). Each sample was added (1:50) to DPPH methanolic solution (25 μM), stored at room temperature for 30 min in dark, and absorbance was measured at 517 nm against blank. The percent antioxidant activity was calculated according to the following formula:

$$\text{Antioxidant activity } (\%) = \left[\left(\text{ABS}_{\text{DPPH}} - \text{ABS}_{\text{sample}}\right)/\text{ABS}_{\text{DPPH}}\right] \times 100$$

In vitro cryogenic TEM and small-angle X-ray scattering analyses showed that CUR-loaded hyalurosomes were nanosized (112–220 nm) with spherical morphology. Skin drug delivery studies suggested that CUR-loaded hyalurosomes significantly enhanced drug permeation across the intact skin and showed approx. 57% of drug accumulated in the SC, 18% in the epidermis, and approx. 16% in the dermis only after 4 h. These findings indicated excellent ability of CUR-loaded hyalurosomes to promote delivery of CUR throughout the skin and thus can be utilized for various dermatological disorders. Cellular toxicity studies suggested that CUR-loaded hyalurosomes were biocompatible, non-toxic to human keratinocytes, could protect keratinocytes from oxidative stress damages, and were able to promote tissue remodeling by increasing cellular proliferation and differentiation.

To evaluate *in vivo* anti-inflammatory activity, female CD-1 mice were shaved and applied with TPA topically on the shaved back. TPA induces oxidative stress, inflammatory reactions, edema, and infiltration of inflammatory cells and loss of epidermis or ulceration. The results demonstrated that animals treated with CUR-loaded hyalurosomes showed minimal signs of inflammation, edema, and redness. The authors proposed that these results were due to greater ability of encapsulated CUR as hyalurosomes to diminish initiation of inflammatory reactions, in comparison to other treatment groups. These results were also in agreement with previous studies by Castangia et al. [21] and El-Refaie et al. [33] who have suggested a greater impact of nanoencapsulation of CUR to enhance its antioxidant, antimicrobial and anti-inflammatory efficacies.

Castangia and colleagues attempted for the nanodelivery of CUR and quercetin (QUE) by encapsulating these drugs in nanovesicles (*e.g.*, liposomes and PEVs). *In vitro* TEM, cryogenic-TEM, and small-angle X-ray scattering analyses showed that CUR-loaded- and QUE-loaded nanovesicles were ultra-small in size (approx. 112–220 nm) with spherical morphology. The nanovesicular encapsulation of CUR and QUE was also evaluated for *in vitro* drug permeation across the new born pig skin using Franz-diffusional vertical cells and calculation of percentage of drug accumulated in various skin layers (epidermis and dermis). The findings demonstrated that as compared to other formulations, nanovesicles of CUR and QUE namely Oramix®CG110-mediated surface modified nanovesicles, showed noticeably greater permeation across the skin and remarkably higher accumulation of the encapsulated drugs into various skin layers. According to the experiment, highest

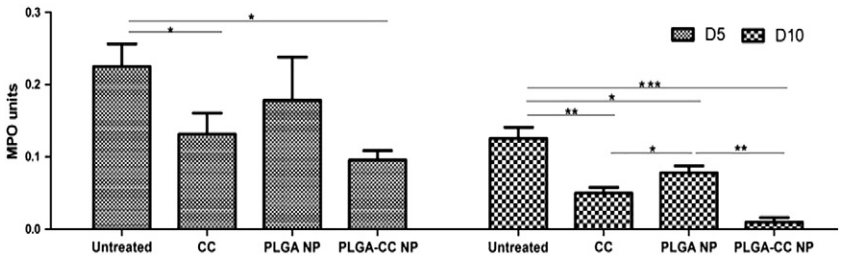

Fig. 3. Inhibition of MPO by CC, PLGA NP and PLGA-CC NP (mean ± SD, n = 3) [73].
Reprinted and reproduced with permission from ELSEVIER B.V. (Copyright © 2013) through Copyright Clearance Centre.

accumulation of CUR and QUE was found in the SC, followed by in the epidermis and then in dermis, respectively [21].

The therapeutic significance of the surface modified nanovesicles was also evaluated *in vivo* using female CD-1® mice (5–6 weeks old, approximately 25–35 g in weight) by investigating edema and MPO activity (which is used to estimate severity of inflammation). These studies revealed that the mice group dressed with surface modified nanovesicles of CUR or QUE demonstrated remarkable control over skin ulceration, curst formation, loss of epidermal integrity, and pathological damage to the epidermis, dermis and the subcutaneous tissues, in comparison to the control groups. Results from MPO activity suggested that PEG-modified nanovesicles and liposomes remarkably suppressed MPO activity by approx. 68% and 59% respectively, in comparison to the control groups. Histology results also showed significantly higher re-epithelization and collagen formation in mice group treated with nanovesicles system as compared to other treatment groups [21].

2.2. Scaffolds (or matrix)-based formulations

2.2.1. Nanocomposite hydrogel

Hydrogel-based delivery systems have also been used for improving pharmaceutical significance and therapeutic applicability of a wide range of pharmacological moieties including growth factors [44], nerolidol [106], stem cells [30], sodium fusidate [72], peptides [42], antibiotics [24,78], hyaluronic acid [20], and CUR [85,148,149].

Recently, a novel nanocomposite hydrogel composed of nano-CUR, CS and oxidized alginate has shown promising ability to accelerate dermal wound repair [85,148,149]. In this study, they evaluated *in vitro* and *in vivo* efficacy of CUR-encapsulated nanocomposite hydrogel which was previously developed by thin-film evaporation method using MPEG-PCL as a carrier/vehicle [83] followed by incorporating into the CS-OA hydrogel. The developed nanocomposite hydrogel was evaluated for *in vitro* stability, release profile, antioxidant activity and *in vivo* wound healing efficacy.

In vitro stability studies demonstrated that the stability of nano-CUR in phosphate buffered saline (PBS, pH 7.4) was significantly increased when encapsulated in nanocomposite hydrogel compared to the unmodified CUR. In case of nano-CUR, 100% of CUR remained intact after 5 h incubation, in comparison to the unmodified CUR that underwent significant rapid degradation (only about 50% of curcumin remained intact after 5 h of incubation) in PBS. The encapsulation of CUR into nanocomposite hydrogel was also evaluated for antioxidant activity and the results showed that there was a slight improvement in antioxidant activity. The release study revealed that the encapsulated nano-CUR was slowly released from CCS-OA hydrogel in a diffusion-controllable manner during initial phase followed by release in corrosion manner from hydrogel during terminal phase.

ROS are generally produced during normal physiologic conditions and can easily initiate the peroxidation of membrane lipids, resulting in the accumulation of lipid peroxides. ROS are also capable of damaging crucial biomolecules such as lipids, nucleic acids, proteins and carbohydrates and may cause DNA damage that can lead to mutations [7]. However, if ROS are not effectively scavenged by cellular constituents, the disease conditions might progress. In this study, Li et al. [85,148,149] demonstrated that the antioxidant activity of nano-CUR was about 99.22%, which was not significantly different than that of unmodified curcumin (approx. 98.73%). This result suggested that incorporated curcumin into polymer to form nano-CUR could not influence the intrinsic antioxidant activity of CUR.

2.2.2. Nanofibers

A great degree of improvement in antioxidant and antimicrobial efficacies of CUR was reported when loaded onto and administered using poly(ε-caprolactone) (PCL)/gum tragacanth (GT) electrospun nanofibers [95]. They developed PCL/GT/CUR-loaded nanofibers by electrospinning technique. Briefly, GT solution (7% w/v) blended vigorously with PCL solution (20% v/v prepared in acetic acid) in 2:1 (PCL/GT mass ratio). After making a homogenous solution, CUR (3% w/w based on solid contents in polymer blend) was introduced into the polymer blend and stirred for 30 min. Afterward, PCL/GT/CUR nanofibers were synthesized by electrospinning technique [95]. The *in vitro* performance of fabricated nanofibers was assessed through *in vitro* release study, antibacterial activity against MRSA and ESBL by broth dilution method [95].

In vitro studies revealed that PCL/GT/CUR nanofibers demonstrated biphasic release profile with approx. 60% of drug released in first hour with subsequent slow release until 20 h. The results of antibacterial activity suggested that the nanofibers demonstrated remarkable antibacterial activity against MRSA (99.9%) and ESBL (85.14%). The results of antibacterial activity of the nanofibers are shown in Fig. 4. These results suggested that CUR-loaded nanofibers are promising effective scaffold for antibacterial applications [95].

2.2.3. Foams (porous silk fibroin scaffold)

Substantial improvements in therapeutic efficacies of the CUR were also suggested by Kasoju and Bora [68] when CUR was fabricated as silk fibroin scaffold. They reported the fabrication of CUR-releasing porous silk fibroin scaffold by a simple mixing of fibroin solution (aqueous) with CUR solution (organic) followed by freeze–thaw of the mixture. The fabrication process is simple, reproducible, and does not require any sophisticated instruments or toxic crosslinking agents. The *in vitro* characterization of the scaffold demonstrated a uniform pore distribution with an average pore size of approx. 115 μm and a degree of swelling of 2.42% and water uptake capacity of 70.81%. Fibroin showed thermal stability up to approx. 280 °C, whereas the encapsulated CUR was disintegrated at around 180 °C. Fourier transform infrared, powder X-ray diffraction, and nuclear magnetic resonance studies together with UV–visible and fluorescence spectroscopy investigations revealed that the solvent (which was used to dissolve CUR) induced conformational transition of fibroin from silk-I to silk-II that led to the formation of water-stable structure. Fluorescence spectroscopy data also suggested the presence of hydrophobic domains in fibroin and encapsulation of CUR in such domains through hydrophobic interactions. Release kinetics and mathematical modeling studies indicated a slow and sustained release profile with diffusion as the predominant mode of release. Further, *in vitro* anticancer, antioxidant, and antimicrobial assays suggested that the biological activity of encapsulated CUR improved significantly [68]. It was anticipated that the CUR-loaded fibroin scaffold could be used in soft tissue replacements including localized postsurgical chemotherapy against tumors, dressing material for quick healing of wounds and burns, and other related applications.

2.3. Hybrid formulations

2.3.1. Nanohybrid scaffolds

A significant improvement in *in vitro* performance of CUR was suggested by Karri et al. [140] after encapsulating CUR in nanohybrid scaffold. The authors attempted the synthesis of a novel nanohybrid scaffold system by encapsulating CUR in CSNPs to improve aqueous solubility and stability of CUR, followed by impregnation of CUR-loaded CSNPs into collagen scaffold (nanohybrid scaffold). The authors prepared CUR-loaded CSNPs by ionic-crosslinking of CS with ionic cross-linker, TPP [140]. The resulting NPs were examined for particle size, zeta potential, morphology, biocompatibility, biodegradability, and *in vitro* release. *In vitro* studies demonstrated that encapsulation of CUR in nanohybrid system improved aqueous solubility, stability, biocompatibility, biodegradability and water uptake of CUR. The release studies demonstrated biphasic release pattern of CUR with burst release in 24 h followed by slow and sustained release. The data obtained suggested that nanohybrid system of CUR demonstrated better sustained release

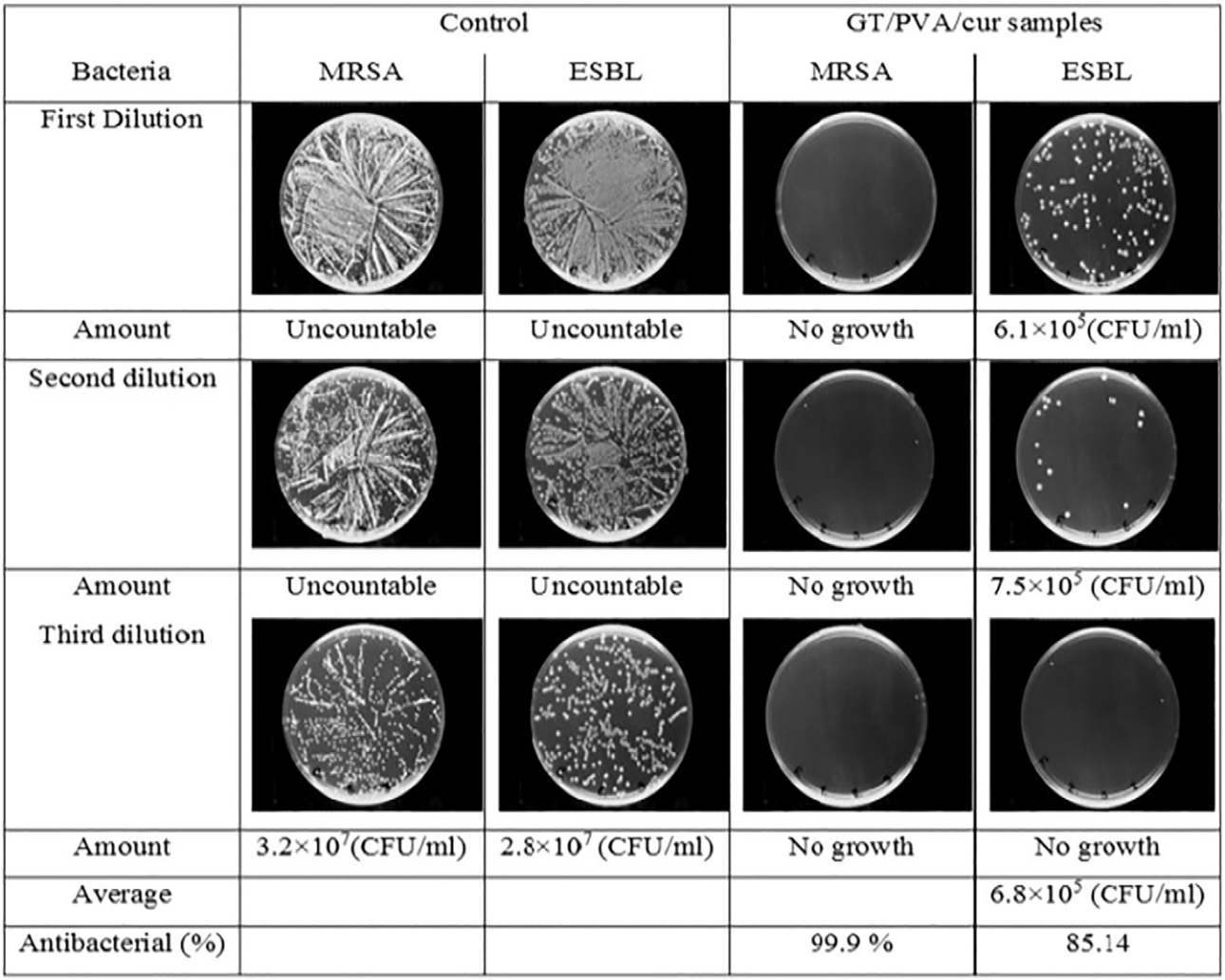

Fig. 4. Antibacterial activity against MRSA and ESBL for samples containing Cur (average CFU/mL) [95].
Reprinted and reproduced with permission from ELSEVIER B.V. (Copyright © 2016) through Copyright Clearance Centre.

pattern compared to CUR-loaded CSNPs that can diminish inflammatory cascades over extended time period and reduce dressing frequency.

In addition to the above mentioned delivery systems, nanoconjugates [9], NLCs [109], SNEDDS [16], nanoemulsion [64], and CUR-CS blend films [86] have also been investigated aiming to improve pharmaceutical significance (solubility, stability, oral bioavailability) and therapeutic feasibility (anti-inflammatory, antioxidant, and antimicrobial activities) of CUR derivatives. These studies demonstrated that encapsulation of CUR in these carrier systems has significantly improved *in vitro* and *in vivo* performance of CUR derivatives. A summary of these advancements and improved antioxidant, anti-inflammatory and antimicrobial activities are presented in Table 1.

3. Summary

Curcumin and its derivatives have gained widespread popularity due to their well-documented anti-inflammatory, antioxidant, anti-infective, and antimicrobial activities. However, hydrophobic nature of the curcumin derivatives along with their poor aqueous solubility, low bioavailability, chemical instability, rapid metabolism and short half-life impose substantial challenges to their effective and target-specific delivery and thus demand the development of newer strategies. These advanced strategies which include nanoparticles, nanovesicles, polymeric micelles, hydrogels, nanofibers, nanohybrid scaffolds, and polymeric blend films have been proven to enhance aqueous solubility, oral bioavailability, stability, and antioxidant, antimicrobial, and anti-inflammatory activities of the curcuminoids. Recent use of advanced delivery systems has been attributed to enhance *in vitro* and *in vivo* performance of curcumin derivatives.

4. Future perspectives

Nevertheless numerous studies have investigated the pharmaceutical significance and therapeutic applicability of the advanced delivery systems in improving *in vitro* and *in vivo* performance of curcumin derivatives; however, much has yet to be explored. Substantial gaps have been identified which include; 1) lack of comparative analysis of various advanced delivery systems for the delivery of curcumin and their therapeutic efficacy, 2) unavailability of safety/toxicity profile data for the advanced delivery systems, 3) lack of evidence-based randomized research specifically exploring therapeutic roles of the advanced delivery systems in improving antioxidant, anti-inflammatory and antibacterial activities, and 4) lack of insight into the large-scale (industrial) production of nanoencapsulated curcumin. Researchers working in the field of nanotechnology can work in the above-mentioned future prospects to further elucidate and comprehend the pharmaceutical significance of the nanocarrier-based delivery systems in improving therapeutic efficacy of the curcumin derivatives and in preventing and treating wide range of inflammatory diseases.

Table 1
Summary of improved antioxidant, anti-inflammatory and antimicrobial activities of curcumin using nanotechnology based delivery systems.

Classification	Delivery systems	Formulation	Study parameters	Major outcome(s)	Ref.	Advantages
Particulate formulations	Nanoparticles	Precirol ATO®5 + Miglyol 812 N/F + CUR + Tween 80 + Kolliphor® P188	1. *In vitro* release 2. Tissue permeability 3. Anti-inflammatory activity against chronic infection	1. Slow release of curcumin from lipid nanocarrier. 2. Significantly higher penetrability of curcumin in intestinal tissues. 3. Significantly greater anti-inflammatory activity in the treatment of inflammatory bowel disease.	[16]	Nanoparticle-based delivery of curcumin improved drug penetration across the biological membranes and improved therapeutic efficacy.
		Tetra-methyl orthosilicate + CS + CUR	1. Release profile 2. Toxicity 3. Antibacterial activity	1. Sustained release of encapsulated curcumin. 2. No sign of cellular toxicity, in comparison to control. 3. Improved antibacterial activity.	[6]	Encapsulation of the curcumin into nanoparticles matrix modify their release profile and improved antibacterial activity.
		Trimethyl chitosan or dimethyl chitosan + TPP + water + benzyl alcohol	1. Release profile 2. Cytotoxicity 3. Biocompatibility	1. Sustained release profile was observed. 2. Curcumin-loaded nanoparticles showed a considerable toxicity against human cervical tumor cells. 3. Acceptable biocompatibility	[130]	Nanoencapsulation of curcumin into nanoparticles improve its safety profile and biocompatibility.
		Catoinic gelatin + sodium alginate + ethylenediamine	1. Release profile 2. Cytotoxicity 3. Intracellular uptake	1. Sustained release. 2. No sign of cytotoxicity was observed in curcumin-loaded nanoparticles. 3. Significant increase in intracellular uptake of curcumin when loaded in polyelectrolyte complex nanoparticles.	[115]	Polyelectrolyte nanoparticles reduce cytotoxicity of curcumin and improve its intracellular uptake.
		PLGA + dichloromethane + CUR + PVA + emulsion – solvent evaporation method	1. *In vitro* release 2. Cell toxicity 3. Anti-inflammatory activity	1. Biphasic release pattern with initial burst release of 40% in first 24 h followed by sustained release over a period of 8 days. 2. No sign of cytotoxicity in human keratinocytes. 3. Significant decrease of MPO activity which indicate significantly higher anti-inflammatory activity of curcumin when fabricated in nanoparticles.	[73]	Delivery of curcumin as PLGA-nanoparticles significantly improve its anti-inflammatory, antioxidant and wound healing activities.
	Liposomes	Ferrous and ferric salt solution + Tween-60 + sodium hydroxide + acetone + CUR	1. Encapsulation efficiency 2. IC50 value 3. Antioxidant activity/free radical scavenging activity	1. Greater encapsulation efficiency (approx. 71%) in nano-magnetoliposomes. 2. IC50 value was significantly lower (64.7791 μg/mL) than control (138.36 μg/mL) which demonstrate increased potency of curcumin in nano-magnetoliposome form. 3. Stronger antioxidant and free radical scavenging activity, in comparison to control.	[1]	Liposomal delivery of curcumin is evidenced to exhibit higher encapsulation efficiency and improved therapeutic efficacy of the payloads.
		–	1. Physicochemical characteristics 2. Antioxidant/free radical scavenging activity 3. Anti-inflammatory activity	1. Prepared liposomes were having nanosize and acceptable physicochemical characteristics 2. Significantly higher 1,1--diphenyl-2-picrylhydrazyl radical scavenging and superoxide dismutase activities compared to control. 3. Significantly higher anti-inflammatory activity in terms of downregulated lipopolysaccharide -induced nitric oxide synthesis and release of interleukin-1β	[14]	Liposomal delivery of curcumin is evidenced to exhibit higher encapsulation efficiency and improved therapeutic efficacy of the payloads.

Table 1 (*continued*)

Classification	Delivery systems	Formulation	Study parameters	Major outcome(s)	Ref.	Advantages
				and tumor necrosis factor-α.		
	Hyalurosomes	Soy phosphatidylcholine + sodium hyaluronate + CUR + ultrasonic disintegrator	1. Skin permeation and retention 2. Cell viability 3. Antioxidant activity 4. Anti-inflammatory activity	1. Significantly higher permeation and percentage of CUR retained in epidermis and dermis. 2. Improved viability of human keratinocytes. 3. Greater antioxidant and free radical scavenging activity. 4. Significantly reduced MPO activity which showed stronger anti-inflammatory potential.	[91]	Incorporation of hyaluronic acid into curcumin-encapsulated nanoparticles significantly improves their therapeutic efficacy.
	Hyaluosomes	Lipoid S100 + Tween 80 + hyaluronic acid + CUR + thin-film evaporation method	1. *In vitro* release 2. Drug retained percentage 3. Wound healing	1. Controlled and sustained release of CUR, in comparison to burst release from CUR dispersion. 2. Significantly enhanced deposition and retention of CUR into various skin layers. 3. Significant increase in wound closure rate with complete healing and no scar at day 10, in comparison to control groups. 4. Enhanced granulation tissue formation, collagen fibers deposition, re-epithelization, and tissue regeneration.	[33]	Incorporation of hyaluronic acid into curcumin-encapsulated nanoparticles can modify release kinetics as well as can improve its therapeutic efficacy.
	Penetration enhancer vesicles (PEVs)	Soybean phospholipids + octyl-decylpolyglucoside + PEG-400 + quercetin + CUR + ultrasonic disintegrator	1. Skin permeation and retention 2. Anti-inflammatory activity	1. Significantly higher permeation and percentage of CUR and quercetin retained in epidermis and dermis. 2. Significantly reduced oedema and MPO activity. 3. Significant reduction in infiltration of inflammatory cells.	[21]	Nanoencapsulation of polyphenols into nanovesicles can improve their pharmaceutical significance and therapeutic feasibility.
	Micelles	PEG–PCL copolymer + dehydrated alcohol + CUR	1. Release profile 2. Antioxidant activity 3. Anti-inflammatory activity	1. Slow and sustained release of CUR. 2. Significantly improved anti-inflammatory activity 3. Significant improvement in antioxidant activity	[46]	Micellar delivery of curcumin can modify its release profile and improve therapeutic efficacy.
Scaffold (or matrix)-based formulation	NLCs-based gels	Glyceryl monostearate + stearic acid + caprylic/capric triglyceride + soya lecithin + CUR + emulsion evaporation – solidification method	1. Skin permeation 2. Anti-inflammatory activity 3. Skin histology	1. Significant increase (approx. 3 times) in skin permeation, in comparison to control formulations. 2. Greater improvement in anti-inflammatory activity of CUR when delivered as NLCs. 3. Remarkable restoration of skin integrity and increased skin thickness.	[109]	NLCs-based *in situ* gel formulation is an efficient tool for the delivery of curcumin and improved therapeutic efficacy.
	Nanofibers	PCL + gum tragacanth + CUR + electrospinning	1. *In vitro* release 2. Antibacterial activity 3. Diabetic wound healing	1. Sustained release of CUR from nanofibers 2. Strong antibacterial activity against MRSA (99.9%) and ESBL (85.14%) bacteria. 3. Faster and efficient wound healing in mice treated with CUR-loaded nanofibers. 4. Enhanced granulation tissue formation, epithelial regeneration, angiogenesis and collagen fibers in mice group	[154]	Nanofibers have been evidenced to significantly improve the wound healing, antioxidant and anti-inflammatory properties.

(*continued on next page*)

Table 1 (*continued*)

Classification	Delivery systems	Formulation	Study parameters	Major outcome(s)	Ref.	Advantages
				treated with CUR-loaded nanofibers.		
Hybrid formulation	Nanoparticle-embedded hydrogel	MPEG-PCL copolymer + linoleic acid + Tween-20 + CS + CUR + rotary evaporation	1. *In vitro* release 2. Cell toxicity 3. Antioxidant activity	1. Initial release of 8.4% of CUR observed in 1 day followed by a sustained release for a period of 5 days. 2. No sign of cytotoxicity after 24 h incubation 3. Slight increase in antioxidant activity (99.23%), in comparison to pure drug (97.49) in term of inhibition of lipid peroxidation.	[85,148,149]	Embedding of curcumin-loaded nanoparticles in hydrogel matrix significantly modify its release rate and improve therapeutic efficacy.
	Nanohybrid scaffold	CUR + PVP K30 + CS + TPP + magnetic stirring	1. *In vitro* drug release 2. Cell toxicity 3. Anti-bacterial activity 4. Wound healing efficacy	1. Sustained release (approx. 56%) of CUR from nanohybrid scaffolds in 72 h compared to CS NPs (82%). 2. Improved antibacterial and wound healing activities.	[140]	Nanohybrid scaffolds is an efficient advanced delivery system to improve wound healing efficacy of curcumin.
	Curcumin-CS blend film	–	1. Physicochemical characteristics 2. Antimicrobial activity	1. Acceptable film microstructure characteristics. 2. Significant improvement in antibacterial activity against *Staphylococcus aureus* and *Rhizoctoniasolani*.	[86]	Physical blending of curcumin with chitosan polymer in the form of film improves its therapeutic efficacy.
	Nanoconjugates	γ-Hydroxy-propylcyclodextrin + TPP + SLS + CUR + spray drying method	1. *In vitro* release 2. Cell toxicity 3. Cell viability	1. Biphasic release pattern with initial burst release of about 10% contents followed by sustained release. 2. No sign of cell toxicity compared to free drug solution. 3. Significant increase in cell viability.	[9]	Chitosan-cyclodextrin based hollow sphere have potential to significantly enhance cell cytotoxicity again carcinoma cells.
		Silver nitrate + glycerol + PVP + CUR	1. Physicochemical characteristics 2. Antibacterial activity	1. Mean particle size of about 10–50 nm with improved encapsulation efficiency. 2. Slow and sustained release profile. 3. Significantly improved antibacterial activity against *E. coli*, *Salmonella* spp., *Staphylococcus aureus* and *Fusarium* spp. in comparison to penicillin and amoxicillin.	[32]	Curcumin-conjugated silver nanoparticles can significantly improve antioxidant and antibacterial efficacies of curcumin.

Declaration of interest

The authors report no declaration of interest in the present work.

Acknowledgement

The authors would like to acknowledge Universiti Teknologi MARA for providing LESTARI grant (600-IRMI/DANA 5/3/LESTARI (0007/2016)) and support in writing the present review article.

References

[1] W. Aadinath, A. Bhushani, C. Anandharamakrishnan, Synergistic radical scavenging potency of curcumin-in-β-cyclodextrin-in-nanomagnetoliposomes, Mater. Sci. Eng. C 64 (1) (2016) 293–302.
[2] B.B. Aggarwal, B. Sung, Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets, Trends Pharmacol. Sci. 30 (2) (2009) 85–94.
[3] B.B. Aggarwal, K.B. Harikumar, Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases, Int. J. Biochem. Cell Biol. 41 (2009) 40–59.
[4] M.Z. Ahmad, S.A. Alkahtani, S. Akhter, F.J. Ahmad, J. Ahmad, M.S. Akhtar, N. Mohsin, B.A. Abdel-Wahab, Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: current state-of-the-art, J. Drug Target. (2015) 1–21.
[6] Aimee E. Krausz, Brandon L. Adler, Vitor Cabral, Mahantesh Navati, Jessica Doerner, Rabab A. Charafeddine, Dinesh Chandra, Hongying Liang, Leslie Gunther, Alicea Clendaniel, Stacey Harper, Joel M. Friedman, Joshua D. Nosanchuk, Adam J. Friedman, Curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent, Nanomed. Nanotechnol. Biol. Med. 11 (1) (2015) 195–206.
[7] T. Ak, I. Gulcin, Antioxidant and radical scavenging properties of curcumin, Chem. Biol. Interact. 174 (2008) 27–37.
[9] Amirali Popat, Surajit Karmakar, Siddharth Jambhrunkar, Chun Xu, Yu. Chengzhong, Curcumin-cyclodextrin encapsulated chitosan nanoconjugates with enhanced solubility and cell cytotoxicity, 117 (2014) 520–527.
[10] P. Anand, A.B. Kunnumakkara, R.A. Newman, B.B. Aggarwal, Bioavailability of curcumin: problems and promises, Mol. Pharm. 4 (2007) 807–818.
[11] N. Apetz, G. Munch, S. Govindaraghavan, E. Gyengesi, Natural compounds and plant extracts as therapeutics against chronic inflammation in Alzheimer's disease—a translational perspective, CNS Neurol. Disord. Drug Targets 13 (2014) 1175–1191.
[12] R. Arora, A. Kuhad, I.P. Kaur, K. Chopra, Curcumin loaded solid lipid nanoparticles ameliorate adjuvant-induced arthritis in rats, Eur. J. Pain 19 (2015) 940–952.
[13] C.E. Astete, C.M. Sabliov, Synthesis and characterization of PLGA nanoparticles, J. Biomater. Sci. Polym. Ed. 17 (2006) 247–289.
[14] P. Basnet, H. Hussain, I. Tho, N. Skalko-Basnet, Liposomal delivery system enhances anti-inflammatory properties of curcumin, J. Pharm. Sci. 101 (2012) 598–609.
[15] Richard Baxter, Kenneth Bramlett, Erol Onel, Stephen Daniels, Impact of local administration of liposome bupivacaine for postsurgical analgesia on wound healing: a review of data from ten prospective, controlled clinical studies, Clin. Ther. 35 (3) (2013) (312–320.e5).
[16] Ana Beloqui, Patrick B. Memvanga, Régis Coco, Sonia Reimondez-Troitiño, Mireille Alhouayek, Giulio G. Muccioli, María José Alonso, Noemi Csaba, María de la Fuente, Véronique Préat, et al., Colloids Surf. B: Biointerfaces 143 (2016) 27–335.

[17] S. Biswas, J.W. Hwang, P.A. Kirkham, I. Rahman, Pharmacological and dietary antioxidant therapies for chronic obstructive pulmonary disease, Curr. Med. Chem. 20 (2013) 1496–1530.
[18] M.K. Bhutani, M. Bishnoi, S.K. Kulkarni, Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes, Pharmacol. Biochem. Behav. 92 (2009) 39–43.
[19] S. Bisht, A. Maitra, Systemic delivery of curcumin: 21st century solutions for an ancient conundrum, Curr. Drug Discov. Technol. 6 (3) (2009) 192–199.
[20] O. Catanzano, V. D'Esposito, S. Acierno, M.R. Ambrosio, C. De Caro, C. Avagliano, P. Russo, R. Russo, A. Miro, F. Ungaro, A. Calignano, P. Formisano, F. Quaglia, Alginate–hyaluronan composite hydrogels accelerate wound healing process, Carbohydr. Polym. 131 (2015) 407–414.
[21] I. Castangia, A. Nácher, C. Caddeo, D. Valenti, A.M. Fadda, O. Díez-Sales, et al., Fabrication of quercetin and curcumin bionanovesicles for the prevention and rapid regeneration of full-thickness skin defects on mice, Acta Biomater. 10 (2014) 1292–1300.
[22] B. Chandran, A. Goel, A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis, Phytother. Res. 26 (2012) 1719–1725.
[23] S. Chuengsamarn, S. Rattanamongkolgul, B. Phonrat, R. Tungtrongchitr, S. Jirawatnotai, Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial, J. Nutr. Biochem. 25 (2014) 144–150.
[24] Chukwuma O. Agubata, Chiadikaobi Okereke, Ifeanyi T. Nzekwe, Remigius I. Onoja, Nicholas C. Obitte, Development and evaluation of wound healing hydrogels based on a quinolone, hydroxypropyl methylcellulose and biodegradable microfibers, Eur. J. Pharm. Sci. 89 (2016) 1–10.
[29] N. Dhillon, B.B. Aggarwal, R.A. Newman, R.A. Wolff, A.B. Kunnumakkara, J.L. Abbruzzese, C.S. Ng, V. Badmaev, R. Kurzrock, Phase II trial of curcumin in patients with advanced pancreatic cancer, Clin. Cancer Res. 14 (2008) 4491–4499.
[30] Y. Dong, W. Wang, 14 – In situ–formed bioactive hydrogels for delivery of stem cells and biomolecules for wound healing, Wound Healing Biomaterials Volume 2: Functional Biomaterials 2016, pp. 289–307.
[32] E. El-Khoury, M. Abiad, Z.G. Kassaify, D. Patra, Green synthesis of curcumin conjugated nanosilver for the applications in nucleic acid sensing and anti-bacterial activity, Colloids Surf. B Biointerfaces 1 (127) (2015) 274–280.
[33] W.M. El-Refaie, Y.S. Elnaggar, M.A. El-Massik, O.Y. Abdallah, Novel curcumin-loaded gel-core hyaluosomes with promising burn-wound healing potential: development, in-vitro appraisal and in-vivo studies, Int. J. Pharm. 486 (2015) 88–98.
[39] Helena Ferreira, Teresa Matamá, Raquel Silva, Carla Silva, Andreia C. Gomesc, Artur Cavaco-Paulo, Functionalization of gauzes with liposomes entrapping an anti-inflammatory drug: a strategy to improve wound healing, React. Funct. Polym. 73 (10) (2013) 1328–1334.
[40] S. Fujisawa, T. Atsumi, M. Ishihara, Y. Kadoma, Cytotoxicity, ROS-generation activity and radical-scavenging activity of curcumin and related compounds, Anticancer Res. 24 (2004) 563–569.
[41] Uri Galili, Kim Wigglesworth, Ussama M. Abdel-Motal, Accelerated healing of skin burns by anti-Gal/α-gal liposomes interaction, Burns 36 (2) (2010) 239–251.
[42] Pasquale Del Gaudio, Felicetta De Cicco, Rita P. Aquino, Patrizia Picerno, Paola Russo, Fabrizio Dal Piaz, Valentina Bizzarro, Raffaella Belvedere, Luca Parente, Antonello Petrella, Evaluation of in situ injectable hydrogels as controlled release device for ANXA1 derived peptide in wound healing, Carbohydr. Polym. 115 (2015) 629–635.
[43] N. Ghalandarlaki, A.M. Alizadeh, S. Shkani-Esfahani, Nanotechnology-applied curcumin for different diseases therapy, Biomed. Res. Int. 2014 (2014) 394264.
[44] Meei Chyn Goh, Youngmin Hwang, Giyoong Tae, Epidermal growth factor loaded heparin-based hydrogel sheet for skin wound healing, Carbohydr. Polym. 147 (2016) 251–260.
[46] C. Gonga, Q. Wu, Y. Wang, D. Zhang, F. Luo, X. Zhao, Y. Wei, Z. Qian, A biodegradable hydrogel system containing curcumin encapsulated in micelles for cutaneous wound healing, Biomaterials 34 (27) (2013) 6377–6387.
[47] D. Gopinath, M.R. Ahmed, K. Gomathi, K. Chitra, P.K. Sehgal, R. Jayakumar, Dermal wound healing processes with curcumin incorporated collagen films, Biomaterials 25 (2004) 1911–1917.
[49] M. Gou, K. Men, H. Shi, M. Xiang, J. Zhang, J. Song, J. Long, Y. Wan, F. Luo, X. Zhao, Z. Qian, Curcumin-loaded biodegradable polymeric micelles for colon cancer therapy in vitro and in vivo, Nano 3 (4) (2011) 1558–1567.
[52] S.T. Hasan, J.M. Zingg, P. Kwan, T. Noble, D. Smith, M. Meydani, Curcumin modulation of high fat diet-induced atherosclerosis and steatohepatosis in LDL receptor deficient mice, Atherosclerosis 232 (2014) 40–51.
[54] Z. Hussain, H. Katas, M.C. Amin, E. Kumulosasi, S. Sahudin, Antidermatitic perspective of hydrocortisone as chitosan nanocarriers: an ex vivo and in vivo assessment using an NC/Nga mouse model, J. Pharm. Sci. 102 (3) (2013) 1063–1075.
[55] Z. Hussain, H. Katas, M.C. Mohd Amin, E. Kumolosasi, F. Buang, S. Sahudin, Self-assembled polymeric nanoparticles for percutaneous co-delivery of hydrocortisone/hydroxytyrosol: an ex vivo and in vivo study using an NC/Nga mouse model, Int. J. Pharm. 444 (2013) 109–119.
[56] Z. Hussain, H. Katas, M.C. Mohd Amin, E. Kumolosasi, Efficient immuno-modulation of TH1/TH2 biomarkers in 2,4-dinitrofluorobenzene-induced atopic dermatitis: nanocarrier-mediated transcutaneous co-delivery of anti-inflammatory and antioxidant drugs, PLoS One 9 (11) (2014) e113–e143.
[57] Z. Hussain, H. Katas, M.C. Mohd Amin, E. Kumolosasi, S. Sahudin, Downregulation of immunological mediators in 2,4-dinitrofluorobenzene-induced atopic dermatitis-like skin lesions by hydrocortisone-loaded chitosan nanoparticles, Int. J. Nanomedicine 9 (2014) 5143–5156.
[58] Z. Hussain, H.E. Thu, S.-F. Ng, S. Khan, H. Katas, Nanoencapsulation, an efficient and promising approach to maximize wound healing efficacy of curcumin: a review of new trends and state-of-the-art, Colloids Surf. B: Biointerfaces 150 (2017) 223–241.
[59] C.R. Ireson, D.J. Jones, S. Orr, M.W. Coughtrie, D.J. Boocock, M.L. Williams, P.B. Farmer, W.P. Steward, A.J. Gescher, Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine, Cancer Epidemiol. Biomark. Prev. 11 (2002) 105–111.
[61] G.C. Jagetia, B.B. Aggarwal, "Spicing up" of the immune system by curcumin, J. Clin. Immunol. 27 (2007) 19–35.
[62] G. Jagetia, G. Rajanikant, Acceleration of wound repair by curcumin in the excision wound of mice exposed to different doses of fractionated gamma radiation, Int. Wound J. 9 (2012) 76–92.
[63] H. Jiang, Z. Wang, Y. Wang, K. Xie, Q. Zhang, Q. Luan, W. Chen, D. Liu, Antidepressant-like effects of curcumin in chronic mild stress of rats: involvement of its anti-inflammatory action, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 47 (2013) 33–39.
[64] Jinglei Li, InCheon Hwang, Xiguang Chen, Hyun Jin Park, Effects of chitosan coating on curcumin loaded nanoemulsion: study on stability and in vitro digestibility, Food Hydrocoll. 60 (2016) 138–147.
[65] B. Joe, M. Vijaykumar, B.R. Lokesh, Biological properties of curcumin-cellular and molecular mechanisms of action, Crit. Rev. Food Sci. Nutr. 44 (2) (2004) 97–111.
[66] V. Kant, A. Gopal, N.N. Pathak, P. Kumar, S.K. Tandan, D. Kumar, Antioxidant and anti-inflammatory potential of curcumin accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats, Int. Immunopharmacol. 20 (2) (2014) 322–330.
[67] N.A. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennernas, A.S. Hussain, H.E. Junginger, S.A. Stavchansky, K.K. Midha, V.P. Shah, G.L. Amidon, Molecular properties of WHO essential drugs and provisional biopharmaceutical classification, Mol. Pharm. 1 (2004) 85–96.
[68] N. Kasoju, U. Bora, Fabrication and characterization of curcumin-releasing silk fibroin scaffold, J. Biomed. Mater. Res. Part B 100B (2012) 1854–1866 2012.
[69] N. Kerdsakundee, S. Mahattanadul, R. Wiwattanapatapee, Development and evaluation of gastroretentive raft forming systems incorporating curcumin-Eudragit(R) EPO solid dispersions for gastric ulcer treatment, Eur. J. Pharm. Biopharm. (2015).
[70] D.S. Kim, J.Y. Kim, Y. Han, Curcuminoids in neurodegenerative diseases, Recent Pat. CNS Drug Discov. 7 (2012) 184–204.
[71] M.H. Kim, S.H. Kim, W.M. Yang, Mechanisms of action of phytochemicals from medicinal herbs in the treatment of Alzheimer's disease, Planta Med. 80 (2014) 1249–1258.
[72] Dong Wuk Kim, Kyung Soo Kim, Youn Gee Seo, Beom-Jin Lee, Young Joon Park, Yu SeokYoun, Jong Oh. Kim, Chul Soon Yong, Sung Giu Jin, Han-Gon Choi, Novel sodium fusidate-loaded film-forming hydrogel with easy application and excellent wound healing, Int. J. Pharm. 495 (1) (2015) 67–74.
[73] Kiran Kumar Chereddy, Régis Coco, Patrick B. Memvanga, Bernard Ucakar, Anne des Rieux, Gaëlle Vandermeulen, Véronique Préat, Combined effect of PLGA and curcumin on wound healing activity, J. Control. Release 171 (2) (2013) 208–215.
[74] M. Kulac, C. Aktas, F. Tulubas, R. Uygur, M. Kanter, M. Erboga, M. Ceber, B. Topcu, O.A. Ozen, The effects of topical treatment with curcumin on burn wound healing in rats, J. Mol. Histol. 44 (1) (2013) 83–90.
[75] B. Kloesch, T. Becker, E. Dietersdorfer, H. Kiener, G. Steiner, Anti-inflammatory and apoptotic effects of the polyphenol curcumin on human fibroblast-like synoviocytes, Int. Immunopharmacol. 15 (2) (2013) 400–405.
[76] A. Kochi, H.J. Lee, S.M. Vithanarachchi, V. Padmini, M.J. Allen, M.H. Lim, Inhibitory activity of curcumin derivatives towards metal-free and metal-induced amyloid-beta aggregation, Curr. Alzheimer Res. 12 (2015) 415–423.
[78] Nelisa Türkoğlu Laçin, Development of biodegradable antibacterial cellulose based hydrogel membranes for wound healing, Int. J. Biol. Macromol. 67 (2014) 22–27.
[79] C.D. Lao, M.T. Ruffin, D. Normolle, D.D. Heath, S.I. Murray, J.M. Bailey, M.E. Boggs, J. Crowell, C.L. Rock, D.E. Brenner, Dose escalation of a curcuminoid formulation, BMC Complement. Altern. Med. 6 (2006) 10.
[80] W.H. Lee, C.Y. Loo, M. Bebawy, F. Luk, R.S. Mason, R. Rohanizadeh, Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century, Curr. Neuropharmacol. 11 (2013) 338–378.
[82] G. Liang, S. Yang, H. Zhou, L. Shao, K. Huang, J. Xiao, Z. Huang, X. Li, Synthesis, crystal structure and anti-inflammatory properties of curcumin analogues, Eur. J. Med. Chem. 44 (2) (2009) 915–919.
[83] X.Y. Li, X.Y. Kong, S. Shi, Y.C. Gu, L. Yang, G. Guo, F. Luo, X. Zhao, Y.Q. Wei, Z.Y. Qian, Biodegradable MPEG-g-Chitosan and methoxy poly (ethylene glycol)-b-poly ([epsilon]-caprolactone) composite films. Part 1: preparation and characterization, Carbohydr. Polym. 79 (2010) 429–436.
[85] Xingyi Li, Shuo Chen, Binjun Zhang, Mei Li, Kai Diao, Zhaoliang Zhang, Yu Xu Jie Li, Xianhuo Wang, Hao Chen, In situ injectable nanocomposite hydrogel composed of curcumin, N,O carboxymethyl chitosan and oxidized alginate for wound healing application, Int. J. Pharm. 437, 1–2 (1) (2012) 110–119.
[86] Yujia Liu, Yanxue Cai, Xueying Jiang, Jinping Wu, Xueyi Le, Molecular interactions, characterization and antimicrobial activity of curcumin–chitosan blend films, Food Hydrocoll. 52 (2016) 564–572.
[87] H. Lv, J. Liu, L. Wang, H. Zhang, S. Yu, Z. Li, F. Jiang, Y. Niu, J. Yuan, X. Cui, W. Wang, Ameliorating effects of combined curcumin and desferrioxamine on 6-OHDA-induced rat mode of Parkinson's disease, Cell Biochem. Biophys. 70 (2014) 1433–1438.
[88] Z. Ma, A. Haddadi, O. Molavi, A. Lavasanifar, R. Lai, J. Samuel, Micelles of poly(ethylene oxide)-b-poly(epsilon-caprolactone) as vehicles for the solubilization, stabilization, and controlled delivery of curcumin, J. Biomed. Mater. Res. A 86 (2008) 300–310.

[89] Kashif Mahmood, Khalid Mahmood Zia, Mohammad Zuber, Mahwish Salman, Muhammad Naveed Anjum, Recent developments in curcumin and curcumin based polymeric materials for biomedical applications: a review, Int. J. Biol. Macromol. 81 (2015) 877–890.
[90] Kashif Mahmood, Iqra Noreen, Muhammad Riaz, Mohammad Zuber, Mahwish Salman, Saima Rehman, Khalid Mahmood Zia, Synthesis and characterization of novel curcumin based polyurethanes varying diisocyanates structure, J. Polym. Res. 23 (2016) 233.
[91] M.L. Manca, I. Castangia, M. Zaru, A. Nácher, D. Valenti, X. Fernàndez-Busquets, A.M. Fadda, M. Manconi, Development of curcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring, Biomaterials 71 (2015) 100–109.
[93] Martha L. Vázquez-González, Ana C. Calpena, Òscar Domènech, M. Teresa Montero, Jordi H. Borrell, Enhanced topical delivery of hyaluronic acid encapsulated in liposomes: a surface-dependent phenomenon, Colloids Surf. B: Biointerfaces 134 (1) (2015) 31–39.
[95] Marziyeh Ranjbar Mohammadi, Shahram Rabbani, S. HajirBahrami, M.T. Joghataei, F. Moayer, Antibacterial performance and in vivo diabetic wound healing of curcumin loaded gum tragacanth/poly(ε-caprolactone) electrospunnanofibers, Mater. Sci. Eng. C 69 (2016) 1183–1191.
[98] S.J. Moghaddam, P. Barta, S.G. Mirabolfathinejad, Z. Ammar-Aouchiche, N.T. Garza, T.T. Vo, R.A. Newman, B.B. Aggarwal, C.M. Evans, M.J. Tuvim, R. Lotan, B.F. Dickey, Curcumin inhibits COPD-like airway inflammation and lung cancer progression in mice, Carcinogenesis 30 (2009) 1949–1956.
[99] Chandana Mohanty, Manasi Das, Sanjeeb K. Sahoo, Sustained wound healing activity of curcumin loaded oleic acid based polymeric bandage in a rat model, Mol. Pharm. 9 (10) (2012) 2801–2811.
[102] S. Mourtas, A.N. Lazar, E. Markoutsa, C. Duyckaerts, S.G. Antimisiaris, Multifunctional nanoliposomes with curcumin-lipid derivative and brain targeting functionality with potential applications for Alzheimer disease, Eur. J. Med. Chem. 80 (2014) 175–183.
[103] S.H. Mun, D.K. Joung, Y.S. Kim, O.H. Kang, S.B. Kim, Y.S. Seo, Y.C. Kim, D.S. Lee, D.W. Shin, K.T. Kweon, D.Y. Kwon, Synergistic antibacterial effect of curcumin against methicillin-resistant *Staphylococcus aureus*, Phytomedicine 20 (8–9) (2013) 714–718.
[104] Mythili Tummalapalli, Bernard Verrier MorganeBerthet, B.L. Deopura, M.S. Alam, Bhuvanesh Gupta, Composite wound dressings of pectin and gelatin with *Aloe vera* and curcumin as bioactive agents, Int. J. Biol. Macromol. 82 (2016) 104–113.
[105] S.F. Nabavi, R. Thiagarajan, L. Rastrelli, M. Daglia, E. Sobarzo-Sanchez, H. Alinezhad, S.M. Nabavi, Curcumin: a natural product for diabetes and its complications, Curr. Top. Med. Chem. (2015).
[106] Maria Onaira Gonçalves Ferreira, Layara Lorrana Ribeiro Leite, IdglanSá de Lima, Humberto Medeiros Barreto, Lívio César Cunha Nunes, Alessandra Braga Ribeiro, Josy Anteveli Osajima, Edson Cavalcanti da Silva Filho, Chitosan Hydrogel in combination with Nerolidol for healing wounds, Carbohydr. Polym. 152 (2016) 409–418.
[107] M.H. Pan, T.M. Huang, J.K. Lin, Biotransformation of curcumin through reduction and glucuronidation in mice, Drug Metab. Dispos. 27 (1999) 486–494.
[108] L. Pari, D. Tewas, J. Eckel, Role of curcumin in health and disease, Arch. Physiol. Biochem. 114 (2008) 127–149.
[109] Ping Chen, Hui Zhang, Shucang Cheng, Guangxi Zhai, Chengwu Shen, Development of curcumin loaded nanostructured lipid carrier based thermosensitive in situ gel for dermal delivery, Colloids Surf. A Physicochem. Eng. Asp. 506 (2016) 356–362.
[111] S. Rivera-Mancia, M.C. Lozada-Garcia, J. Pedraza-Chaverri, Experimental evidence for curcumin and its analogs for management of diabetes mellitus and its associated complications, Eur. J. Pharmacol. 756 (2015) 30–37.
[114] A. Sahebkar, Dual effect of curcumin in preventing atherosclerosis: the potential role of pro-oxidant-antioxidant mechanisms, Nat. Prod. Res. 29 (2015) 491–492.
[115] P.R. Sarika, Nirmala Rachel James, Polyelectrolyte complex nanoparticles from cationised gelatin and sodium alginate for curcumin delivery, Carbohydr. Polym. 148 (2016) 354–361.
[116] K. Schmitz, J. Barthelmes, L. Stolz, S. Beyer, O. Diehl, I. Tegeder, "Disease modifying nutricals" for multiple sclerosis, Pharmacol. Ther. 148 (2015) 85–113.
[121] Mei Shao, Zahid Hussain, Hnin Ei Thu, Shahzeb Khan, Haliza Katas, Tarek A. Ahmed, Minaketan Tripathy, Jing Leng, Hua-Li Qin, Syed Nasir Abbas Bukhari, Drug nanocarrier, the future of atopic diseases: advanced drug delivery systems and smart management of disease, Colloids Surf. B: Biointerfaces 1 (147) (2016) 475–491.
[125] S. Singh, From exotic spice to modern drug? Cell 130 (2007) 765–768.
[126] R.K. Singh, D. Rai, D. Yadav, A. Bhargava, J. Balzarini, E. De Clercq, Synthesis, antibacterial and antiviral properties of curcumin bioconjugates bearing dipeptide, fatty acids and folic acid, Eur. J. Med. Chem. 45 (2010) 1078–1086.
[128] C.R.A. Souza, S.F. Osme, M.B.A. Gloria, Stability of curcuminoid pigments in model systems, J. Food Process. Preserv. 21 (1997) 353–363.
[130] Suelen P. Facchi, Débora B. Scariot, Pedro V.A. Bueno, Paulo R. Souza, Luana C. Figueiredo, Heveline D.M. Follmann, Cátia S. Nunes, Johny P. Monteiro, Elton G. Bonafé, Celso V. Nakamura, Edvani C. Muniz, Alessandro F. Martins, Preparation and cytotoxicity of N-modified chitosan nanoparticles applied in curcumin delivery, Int. J. Biol. Macromol. 87 (2016) 237–245.
[131] M. Sun, X. Su, B. Ding, X. He, X. Liu, A. Yu, H. Lou, G. Zhai, Advances in nanotechnology-based delivery systems for curcumin, Nanomedicine (London) 7 (2012) 1085–1100.
[132] M. Suzuki, T. Betsuyaku, Y. Ito, K. Nagai, N. Odajima, C. Moriyama, Y. Nasuhara, M. Nishimura, Curcumin attenuates elastase- and cigarette smoke-induced pulmonary emphysema in mice, Am. J. Physiol. Lung Cell. Mol. Physiol. 296 (2009) L614–L623.
[134] R.L. Thangapazham, S. Sharad, R.K. Maheshwari, Skin regenerative potentials of curcumin, Biofactors 39 (1) (2013) 141–149.
[136] H.H. Tonnesen, M. Masson, T. Loftsson, Studies of curcumin and curcuminoids. XXVII. Cyclodextrincomplexation: solubility, chemical and photochemical stability, Int. J. Pharm. 244 (2002) 127–135.
[137] V. Torchilin, Multifunctional nanocarriers, Adv. Drug Deliv. Rev. 58 (14) (2006) 1532–1555.
[138] Y.M. Tsai, C.F. Chien, L.C. Lin, T.H. Tsai, Curcumin and its nano-formulation: the kinetics of tissue distribution and blood–brain barrier penetration, Int. J. Pharm. 416 (2011) 331–338.
[140] Veera Venkata Satyanarayana Reddy Karri, Gowthamarajan Kuppusamy, Siddhartha Venkata Talluri, Sai Sandeep Mannemala, Radhakrishna Kollipara, Ashish Devidas Wadhwani, Shashank Mulukutla, Kalidhindi Rama Satyanarayana Raju, Rajkumar Malayandi, Curcumin loaded chitosan nanoparticles impregnated into collagen-alginate scaffolds for diabetic wound healing, Int. J. Biol. Macromol. 93 (2016) 1519–1529, http://dx.doi.org/10.1016/j.ijbiomac.2016.05.038.
[141] Vinay Kant, Dhirendra Kumar AnuGopal, Nitya N. Pathak, Mahendra Ram, Babu L. Jangir, Surendra K. Tandan, Dinesh Kumar, Curcumin-induced angiogenesis hastens wound healing in diabetic rats, J. Surg. Res. 193 (2015) 978–988.
[142] Karola Vorauer-Uhl, Eckhard Fürnschlief, Andreas Wagner, Boris Ferko, Hermann Katinger, Topically applied liposome encapsulated superoxide dismutase reduces postburn wound size and edema formation, Eur. J. Pharm. Sci. 14 (2001) 63–67.
[143] B. Wahlstrom, G. Blennow, A study on the fate of curcumin in the rat, Acta Pharmacol. Toxicol. (Copenh) 43 (1978) 86–92.
[144] S. Wang, M. Tan, Z. Zhong, M. Chen, Y. Wang, Nanotechnologies for Curcumin: an ancient puzzler meets modern solutions, J. Nanomater. 2011 (2011) 1–8.
[147] Qi Xiang, Jian Xiao, Hongbo Zhang, Zhang Xie, Meifei Lu, Hui Zhang, Su Zhijian, Wen Zhao, Cai Lin, Yadong Huang, Xiaokun Li, Preparation and characterisation of bFGF-encapsulated liposomes and evaluation of wound-healing activities in the rat, Burns 37 (2011) 886–895.
[148] Xingyi Li, Kaihui Nan, Lingli Li, Zhaoliang Zhang, Hao Chen, In vivo evaluation of curcumin nanoformulation loaded methoxypoly(ethylene glycol)-graft-chitosan composite film for wound healing application, Carbohydr. Polym. 88 (2012) 84–90.
[149] Xingyi Li, Shuo Chen, Binjun Zhang, Mei Li, Kai Diao, Zhaoliang Zhang, Yu Xu Jie Li, Xianhuo Wang, Hao Chen, In situ injectable nanocomposite hydrogel composed of curcumin, N,O carboxymethyl chitosan and oxidized alginate for wound healing application, Int. J. Pharm. 437 (2012) 110–119.
[150] S.K. Yadav, A.K. Sah, R.K. Jha, P. Sah, D.K. Shah, Turmeric (curcumin) remedies gastroprotective action, Pharmacogn. Rev. 7 (2013) 42–46.
[151] Y. Yang, X. Wu, Z. Wei, Y. Dou, D. Zhao, T. Wang, D. Bian, B. Tong, Y. Xia, Y. Xia, Y. Dai, Oral curcumin has anti-arthritic efficacy through somatostatin generation via cAMP/PKA and Ca(2+)/CaMKII signaling pathways in the small intestine, Pharmacol. Res. 95-96 (2015) 71–81.
[152] C. Yang, X. Su, A. Liu, L. Zhang, A. Yu, Y. Xi, G. Zhai, Advances in clinical study of curcumin, Curr. Pharm. Des. 19 (11) (2013) 1966–1973.
[153] Fatima Zia, Khalid Mahmood Zia, Mohammad Zuber, Saima Rehman, Shazia Tabasum, Salma Sultana, Synthesis and characterization of chitosan/curcumin blends based polyurethanes, Int. J. Biol. Macromol. 92 (2016) 1074–1081.
[154] M. Ranjbar-Mohammadi, S. Rabbani, S.H. Bahrami, M.T. Joghataei, F. Moayer, Antibacterial performance and in vivo diabetic wound healing of curcumin loaded gum tragacanth/poly((-caprolactone) electrospun nanofibers, Mat. Sci. Eng. C 69 (2016) 1183–1191.
[155] B. Meng, J. Li, H. Cao, Antioxidant and anti-inflammatory activities of curcumin on diabetes mellitus and its complications, Curr. Pharm. Des. 19 (11) (2013) 2101–2113.