ANNUAL REVIEWS

Annual Review of Food Science and Technology

Curcumin: Recent Advances in the Development of Strategies to Improve Oral Bioavailability

Katherine Z. Sanidad,[1,2,*] Elvira Sukamtoh,[1,*] Hang Xiao,[1,2] David Julian McClements,[1] and Guodong Zhang[1,2]

[1]Department of Food Science, University of Massachusetts, Amherst, Massachusetts 01003, USA; email: mcclements@foodsci.umass.edu, guodongzhang@umass.edu

[2]Molecular and Cellular Biology Graduate Program, University of Massachusetts, Amherst, Massachusetts 01003, USA

Annu. Rev. Food Sci. Technol. 2019. 10:597–617

First published as a Review in Advance on January 11, 2019

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-032818-121738

*These authors contributed equally to this review.

Keywords

curcumin, oral bioavailability, delivery systems, excipient systems, colloidal dispersions, emulsions

Abstract

Substantial human and preclinical studies have shown that curcumin, a dietary compound from turmeric, has a variety of health-promoting effects including but not limited to antioxidant, antimicrobial, anti-inflammatory, and anticancer actions. However, curcumin has poor bioavailability, and high doses of curcumin are usually needed to exert its health-promoting effects in vivo, limiting its applications for disease prevention. Here, we discuss the health-promoting effects of curcumin, factors limiting its bioavailability, and strategies to improve its oral bioavailability.

INTRODUCTION

Curcumin is a yellow pigment derived from turmeric, a rhizome from the herb *Curcuma longa*. Turmeric is commonly used as the main ingredient in curry spices and provides their distinctive colors and flavors. Traditionally, turmeric has been used for centuries as an ingredient for medicinal spice mixtures and as part of Ayurveda or Chinese medicine to promote health (Ammon & Wahl 1991, Shishodia et al. 2005). Over the past few decades, substantial studies have shown that curcumin has a variety of health-promoting effects, including but not limited to antioxidant, antimicrobial, anti-inflammatory, and anticancer actions (Aggarwal et al. 2003, Menon & Sudheer 2007). Currently, many human studies evaluate the health-promoting effects of curcumin. However, curcumin has poor bioavailability (Prasad et al. 2014); therefore, high doses of curcumin are typically needed to exert its health-promoting effects in vivo (Vareed et al. 2008). Long-term intake of high-dose curcumin could cause adverse effects and reduce compliance, limiting the application of curcumin for disease prevention (Aggarwal & Sung 2009, Vareed et al. 2008). Here, we discuss the health-promoting effects of curcumin, factors limiting its bioavailability, and strategies to improve its oral bioavailability.

HEALTH BENEFITS AND BIOLOGICAL ACTIVITIES OF CURCUMIN

Curcumin is among the most promising dietary compounds for reducing the risks of a variety of diseases because of its anti-inflammatory and antioxidant properties, which have been characterized in various in vitro cellular, molecular, and in vivo animal studies. Because of the promising efficacy and low toxicity of curcumin, many clinical trials have since been conducted to evaluate the therapeutic applications of curcumin on diseases relating to oxidative stress and chronic inflammation, including but not limited to arthritis, cancer, and metabolic syndrome (MetS). The following section describes the mechanisms behind curcumin's properties, summarizes some of these human clinical trials, and further describes recent human trials that address concerns about improvements for the bioavailability of curcumin.

Effects of Curcumin on Inflammation

As has been widely reported, one of the most beneficial characteristics of curcumin is its anti-inflammatory property. Cellular and molecular studies have shown that curcumin is able to decrease essential pathways regulating inflammation, including nuclear factor kappa B (NF-κB), cyclooxygenase (COX), and lipoxygenase pathways, which leads to a decrease in proinflammatory cytokine levels and a decrease in prostaglandin production (Chan 1995, Huang et al. 1991, Killian et al. 2012, Midura-Kiela et al. 2012, Singh & Aggarwal 1995). This decrease of cytokines and prostaglandins also affects the subsequent signal transduction pathways in which they are involved (Aggarwal et al. 2006, Li et al. 2004, Midura-Kiela et al. 2012). Also, curcumin has been used to alleviate inflammation in animal models of colon inflammation (Sugimoto et al. 2002, Venkataranganna et al. 2007). Because of these studies, curcumin is being considered as a therapeutic for many diseases related to chronic inflammation. In fact, some consider curcumin a replacement for nonsteroidal anti-inflammatory drugs (NSAIDs) because it shares similar mechanisms to those of NSAIDS, is a naturally occurring compound, and exhibits fewer long-term adverse effects (Aggarwal & Harikumar 2009).

Chuengsamarn et al. (2014) studied the effects of curcumin treatment on atherosclerosis, an inflammation-associated cardiovascular condition, in type 2 diabetes patients. A curcumin dose of

1.5 g/day was given to 240 patients for 9 months. At the end of the treatment period, there was a decrease in pulse wave velocity (PWV), an accepted marker of atherosclerosis, in curcumin-treated patients. In addition to decreased PWV, curcumin-treated patients also had decreased atherosclerosis risk factors, including decreased insulin resistance, triglycerides, uric acid, and visceral and total body fat.

Researchers have also considered curcumin for the treatment of ulcerative colitis (UC), an inflammatory bowel disease that causes ulcers in the digestive tract due to long-lasting chronic inflammation. To determine whether adjuvant curcumin treatment can induce remission in patients with UC, Lang et al. (2015) gave 50 patients with active mild-to-moderate UC either curcumin capsules (Cur-Cure, containing 95% pure curcumin) at a dose of 3 g/day or a placebo for one month. Their findings showed that 14 out of 26 (53.8%) patients were able to achieve clinical remission, as defined by the Simple Clinical Colitis Activity Index, whereas 0 patients treated with placebo had induction of remission. Furthermore, another trial showed that not only could adjuvant curcumin treatment induce clinical remission, but it could also prevent the relapse of UC (Hanai et al. 2006). Ninety patients with quiescent UC were given either 2 g/day of curcumin or placebo for 6 months. At the end of the trial, only 2 (4.65%) patients in the curcumin treatment group relapsed compared with 8 (20.51%) patients in the placebo treatment group. Also, curcumin-treated patients showed improvement in the Clinical Activity Index and Endoscopic Index compared with placebo-treated patients.

Effects of Curcumin on Oxidative Stress

Curcumin can protect the body from reactive oxygen species and other free radicals that can potentially damage DNA, thus leading to mutations that increase the risk of tumor formation. This ability is due to its antioxidative properties, including metal chelating, radical scavenging, and hydrogen peroxide scavenging (Ak & Gülçin 2008, Manikandan et al. 2004, Motterlini et al. 2000). Because of its antioxidative properties, human clinical trials were used to evaluate further the effect of curcumin on conditions under which oxidative stress is a concern.

Radiotherapy is an important method for the treatment of cancer, but it can produce active oxygen radicals that may increase oxidative stress in the body. Therefore, Hejazi et al. (2016) evaluated the effect of curcumin supplementation on the oxidative status of patients with prostate cancer who would undergo radiotherapy. Forty patients were given either curcumin with a dose of 3 g/day or placebo, starting 1 week before the initiation of radiotherapy and continuing until 3 months after their radiotherapy ended. Curcumin-treated patients had an increase in plasma total antioxidant capacity and a decrease in superoxide dismutase (SOD) activity—both effects suggesting a decrease in oxidative stress—after radiotherapy compared with the placebo-treated patients.

Oxidative stress also plays a role in MetS, which can increase the risk of cardiovascular disease and diabetes (Roberts & Sindhu 2009). Oxidative stress has also been implicated in osteoarthritis (Lepetsos & Papavassiliou 2016). Because of this, Panahi et al. (2015, 2016) evaluated the effects of curcumin on oxidative stress and inflammation in subjects with MetS and knee osteoarthritis. One-hundred subjects with MetS were given either 1 g/day of curcumin, with the addition of 10 mg/day piperine to boost bioavailability (Shoba et al. 1998), or placebo, whereas the subjects with osteoarthritis were given 1.5 g/day curcumin with 15 mg/day of piperine or placebo. In both trials, subjects in the curcumin group had improved serum SOD activities and a decrease in malondialdehyde concentration, both of which suggest that there was a decrease in oxidative stress compared with subjects in the placebo group. In addition, C-reactive protein concentrations in plasma of curcumin-treated subjects were also decreased, suggesting a decrease in inflammation.

Effects of Curcumin on Cancer

Curcumin displays potent anticancer effects through several mechanisms, including the above-mentioned anti-inflammatory mechanisms as well as through (*a*) inhibition of proliferation via cell cycle arrest and apoptosis, cell migration, and invasion of human cancer cell lines (Aggarwal et al. 2006; Anto et al. 2002; Cheng et al. 2007; Li et al. 2004, 2005; Mudduluru et al. 2011; Watson et al. 2008); (*b*) suppression of angiogenesis and lymphangiogenesis, both of which play a role in tumor growth and metastasis (Arbiser et al. 1998, Ejaz et al. 2009, Li et al. 2005, Wang et al. 2015); and (*c*) increases in the number of tumor suppressor proteins (Chen et al. 2008). Curcumin has demonstrated its anticancer effects in several animal models of certain cancers, including pancreatic, colon, and breast cancer (Bachmeier et al. 2007, Huang et al. 1994, Rao et al. 1995).

Because of the therapeutic potential of curcumin for the treatment of cancer, researchers further evaluated curcumin in clinical trials. Cheng et al. (2001) conducted the first clinical study to test and determine a biologically active dose of curcumin for cancer treatment. Twenty-five patients that had the following varying cancers and conditions were chosen: urinary bladder cancer, uterine cervical intraepithelial neoplasm, intestinal metaplasia in the stomach, oral leukoplakia, and arsenic-related Bowen's disease of the skin. These patients were given a starting oral curcumin dose of 0.5 g/day, which was steadily doubled to 12 g, depending on lack of toxicity. Seven of the patients saw a histologic improvement of precancerous lesions and the dose of 8 g/day was shown to be the most effective and promising.

Using the oral dose of 8 g/day of curcumin, Dhillon et al. (2008) proceeded with a Phase II trial to study the effect of curcumin in patients with pancreatic cancer. Among the 21 patients with adenocarcinoma of the pancreas that were given curcumin, only 2 showed a decrease in tumor pathology. Still, most patients had decreased NF-κB, COX2, and pSTAT3 activation—all of which are important in the body's inflammatory response—in their peripheral blood mononuclear cells.

FACTORS LIMITING THE BIOAVAILABILITY OF CURCUMIN

Substantial studies have shown that curcumin has poor bioavailability and a weak pharmacokinetics profile: Notably, a previous study showed that after a single oral dose of 10 or 12 g of curcumin, the free form of curcumin was barely detected in human plasma (Vareed et al. 2008). As a result, high doses of curcumin are usually needed to exert its health-promoting effects in vivo (Vareed et al. 2008). In their review, Prasad et al. (2014) discuss in detail the bioavailability of curcumin. A recent Phase IIα clinical trial showed that oral administration of 4 g/day curcumin for 30 days caused a 40% reduction in aberrant crypt foci, a biomarker for colorectal neoplasia, whereas at a lower dose (1 g/day) curcumin had no effect (Carroll et al. 2011). As discussed above, many human studies support that high doses of curcumin (several grams of curcumin per day) are needed to exert health-promoting effects. Long-term intake of high-dose curcumin could cause adverse effects and reduce compliance, limiting the application of curcumin for disease prevention (Vareed et al. 2008). The low bioavailability of curcumin is caused by many mechanisms, including low solubility in aqueous gastrointestinal fluids, low chemical stability at physiological pH, low absorption in the gastrointestinal tract (GIT), and rapid metabolism in the GIT and liver. Below, we discuss the factors limiting the bioavailability of curcumin.

Bioaccessibility

For nutraceuticals, in this case curcumin, to exert biological activities, they need to be bioaccessible to be absorbed into the GIT epithelium and then transported into the systemic circulation. For

that, solubilization of the compounds in the aqueous gastrointestinal fluids is crucial. Curcumin is a highly hydrophobic compound, and therefore it has poor solubility in the aqueous fluids leading to poor bioaccessibility (Tønnesen & Karlsen 1985).

In addition, recent research showed that curcumin has poor stability in aqueous solution and that it rapidly degrades in aqueous solution in a pH-dependent manner: At a pH of 3–6.5, the half-life of curcumin is ~100–200 minutes; at a pH of 7.2–8.0, the half-life of curcumin dramatically reduces to as short as 1–9 minutes. With the presence of proteins, chemical degradation of curcumin is slower but still processes at a significant rate. Within 1 h, ~20% of curcumin degrades in human blood and in a cell culture medium with 10% fetal bovine serum (Gordon et al. 2015, Griesser et al. 2011, Nimiya et al. 2016, Schneider et al. 2015, Wang et al. 1997). Regarding the underlying mechanism, recent studies showed that the chemical degradation of curcumin at physiological pH is mediated by a radical-dependent oxidation process (Gordon et al. 2015, Griesser et al. 2011, Nimiya et al. 2016, Schneider et al. 2015). It is proposed that the first step of curcumin degradation is hydrogen abstraction from the phenolic group to form a curcumin phenolic radical, which then migrates to the conjugated heptadienedione chain and reacts with oxygen to generate various degradation products. The radical could be then transferred to another curcumin molecule, leading to oxidation of another curcumin molecule and resulting in a chain reaction causing rapid curcumin degradation (Schneider et al. 2015). Bicyclopentadione, an autoxidation product of curcumin, has been shown to be the most abundant degradation product of curcumin at physiological pH (Gordon et al. 2015, Griesser et al. 2011, Schneider et al. 2015). Our recent study showed that coadministration of radical scavenging antioxidants suppressed autoxidation of curcumin at physiological pH and enhanced its chemical stability and biological activity (Nimiya et al. 2016), further supporting the idea that the chemical degradation of curcumin in aqueous solution is mainly mediated by a redox-dependent mechanism.

The chemical degradation of curcumin in aqueous solution leads to the formation of a series of compounds, including alkaline hydrolysis products, such as ferulic acid, vanillin, ferulaldehyde, and feruloyl methane, and autoxidation products such as bicyclopentadione (Gordon et al. 2015, Griesser et al. 2011, Schneider et al. 2015). Compared with curcumin, the biological activities of these compounds are generally less active or inactive (see Zhu et al. 2017). Therefore, it is feasible that the chemical degradation of curcumin in aqueous solution could contribute to poor bioavailability and reduced activity of curcumin, although it remains to be determined whether the chemical degradation of curcumin could indeed happen in vivo.

Coingestion of curcumin with lipids can help increase curcumin solubility and bioaccessibility through encapsulation of curcumin into mixed micelles formed from hydrolysis of the lipid in the GIT. This mixture not only helps protect curcumin from degradation but also increases its chance to be absorbed into the GIT epithelium lining. The length of the fatty acid chains and degree of saturation determines the solubility of nutraceuticals in the mixed micelles. In this case, medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) have been reported to be suitable vehicles for increasing the solubility and bioaccessibility of curcumin (Zou et al. 2015c, 2016a).

Absorption

One reason for the low bioavailability of curcumin is its poor absorption. The main absorption site of curcumin in the GIT is in the small intestine (Ravindranath & Chandrasekhara 1980). However, curcumin is a lipophilic phenolic compound, which makes it difficult to orally administer the curcumin to be absorbed by the small intestine epithelium cells (Prasad et al. 2014). Even if it were absorbed into the epithelium, its hydrophobic property would cause it to be flushed back into the lumen through the efflux system. A previous study showed that after a dosage of

10–400 mg [^{3}H]curcumin in animals, the primary route to eliminating curcumin was through feces, suggesting poor absorption of curcumin (Ravindranath & Chandrasekhara 1982). Piperine, an active compound derived from peppers, had been reported to be able to reduce efflux transport back to the lumen by modulating cell membrane dynamics and altering the lipid fluidity due to its apolar nature (Khajuria et al. 2002).

Tissue Distribution

After being absorbed and circulated, how curcumin is distributed throughout the body tissues is an important factor for its biological activities. However, few studies have been conducted to address this issue. Ravindranath & Chandrasekhara (1980) showed that only traces of free-formed curcumin were found in the liver and kidney of rats after oral administration of 400 mg of curcumin. Another study using tritium-labeled curcumin showed that after a dosage of 10–400 mg [^{3}H]curcumin, radioactivity was detectable in the blood, liver, and kidney of the treated animal (Ravindranath & Chandrasekhara 1982). More studies are needed to assess the tissue distribution of curcumin using different administration processes.

Metabolic Transformation

After oral intake, curcumin undergoes rapid metabolic reduction (Phase I metabolism) and conjugation (Phase II metabolism) in tissues such as those of the GIT and liver, which contributes to its poor systemic bioavailability. Curcumin could be metabolized by NADPH-reductase to generate a series of reduction products, including dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin (Lin et al. 2000, Pan et al. 1999). Notably, Hassaninasab et al. (2011) showed that human gut bacteria *E. coli* could also catalyze the reductive metabolism of curcumin through the unique bacterial enzyme CurA (NADPH-dependent curcumin or dihydrocurcumin reductase). The metabolism of curcumin by CurA leads to the formation of dihydrocurcumin and tetrahydrocurcumin, and the lack of further reduction products suggests that the CurA enzyme can catalyze only the reduction of the C=C bond, not the C=O bond.

Curcumin has two phenolic groups, making it susceptible for metabolization by Phase II detoxification enzymes such as glucuronosyltransferase and sulfotransferase, leading to the formation of glucuronide and sulfate conjugates, respectively. A study in mice with oral administration of 0.1 g/kg of curcumin yielded a peak plasma concentration of free curcumin of only 2.25 μg/ml (Pan et al. 1999). Another study in rats showed that free-form curcumin was completely undetectable in plasma within 1 h after a 40 mg/kg intravenous dose. On the basis of enzymatic hydrolysis studies, the significant curcumin metabolites observed were curcumin glucuronide and curcumin sulfate (Ireson et al. 2001). Human studies also showed that after oral administration of curcumin, most of the curcumin found in the plasma was in its conjugate forms, with a ratio of curcumin glucuronide to curcumin sulfate of 1.92:1 (Vareed et al. 2008). Compared with curcumin, curcumin glucuronide and curcumin sulfate have been shown to be less active or inactive (Wang et al. 2015, Zhu et al. 2017); therefore, the Phase II metabolism leads to reduced biological activities of curcumin.

Along with enzymatic Phase I and Phase II metabolisms, curcumin has an α,β-unsaturated carbonyl moiety, which can react with protein thiols to form covalently linked protein conjugates via a Michael reaction. Therefore, it is likely that after consumption of curcumin, a proportion of curcumin can enter intracellular space and react with protein thiols to form intracellular protein adducts. This process could also contribute to the low circulating concentration of free-form curcumin after curcumin consumption. The biological significance of the curcumin–protein adduct

formation requires more study. Previous research showed that the cysteine residues (or protein thiols) play critical roles in regulating many critical biological processes. For example, covalent modification of cysteine residues of Keap1 proteins leads to the disruption of the Keap1-Nrf2 complex and activation of the Nrf2-mediated Phase II detoxification signaling pathway (Zhang & Hannink 2003). Recent research showed that curcumin could covalently modify a signaling protein termed casein kinase I gamma, which plays a critical role in the biological action of curcumin (Abegg et al. 2015). Therefore, the formation of curcumin–protein adducts could contribute to the biological effects of curcumin.

FOOD MATRIX DESIGN STRATEGIES FOR IMPROVING CURCUMIN BIOAVAILABILITY

Curcumin may be delivered to consumers in various forms. Curcumin is naturally present in turmeric, which is used as a colorant and spice in many food products, particularly in Asian countries. Alternatively, curcumin may be isolated from its natural environment, purified, and then used as a nutraceutical ingredient in processed foods and beverages (McClements & Xiao 2012, Oehlke et al. 2014, Ting et al. 2014, Wang et al. 2014, Yada et al. 2014). The problems associated with the low oral bioavailability of curcumin can be overcome by carefully designing food matrices (McClements & Xiao 2014). In this section, we consider the following two approaches to improving the bioavailability of curcumin in natural or processed foods that depend on food matrix design:

- Delivery systems*:* In this case, curcumin is isolated from its usual environment and then encapsulated within a suitable delivery system, which may take the form of a curcumin-enriched food or beverage, such as a drink, sauce, dip, yogurt, spread, or bread. In many of these applications, curcumin would have to be encapsulated within a colloidal delivery system that is then mixed with the food or beverage. This delivery system would have to be designed to be compatible with the food matrix and to enhance the bioavailability of the curcumin after ingestion.
- Excipient systems: In this case, the curcumin is left in its typical environment, such as in turmeric powder or a supplement (pill, capsule, or tablet). This powder or supplement is then coingested with an excipient food whose composition and structure are carefully designed to enhance the bioavailability of the curcumin. The precise nature of the excipient food is determined by the physicochemical and sensory requirements of the food or beverage product (e.g., appearance, flavor, texture, and stability), as well as the major factors that typically inhibit its bioavailability (e.g., bioaccessibility, absorption, or transformation).

Colloidal dispersions, which consist of small particles dispersed within an aqueous solution, can be used to create both delivery and excipient systems suitable for improving the oral bioavailability of curcumin. In the following section, we review several colloidal systems that have strong potential for application in foods and beverages. Only emulsions have so far been investigated for their potential to act as excipient systems for curcumin, but other systems may also be effective.

Colloidal Delivery and Excipient Systems

In recent years, there have been major advances in the design and fabrication of food-grade colloidal dispersions that can be used as delivery or excipient systems (McClements 2012, Ting et al. 2014, Wang et al. 2014, Yada et al. 2014). Numerous types of colloidal delivery systems have been developed for this purpose, including emulsions, microemulsions, nanoemulsions, liposomes,

solid lipid nanoparticles (SLNs), biopolymer nanoparticles, and microgels. Each type of colloidal dispersion has certain advantages and limitations for specific applications, and many factors have to be considered when deciding on the most appropriate for a particular application. Some of the most important factors are (*a*) the molecular and physicochemical attributes of the bioactive to be encapsulated (such as polarity, charge, molecular weight, and chemical sensitivity); (*b*) the nature of the food matrix (such as appearance, rheology, flavor profile); (*c*) the environmental stresses the food experiences during manufacturing, storage, and utilization (such as pH, ionic strength, water activity, light exposure, oxygen levels, and temperature profile); (*d*) the ease, robustness, and cost of manufacture; (*e*) consumer perception and labeling requirements; and (*f*) government regulations. Various colloidal delivery systems have been investigated for their potential to encapsulate, protect, and deliver curcumin (for review, see Ahmad et al. 2016, Di Martino et al. 2017, Mahmood et al. 2015, Mehanny et al. 2016, Nayak et al. 2016, Subramanian et al. 2016). Many of these systems were initially developed for the pharmaceutical industry and are assembled using ingredients or processing methods that would not be suitable for food applications. However, some of them can be constructed from food-grade ingredients using commercially viable production methods, and could, therefore, be utilized in food or beverage applications.

In the remainder of this section, we provide a brief overview of some of the most essential food-grade colloidal systems that have been developed to improve the efficacy of curcumin and highlight their advantages and limitations for application in functional foods and beverages.

Micelles and Microemulsions. Micelles are relatively small colloidal particles that form spontaneously when certain types of surfactants are dispersed in water (Paul & Moulik 1997). The surfactant molecules assemble so that their nonpolar tails are located in the interior of the particle, while the polar heads are located at the exterior of the particle. The main driving force for the adoption of this structure is the hydrophobic effect, i.e., the tendency to minimize the thermodynamically unfavorable interactions between the nonpolar surfactant tails and the surrounding water molecules (Israelachvili 2011). Micelles are usually formed from relatively hydrophilic nonionic or ionic surfactants [hydrophile-lipophile balance (HLB) > 10], such as Tweens and sodium dodecyl sulfate (SDS). Microemulsions have relatively similar structures to micelles, consisting of a hydrophobic core of surfactant tails and oil molecules surrounded by a hydrophilic shell of surfactant head groups. Microemulsions are usually formed from a combination of surfactants, oil, and possibly cosurfactants. Micelles and microemulsions can solubilize nonpolar curcumin molecules into their hydrophobic cores, and thereby increase their water solubility and alter their transport properties (Narang et al. 2007). Microemulsions would be expected to solubilize more curcumin molecules than micelles because their hydrophobic cores are larger, and therefore they have a higher solubilization capacity. Typically, micelles have diameters between approximately 5 and 15 nm (the length of two surfactant molecules), whereas microemulsions have dimensions ranging from approximately 10 to 100 nm (because they may also contain an oil core). Micelles and microemulsions tend to have a spherical shape, although nonspherical shapes can be obtained for certain types of surfactants and environmental conditions.

At the relatively low concentrations used in foods, micelles and microemulsions tend to have relatively low viscosities, but they may be highly viscous or gel-like when used at higher concentrations. Suspensions of micelles tend to be optically transparent because the colloidal particles are much smaller than the wavelength of light. However, the appearance of microemulsion suspensions may vary from clear to turbid to opaque depending on the size of the particles they contain. Micelles and microemulsions are thermodynamically stable systems, and therefore they should remain stable once they have been formed. However, the structure of these systems is often sensitive to environmental conditions (such as temperature, dilution, and ionic strength), and so changes

in these conditions can lead to changes in their stability. The relatively high levels of surfactants used to formulate micelles and microemulsions can lead to flavor problems, as some surfactants have unpleasant bitter or soapy tastes.

Curcumin has been incorporated into microemulsions fabricated from food-grade ingredients, such as Tween 20, lecithin, vitamin E, and ethanol (Bergonzi et al. 2014). These microemulsions were shown to increase the water dispersibility of curcumin considerably, i.e., by 1,000- to 10,000-fold depending on the system composition. They were also shown to increase the permeation rate of curcumin through membranes, which may be useful for increasing its absorption through epithelial cells. The particle size of the curcumin-loaded microemulsions was relatively low (<20 nm), which meant that they were optically transparent, which would be an advantage for some applications. Microemulsions with similar attributes have also been fabricated using Tween 80, lecithin, and ethyl oleate, which are also all food-grade ingredients (Lin et al. 2009). The rate of chemical degradation of curcumin in aqueous solutions has been shown to be greatly reduced (300–500-fold) when it is incorporated into surfactant micelles (Naksuriya et al. 2016); this is in part because the curcumin is trapped within the nonpolar core of the micelles and therefore isolated from hydrophilic species that normally promote its degradation. Recent studies have shown that curcumin can be incorporated into micelles fabricated from chemically modified food carbohydrates (octenylsuccinated corn dextrin), which greatly increased its water solubility (Ye et al. 2017). Yu & Huang (2011) showed that curcumin solubilized within the mixed micelles formed after lipid digestion facilitates its transport across model epithelial cells. Furthermore, animal studies have shown that administration of curcumin in the form of microemulsions increases their oral bioavailability (Cui et al. 2009, Wu et al. 2011). In summary, these studies have shown that micelles and microemulsions can increase the water dispersibility, chemical stability, bioaccessibility, absorption, and overall bioavailability of curcumin.

The potential advantages of using micelles or microemulsions to encapsulate curcumin are that they are relatively easy to prepare, can be optically transparent, and are thermodynamically stable. However, they typically require relatively large quantities of synthetic surfactants, which is undesirable from a cost, taste, toxicity, and consumer acceptability perspective. Moreover, they tend to have a relatively low loading capacity compared to some of the other systems discussed.

Liposomes. Liposomes are usually assembled from phospholipid molecules that self-assemble into bilayer structures where the nonpolar tails are in contact with each other while the polar heads are in contact with water (Maherani et al. 2011; Mozafari et al. 2008a,b; Taylor et al. 2005). Typically, the bilayers are organized into one (unilamellar) or more (multilamellar) concentric rings that trap a pool of water within their interior. The main driving force for the formation of the bilayer structures is the hydrophobic effect, whereas the size of the liposomes is determined by their optimum curvature (Israelachvili 2011). These systems can be referred to as nanoliposomes ($d < 200$ nm) or liposomes ($d > 200$ nm) depending on their average particle diameters. Liposomes can be fabricated using a variety of different preparation methods, including film evaporation, injection, sonication, and microfluidization methods (Maherani et al. 2011; Mozafari et al. 2008a,b), which vary considerably in their suitability for large-scale economic production.

Many studies have shown that curcumin can be successfully encapsulated in liposomes formulated from food-grade phospholipids, such as those isolated from eggs, milk, fish, or soybeans (Hasan et al. 2016, Jin et al. 2016, Pandelidou et al. 2011). Encapsulation of curcumin in liposomes enhances its water dispersibility and increases its chemical stability (X. Chen et al. 2015) presumably by isolating it from components in the aqueous phase that normally promote degradation. Other in vitro studies have shown that encapsulation of curcumin in liposomes increases its water dispersibility and antioxidant and anti-inflammatory properties (Basnet et al. 2012). In vivo

studies using rats have shown that the oral bioavailability and bioactivity of curcumin is improved when it is encapsulated in liposomes (Takahashi et al. 2009). Indeed, the bioavailability [area under the curve (AUC)] was ~20-fold higher and the antioxidant activity was ~2- or 3-fold higher for rats administered encapsulated curcumin compared to those administered free curcumin. A study showed that coating curcumin-loaded liposomes with cationic chitosan using an electrostatic deposition method improved its storage stability, encapsulation efficiency, mucoadhesive properties, and bioavailability (Shin et al. 2013). Therefore, this coating approach may be useful for enhancing the functionality of liposomes in food applications. In summary, the encapsulation of curcumin in liposomes has been shown to improve its water dispersibility, chemical stability, bioaccessibility, and bioavailability.

One of the advantages of using liposomes is that they can be used to solubilize hydrophilic, amphiphilic, and lipophilic agents within the same colloidal system and that they can be fabricated entirely from natural food ingredients (phospholipids). However, two of the major challenges to using liposomes commercially is that they are difficult to produce economically on a large scale and that they have relatively low stability under the environmental conditions found in many foods. However, this latter challenge may be overcome by coating the liposomes with a layer of biopolymers.

Emulsions and nanoemulsions. Oil-in-water emulsions and nanoemulsions consist of small oil droplets dispersed within an aqueous phase (McClements 2011, McClements & Rao 2011). Emulsions contain relatively large droplets ($d > 100$ nm), whereas nanoemulsions contain relatively small droplets ($d < 100$ nm). For the sake of convenience, both of these systems will be referred to as emulsions. The oil droplets are coated by a layer of emulsifier molecules that helps to prevent them from aggregating by generating repulsive colloidal interactions between them. The most commonly used emulsifiers in the food industry are small molecule surfactants, phospholipids, proteins, and polysaccharides (McClements 2015). Emulsions may be formed using high-intensity methods (such as high shear mixing, colloid mills, high-pressure homogenization, microfluidization, or sonication) or using low-intensity methods (such as phase inversion temperature or spontaneous emulsification) (McClements 2011, McClements & Rao 2011). For delivery systems, the curcumin is typically dispersed in the oil phase before forming the emulsion. For excipient systems, the emulsion would be mixed with food or supplements that contained curcumin. After being introduced into emulsions, curcumin molecules will be predominately located within the hydrophobic interior of the oil droplets, but some of them may also be located close to the oil–water interface because of the polar groups on the curcumin. Several studies have examined the possibility of using emulsion-based systems to improve the bioavailability of curcumin.

The water dispersibility of curcumin can be greatly increased by incorporating it into emulsions because it is solubilized within the hydrophobic core of the oil droplets (Ahmed et al. 2012, Kumar et al. 2012). In this case, the total amount of curcumin that can be incorporated into the system is limited by its oil solubility (see Bergonzi et al. 2014, Jang et al. 2014) and the oil droplet concentration. Research has shown that the stability of curcumin to chemical degradation is enhanced when it is dispersed within oil droplets rather than present in aqueous solutions (Kharat et al. 2017). Presumably, this is because curcumin is protected from hydrophilic species within the aqueous phase that would typically promote its degradation (such as hydroxyl ions). Studies in our laboratory have also shown that curcumin may be protected from metabolism when it is incorporated in oil droplets compared to when it is dissolved in aqueous GIT solutions. The encapsulation of curcumin in triacylglycerol emulsions can also increase its bioaccessibility in gastrointestinal fluids (Ahmed et al. 2012). The triacylglycerols are converted into free fatty acids and monoacylglycerols due to the action of lipase in the small intestine. These lipid

digestion products then interact with bile salts and phospholipids to form mixed micelles that can solubilize the curcumin in their hydrophobic interiors. The small micelles then transport the curcumin through the mucus layer and to the surfaces of the epithelium cells where it can be absorbed.

Emulsions have been used as both delivery and excipient systems for curcumin. In vitro studies using a simulated GIT have shown that the bioavailability of powdered curcumin can be improved by coingesting curcumin with excipient nanoemulsions (Zou et al. 2016b). The droplet size, composition, concentration, and interfacial properties were shown to impact the bioavailability of curcumin due to their influence on its bioaccessibility and transformation (Zou et al. 2015a,b,c; 2016a).

In vitro and in vivo studies have shown that encapsulation of curcumin within nanoemulsions improves its bioavailability when compared to curcumin crystals dispersed in water (Yu & Huang 2012). In particular, the curcumin levels in the plasma of mice were much higher after they were administered curcumin in the form of nanoemulsions rather than crystals. For example, the bioavailability was 9.3-fold higher for the nanoemulsion than for the crystals. Another study showed that the encapsulation of curcumin within nanoemulsions containing lipid droplets coated with chitosan increased the plasma levels of rats compared to curcumin crystals (Vecchione et al. 2016). In this case, the oral bioavailability was 33-fold higher for the curcumin in the nanoemulsion form than in the crystalline form. Moreover, including piperine in the nanoemulsions caused a further increase in curcumin bioavailability so that it became 64-fold higher than crystalline curcumin, which was attributed to the ability of the piperine to block the efflux transporters in epithelial cells. In another study using rats, Jang et al. (2014) showed that encapsulation of curcumin in spray-dried nanoemulsions improved the oral bioavailability of curcumin approximately sevenfold compared to curcumin crystals. In vitro studies have shown that the GIT fate of curcumin encapsulated in nanoemulsions stabilized by biopolymers depends on the interfacial composition, i.e., lactoferrin or lactoferrin-alginate (Pinheiro et al. 2016). In particular, this study showed that bioavailability of curcumin increased as the level of lipid digestion increased, which highlights the importance of the formation of mixed micelles on the bioaccessibility of curcumin. Studies have shown that the bioavailability and bioactivity of curcumin encapsulated in emulsions can be improved by also including piperine in the oil phase (Gulseren et al. 2014), given piperine can inhibit efflux mechanisms.

Joung et al.'s (2016) study showed that curcumin-loaded nanoemulsions can be successfully incorporated into commercial food products, such as milk. This study demonstrated that the addition of the emulsified curcumin reduced the lipid oxidation in the milk. Studies have also shown that curcumin loaded emulsions can be converted into a powdered form using spray drying (Jang et al. 2014), which would be useful for many commercial applications in foods and beverages.

The main advantage of using emulsions and nanoemulsions is that they can be fabricated entirely from natural food-grade ingredients using widely used processing methods (McClements 2015). Consequently, they can be produced on a large scale at a relatively low cost, which makes them one of the most commercially viable colloidal delivery or excipient systems for application in the food industry. The main disadvantage is that they are thermodynamically unstable systems, and therefore they always tend to break down over time, which occurs due to physicochemical mechanisms such as gravitational separation, flocculation, coalescence, Ostwald ripening, and phase inversion (McClements 2015). Nevertheless, they can usually be designed to overcome these problems through careful ingredient selection.

Solid lipid nanoparticles. SLNs have many similar characteristics as oil-in-water nanoemulsions, except that the lipid particles are solid rather than liquid (McClements et al. 2009, Weiss et al.

2008). Typically, a nanoemulsion is formed first by homogenizing an oil phase with a high melting point (T_m) and an aqueous phase containing a hydrophilic surfactant together at a temperature $>T_m$. After formation, the nanoemulsion is cooled below T_m, which causes the lipid phase to become fully or partially solidified. The resulting SLN suspension consists of solidified lipid particles coated by a layer of emulsifier. For delivery systems, the hydrophobic curcumin molecules are usually dispersed in the molten oil phase before forming the nanoemulsions. Consequently, they can be trapped within the hydrophobic interior of the SLNs when the system is cooled. The presence of a solid lipid matrix around the curcumin molecules should enhance their stability by inhibiting molecular diffusion processes (Weiss et al. 2008). However, one must carefully select an appropriate lipid phase and emulsifier when designing SLN systems; otherwise, they may be physically or chemically unstable. The solidification of certain types of lipid phases can promote expulsion of the encapsulated bioactive agent or aggregation of the SLNs (Helgason et al. 2009a,b). Bioactive expulsion can occur when the lipid phase forms highly ordered crystalline structures that cannot accommodate the bioactive molecules, and so they are expelled to the surface of the particles or into the aqueous phase, where they are more susceptible to chemical degradation. Particle aggregation can occur when the lipid particles change from a spherical shape to an irregular shape, given this increases the surface area of the system. Consequently, there may be insufficient emulsifier molecules present to completely cover the surfaces of the lipid nanoparticles, which can lead to particle aggregation due to the hydrophobic effect. For these reasons, some researchers have developed nanostructured lipid carriers to encapsulate hydrophobic bioactives (Tamjidi et al. 2013). In this case, a lipid phase is selected that does not crystallize into a highly ordered structure, thereby improving its ability to retain the bioactive within the particle interiors and inhibiting the shape change that usually leads to particle aggregation.

Encapsulation of curcumin within SLNs has been shown to increase its water dispersibility and bioactivity (Yadav et al. 2009, Yen et al. 2010) as well as improve its chemical stability in aqueous solutions (Jiang et al. 2017). Also, in vitro studies have shown that curcumin encapsulation in SLNs increases the amount absorbed by model epithelial cells (Guri et al. 2013). In vivo studies using rats showed that administration of curcumin in SLNs greatly improved its bioavailability when compared to free curcumin (Ji et al. 2016). Indeed, these researchers showed that there was more than a 12-fold increase in bioavailability when the curcumin was encapsulated in SLNs (Ji et al. 2016). Recently, researchers have used SLNs to coencapsulate two different kinds of nutraceuticals in a single delivery system: curcumin and tea polyphenols (Li et al. 2017). These delivery systems were then shown to have good anticancer activity using an in vitro model. The bioavailability and bioactivity of curcumin in SLNs can be improved by coencapsulating it with piperine (Tang et al. 2017), given this phytochemical can inhibit efflux mechanisms.

A variety of different lipid phases have been used to form curcumin-loaded SLNs, including shea butter (Ali et al. 2016), glycerol stearate (Ramalingam et al. 2016), trimyristin, tristearin (Jiang et al. 2017), tripalmitin (Puglia et al. 2013), palmitic acid (Ramalingam et al. 2016), cholesterol (Jourghanian et al. 2016), and mono-, di-, and tri-acylglycerol mixtures of behenic acid (Righeschi et al. 2016). These lipid phases vary in their physicochemical properties (such as T_m), label friendliness, and cost. For food applications, it would be advantageous to use an edible high-melting-point lipid whose melting temperature was above ambient, but not too high, or else it would be difficult to prepare the SLNs.

One of the major advantages of SLNs is that they can potentially be fabricated on a large scale using existing commercial equipment, such as high-pressure homogenizers. Also, if they are formulated correctly, they can lead to delivery systems that provide good long-term physical and chemical stability. However, the major limitations are that they are often highly prone to bioactive expulsion and particle aggregation if not formulated correctly. In addition, the utilization

of high-melting-point fats (such as saturated fats) may not be perceived as being beneficial for health purposes.

Biopolymer particles. This type of colloidal dispersion consists of biopolymer-rich particles suspended in an aqueous solution and covers a variety of different systems, including biopolymer nanoparticles, microgels, and hydrogel beads (Chen et al. 2006, Joye & McClements 2014, Shewan & Stokes 2013, Wang et al. 2014). The size of the biopolymer particles may vary from approximately 50 to 1,000 nm, depending on the ingredients and preparation method used. Typically, the biopolymers within the particles are physically or chemically cross-linked with each other to form a three-dimensional network that can trap solvent and bioactive components inside. The biopolymers used may be hydrophobic (such as zein or gliadin) or hydrophilic (such as alginate, carrageenan, pectin, or whey protein) (Joye & McClements 2014). For hydrophobic biopolymers, the nonpolar curcumin molecules can be directly added to the biopolymer phase before particle formation. For hydrophilic biopolymers, the curcumin normally has to be trapped inside lipid droplets (or other colloidal particles with hydrophobic cores) before it is added to the biopolymer phase. Biopolymer particles can be fabricated using a variety of different methods, including antisolvent precipitation, injection–gelation, phase separation–gelation, and emulsion templating methods (Joye & McClements 2014, Wang et al. 2014). The interior of the biopolymer particles can often be made to control the retention, release, and stability characteristics of the encapsulated components. For example, the pore size or interactions between the curcumin and biopolymer network can be controlled, or antioxidants can be added.

Recent studies have shown that curcumin-loaded oil droplets can be encapsulated within microgels fabricated from food-grade polysaccharides (Zhang et al. 2016). These microgels were formed by the injection of solutions of anionic polysaccharides (alginate or carrageenan) into solutions containing cationic ions (calcium or potassium) that promote cross-linking. The bioaccessibility of the curcumin under small intestine conditions was reduced when it was encapsulated in the microgels, which was attributed to their ability to inhibit the access of the digestive enzymes to the encapsulated lipid droplets. Nguyen et al. (2014) encapsulated curcumin within pectin microgels and showed that its release rate depended on the nature of the emulsifier used to solubilize the curcumin.

Zou et al. (2016b) encapsulated curcumin within protein nanoparticles formed using an antisolvent precipitation method. In this case, a mixture of curcumin and zein dissolved in an ethanol solution (solvent) was injected into water (antisolvent), which led to the spontaneous formation of small protein particles with the curcumin trapped inside. The loading capacity of the curcumin in the protein nanoparticles (12%) was appreciably higher than that in nanoliposomes (3%) or nanoemulsions (0.4%). Also, the chemical stability of the curcumin was similar or higher in the protein nanoparticles (41%) than in nanoliposomes (21%) or nanoemulsions (40%). Conversely, the bioaccessibility of the curcumin was considerably lower in the protein nanoparticles (52%) than in nanoliposomes (74%) or nanoemulsions (92%). These results highlight the advantages and disadvantages of different kinds of delivery systems for curcumin.

Encapsulating curcumin in various other types of protein nanoparticles, including those assembled from whey proteins (Teng et al. 2014), caseins, BSA (Nadi et al. 2015), soy proteins (F.P. Chen et al. 2015, David et al. 2015), corn protein (Wang et al. 2016), zein (Zou et al. 2017), and gelatin (Gomez-Estaca et al. 2015), has improved the water dispersibility, chemical stability, release characteristics, and/or bioavailability of curcumin.

Encapsulation of curcumin in biopolymer particles consisting of κ-carrageenan and lysozyme was shown to increase its dispersibility and chemical stability in aqueous solutions (Xu et al. 2014). Presumably, the proteins acted as antioxidants that could inhibit the chemical degradation of the

curcumin molecules. Curcumin encapsulation within casein nanoparticles has also been shown to increase its dispersibility, chemical stability, and bioactivity (Pan et al. 2014). The protein nanoparticles formed in this study were relatively small (d = 100–215 nm) and led to the formation of optically transparent solutions, which may be advantageous for certain applications in foods and beverages.

The main advantage of using biopolymer particles to encapsulate curcumin is that they can be fabricated entirely from natural ingredients, such as proteins and polysaccharides. Also, there is considerable flexibility in designing their functional attributes by using different kinds of biopolymers and fabrication methods. The main disadvantages are that it is often difficult to scale-up laboratory methods of fabricating biopolymer particles for large-scale commercial production. In addition, the colloidal particles formed are often relatively large, which can lead to problems with gravitational separation and mouthfeel.

CONCLUSIONS

There has been a major interest in the creation of functional foods and beverages that are fortified with curcumin due to its perceived health benefits. However, there are many challenges associated with incorporating curcumin into commercial foods and beverages because of its low water solubility, poor chemical stability, and low bioavailability. This article has reviewed the major factors limiting the bioavailability of curcumin, as well as the methods that have been developed to overcome these limitations. In particular, we focused on the utilization of various kinds of colloidal delivery systems to improve the oral bioavailability of curcumin and highlighted their relative advantages and disadvantages.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This material is based on work supported by the Cooperative State Research, Extension, Education Service of the United States Department of Agriculture (USDA); Massachusetts Agricultural Experiment Station Project 831; USDA NRI Grants 2011–03539, 2013–03795, 2011–67021, and 2014–67021; and USDA NIFA Grant 2016–67017–24423.

LITERATURE CITED

Abegg D, Frei R, Cerato L, Prasad Hari D, Wang C, et al. 2015. Proteome-wide profiling of targets of cysteine reactive small molecules by using ethynyl benziodoxolone reagents. *Angew. Chem. Int. Ed.* 54:10852–57

Aggarwal BB, Harikumar KB. 2009. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int. J. Biochem. Cell Biol.* 41:40–59

Aggarwal BB, Kumar A, Bharti AC. 2003. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.* 23:363–98

Aggarwal BB, Sung B. 2009. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol. Sci.* 30:85–94

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. 2006. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IκBα kinase and Akt activation. *Mol. Pharmacol.* 69:195–206

Ahmad MZ, Alkahtani SA, Akhter S, Ahmad FJ, Ahmad J, et al. 2016. Progress in nanotechnology-based drug carrier in designing of curcumin nanomedicines for cancer therapy: current state-of-the-art. *J. Drug Target.* 24:273–93

Ahmed K, Li Y, McClements DJ, Xiao H. 2012. Nanoemulsion- and emulsion-based delivery systems for curcumin: encapsulation and release properties. *Food Chem.* 132:799–807

Ak T, Gülçin İ. 2008. Antioxidant and radical scavenging properties of curcumin. *Chemico-Biological Interact.* 174:27–37

Ali HH, Michaux F, Ntsama ISB, Durand P, Jasniewski J, Linder M. 2016. Shea butter solid nanoparticles for curcumin encapsulation: influence of nanoparticles size on drug loading. *Eur. J. Lipid Sci. Technol.* 118:1168–78

Ammon HP, Wahl MA. 1991. Pharmacology of *Curcuma longa*. *Planta Medica* 57:1–7

Anto RJ, Mukhopadhyay A, Denning K, Aggarwal BB. 2002. Curcumin (diferuloylmethane) induces apoptosis through activation of caspase-8, BID cleavage and cytochrome c release: its suppression by ectopic expression of Bcl-2 and Bcl-xl. *Carcinogenesis* 23:143–50

Arbiser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, et al. 1998. Curcumin is an in vivo inhibitor of angiogenesis. *Mol. Med.* 4:376–83

Bachmeier B, Nerlich AG, Iancu CM, Cilli M, Schleicher E, et al. 2007. The chemopreventive polyphenol Curcumin prevents hematogenous breast cancer metastases in immunodeficient mice. *Cell Physiol. Biochem.* 19:137–52

Basnet P, Hussain H, Tho I, Skalko-Basnet N. 2012. Liposomal delivery system enhances anti-inflammatory properties of curcumin. *J. Pharm. Sci.* 101:598–609

Bergonzi MC, Hamdouch R, Mazzacuva F, Isacchi B, Bilia AR. 2014. Optimization, characterization and *in vitro* evaluation of curcumin microemulsions. *LWT Food Sci. Technol.* 59:148–55

Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, et al. 2011. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev. Res. (Phila.)* 4:354–64

Chan MM. 1995. Inhibition of tumor necrosis factor by curcumin, a phytochemical. *Biochem. Pharmacol.* 49:1551–56

Chen FP, Li BS, Tang CH. 2015. Nanocomplexation of soy protein isolate with curcumin: influence of ultrasonic treatment. *Food Res. Int.* 75:157–65

Chen H-W, Lee J-Y, Huang J-Y, Wang C-C, Chen W-J, et al. 2008. Curcumin inhibits lung cancer cell invasion and metastasis through the tumor suppressor HLJ1. *Cancer Res.* 68:7428–38

Chen LY, Remondetto GE, Subirade M. 2006. Food protein-based materials as nutraceutical delivery systems. *Trends Food Sci. Technol.* 17:272–83

Chen X, Zou LQ, Niu J, Liu W, Peng SF, Liu CM. 2015. The stability, sustained release and cellular antioxidant activity of curcumin nanoliposomes. *Molecules* 20:14293–311

Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, et al. 2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.* 21:2895–900

Cheng Y, Kozubek A, Ohlsson L, Sternby B, Duan RD. 2007. Curcumin decreases acid sphingomyelinase activity in colon cancer Caco-2 cells. *Planta Med.* 73:725–30

Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S. 2014. Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. *J. Nutr. Biochem.* 25:144–50

Cui J, Yu B, Zhao Y, Zhu WW, Li HL, et al. 2009. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. *Int. J. Pharm.* 371:148–55

David S, Zagury Y, Livney YD. 2015. Soy β-conglycinin–curcumin nanocomplexes for enrichment of clear beverages. *Food Biophys.* 10:195–206

Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnumakkara AB, et al. 2008. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin. Cancer Res.* 14:4491–99

Di Martino RMC, Luppi B, Bisi A, Gobbi S, Rampa A, et al. 2017. Recent progress on curcumin-based therapeutics: a patent review (2012–2016). Part I: Curcumin. *Expert Opin. Ther. Pat.* 27:579–90

Ejaz A, Wu D, Kwan P, Meydani M. 2009. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *J. Nutr.* 139:919–25

Gomez-Estaca J, Gavara R, Hernandez-Munoz P. 2015. Encapsulation of curcumin in electrosprayed gelatin microspheres enhances its bioaccessibility and widens its uses in food applications. *Innovative Food Sci. Emerg. Technol.* 29:302–7

Gordon ON, Luis PB, Sintim HO, Schneider C. 2015. Unraveling curcumin degradation: autoxidation proceeds through spiroepoxide and vinylether intermediates en route to the main bicyclopentadione. *J. Biol. Chem.* 290:4817–28

Griesser M, Pistis V, Suzuki T, Tejera N, Pratt DA, Schneider C. 2011. Autoxidative and cyclooxygenase-2 catalyzed transformation of the dietary chemopreventive agent curcumin. *J. Biol. Chem.* 286:1114–24

Gulseren I, Guri A, Corredig M. 2014. Effect of interfacial composition on uptake of curcumin-piperine mixtures in oil in water emulsions by Caco-2 cells. *Food Funct.* 5:1218–23

Guri A, Gulseren I, Corredig M. 2013. Utilization of solid lipid nanoparticles for enhanced delivery of curcumin in cocultures of HT29-MTX and Caco-2 cells. *Food Funct.* 4:1410–19

Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, et al. 2006. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin. Gastroenterol. Hepatol.* 4:1502–6

Hasan M, Ben Messaoud G, Michaux F, Tamayol A, Kahn CJF, et al. 2016. Chitosan-coated liposomes encapsulating curcumin: study of lipid-polysaccharide interactions and nanovesicle behavior. *RSC Adv.* 6:45290–304

Hassaninasab A, Hashimoto Y, Tomita-Yokotani K, Kobayashi M. 2011. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. *PNAS* 108:6615–20

Hejazi J, Rastmanesh R, Taleban FA, Molana SH, Hejazi E, et al. 2016. Effect of curcumin supplementation during radiotherapy on oxidative status of patients with prostate cancer: a double blinded, randomized, placebo-controlled study. *Nutr. Cancer* 68:77–85

Helgason T, Awad TS, Kristbergsson K, Decker EA, McClements DJ, Weiss J. 2009a. Impact of surfactant properties on oxidative stability of beta-carotene encapsulated within solid lipid nanoparticles. *J. Agric. Food Chem.* 57:8033–40

Helgason T, Awad TS, Kristbergsson K, McClements DJ, Weiss J. 2009b. Effect of surfactant surface coverage on formation of solid lipid nanoparticles (SLN). *J. Colloid Interface Sci.* 334:75–81

Huang MT, Lou YR, Ma W, Newmark HL, Reuhl KR, Conney AH. 1994. Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. *Cancer Res.* 54:5841–47

Huang MT, Lysz T, Ferraro T, Abidi TF, Laskin JD, Conney AH. 1991. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. *Cancer Res.* 51:813–19

Ireson C, Orr S, Jones DJ, Verschoyle R, Lim CK, et al. 2001. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat *in vivo*, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E_2 production. *Cancer Res.* 61:1058–61

Israelachvili J. 2011. *Intermolecular and Surface Forces*. London: Academic. 3rd ed.

Jang DJ, Kim ST, Oh E, Lee K. 2014. Enhanced oral bioavailability and antiasthmatic efficacy of curcumin using redispersible dry emulsion. *Bio-Medical Mater. Eng.* 24:917–30

Ji HY, Tang JL, Li MT, Ren JM, Zheng NN, Wu LH. 2016. Curcumin-loaded solid lipid nanoparticles with Brij78 and TPGS improved in vivo oral bioavailability and in situ intestinal absorption of curcumin. *Drug Deliv.* 23:459–70

Jiang S, Zhu RR, He XL, Wang J, Wang M, et al. 2017. Enhanced photocytotoxicity of curcumin delivered by solid lipid nanoparticles. *Int. J. Nanomedicine* 12:167–78

Jin HH, Lu Q, Jiang JG. 2016. Curcumin liposomes prepared with milk fat globule membrane phospholipids and soybean lecithin. *J. Dairy Sci.* 99:1780–90

Joung HJ, Choi MJ, Kim JT, Park SH, Park HJ, Shin GH. 2016. Development of food-grade curcumin nanoemulsion and its potential application to food beverage system: antioxidant property and in vitro digestion. *J. Food Sci.* 81:N745–N53

Jourghanian P, Ghaffari S, Ardjmand M, Haghighat S, Mohammadnejad M. 2016. Sustained release curcumin loaded solid lipid nanoparticles. *Adv. Pharm. Bull.* 6:17–21

Joye IJ, McClements DJ. 2014. Biopolymer-based nanoparticles and microparticles: fabrication, characterization, and application. *Curr. Opin. Colloid Interface Sci.* 19:417–27

Khajuria A, Thusu N, Zutshi U. 2002. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. *Phytomedicine* 9:224–31

Kharat M, Du ZY, Zhang GD, McClementes DJ. 2017. Physical and chemical stability of curcumin in aqueous solutions and emulsions: impact of pH, temperature, and molecular environment. *J. Agric. Food Chem.* 65:1525–32

Killian PH, Kronski E, Michalik KM, Barbieri O, Astigiano S, et al. 2012. Curcumin inhibits prostate cancer metastasis in vivo by targeting the inflammatory cytokines CXCL1 and-2. *Carcinogenesis* 33:2507–19

Kumar A, Ahuja A, Ali J, Baboota S. 2012. Curcumin loaded nano globules for solubility enhancement: preparation, characterization and ex vivo release study. *J. Nanosci. Nanotechnol.* 12:8293–302

Lang A, Salomon N, Wu JC, Kopylov U, Lahat A, et al. 2015. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. *Clin. Gastroenterol. Hepatol.* 13:1444–9e1

Lepetsos P, Papavassiliou AG. 2016. ROS/oxidative stress signaling in osteoarthritis. *Biochim. Biophys. Acta* 1862:576–91

Li L, Aggarwal BB, Shishodia S, Abbruzzese J, Kurzrock R. 2004. Nuclear factor-κB and IκB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis. *Cancer* 101:2351–62

Li L, Braiteh FS, Kurzrock R. 2005. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. *Cancer* 104:1322–31

Li R, Jia K, Chen XG, Xiao HT. 2017. A novel curcuminoid-tea polyphenol formulation: preparation, characterization, and in vitro anti-cancer activity. *J. Food Biochem.* 41:e12332

Lin CC, Lin HY, Chen HC, Yu MW, Lee MH. 2009. Stability and characterisation of phospholipid-based curcumin-encapsulated microemulsions. *Food Chem*. 116:923–28

Lin JK, Pan MH, Lin-Shiau SY. 2000. Recent studies on the biofunctions and biotransformations of curcumin. *BioFactors* 13:153–58

Maherani B, Arab-Tehrany E, Mozafari MR, Gaiani C, Linder M. 2011. Liposomes: a review of manufacturing techniques and targeting strategies. *Curr. Nanosci.* 7:436–52

Mahmood K, Zia KM, Zuber M, Salman M, Anjum MN. 2015. Recent developments in curcumin and curcumin based polymeric materials for biomedical applications: a review. *Int. J. Biol. Macromol.* 81:877–90

Manikandan P, Sumitra M, Aishwarya S, Manohar BM, Lokanadam B, Puvanakrishnan R. 2004. Curcumin modulates free radical quenching in myocardial ischaemia in rats. *Int. J. Biochem. Cell Biol.* 36:1967–80

McClements DJ. 2011. Edible nanoemulsions: fabrication, properties, and functional performance. *Soft Matter* 7:2297–316

McClements DJ. 2012. Advances in fabrication of emulsions with enhanced functionality using structural design principles. *Curr. Opin. Colloid Interface Sci.* 17:235–45

McClements DJ. 2015. *Food Emulsions: Principles, Practices, and Techniques*. Boca Raton, FL: CRC Press

McClements DJ, Decker EA, Park Y, Weiss J. 2009. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. *Crit. Rev. Food Sci. Nutr.* 49:577–606

McClements DJ, Rao J. 2011. Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. *Crit. Rev. Food Sci. Nutr.* 51:285–330

McClements DJ, Xiao H. 2012. Potential biological fate of ingested nanoemulsions: influence of particle characteristics. *Food Funct*. 3:202–20

McClements DJ, Xiao H. 2014. Excipient foods: designing food matrices that improve the oral bioavailability of pharmaceuticals and nutraceuticals. *Food Funct.* 5:1320–33

Introduces the idea of excipient foods specifically designed to increase the oral bioavailability of nutraceuticals.

Mehanny M, Hathout RM, Geneidi AS, Mansour S. 2016. Exploring the use of nanocarrier systems to deliver the magical molecule; curcumin and its derivatives. *J. Control Release* 225:1–30

Menon VP, Sudheer AR. 2007. Antioxidant and anti-inflammatory properties of curcumin. *Adv. Exp. Med. Biol.* 595:105–25

Midura-Kiela MT, Radhakrishnan VM, Larmonier CB, Laubitz D, Ghishan FK, Kiela PR. 2012. Curcumin inhibits interferon-gamma signaling in colonic epithelial cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* 302:G85–96

Motterlini R, Foresti R, Bassi R, Green CJ. 2000. Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radic. Biol. Med.* 28:1303–12

Mozafari MR, Johnson C, Hatziantoniou S, Demetzos C. 2008a. Nanoliposomes and their applications in food nanotechnology. *J. Liposome Res.* 18:309–27

Mozafari MR, Khosravi-Darani K, Borazan GG, Cui J, Pardakhty A, Yurdugul S. 2008b. Encapsulation of food ingredients using nanoliposome technology. *Int. J. Food Prop.* 11:833–44

Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, et al. 2011. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. *Biosci. Rep.* 31:185–97

Nadi MM, Kooshk MRA, Mansouri K, Ghadami SA, Amani M, et al. 2015. Comparative spectroscopic studies on curcumin stabilization by association to bovine serum albumin and casein: a perspective on drug-delivery application. *Int. J. Food Prop.* 18:638–59

Naksuriya O, van Steenbergen MJ, Torano JS, Okonogi S, Hennink WE. 2016. A kinetic degradation study of curcumin in its free form and loaded in polymeric micelles. *AAPS J.* 18:777–87

Narang AS, Delmarre D, Gao D. 2007. Stable drug encapsulation in micelles and microemulsions. *Int. J. Pharm.* 345:9–25

Nayak PA, Mills T, Norton I. 2016. Lipid based nanosystems for curcumin: past, present and future. *Curr. Pharm. Des.* 22:4247–56

Nguyen ATB, Winckler P, Loison P, Wache Y, Chambin O. 2014. Physico-chemical state influences in vitro release profile of curcumin from pectin beads. *Colloids Surfaces B* 121:290–98

Nimiya Y, Wang W, Du Z, Sukamtoh E, Zhu J, et al. 2016. Redox modulation of curcumin stability: Redox active antioxidants increase chemical stability of curcumin. *Mol. Nutr. Food Res.* 60:487–94

Nice overview of the evidence supporting the utilization of different nanoscale delivery systems for nutraceuticals.

Oehlke K, Adamiuk M, Behsnilian D, Graf V, Mayer-Miebach E, et al. 2014. Potential bioavailability enhancement of bioactive compounds using food-grade engineered nanomaterials: a review of the existing evidence. *Food Funct.* 5:1341–59

Pan K, Luo YC, Gan YD, Baek SJ, Zhong QX. 2014. pH-driven encapsulation of curcumin in self-assembled casein nanoparticles for enhanced dispersibility and bioactivity. *Soft Matter* 10:6820–30

Pan MH, Huang TM, Lin JK. 1999. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab. Dispos.* 27:486–94

Panahi Y, Alishiri GH, Parvin S, Sahebkar A. 2016. Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: results of a randomized controlled trial. *J. Diet. Suppl.* 13:209–20

Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. 2015. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. *Clin. Nutr.* 34:1101–8

Pandelidou M, Dimas K, Georgopoulos A, Hatziantoniou S, Demetzos C. 2011. Preparation and characterization of lyophilised EGG PC liposomes incorporating curcumin and evaluation of its activity against colorectal cancer cell lines. *J. Nanosci. Nanotechnol.* 11:1259–66

Paul BK, Moulik SP. 1997. Microemulsions: an overview. *J. Dispers. Sci. Technol.* 18:301–67

Pinheiro AC, Coimbra MA, Vicente AA. 2016. In vitro behaviour of curcumin nanoemulsions stabilized by biopolymer emulsifiers—effect of interfacial composition. *Food Hydrocolloids* 52:460–67

Prasad S, Tyagi AK, Aggarwal BB. 2014. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer Res. Treat.* 46:2–18

Puglia C, Offerta A, Rizza L, Zingale G, Bonina F, Ronsisvalle S. 2013. Optimization of curcumin loaded lipid nanoparticles formulated using high shear homogenization (HSH) and ultrasonication (US) methods. *J. Nanosci. Nanotechnol.* 13:6888–93

Ramalingam P, Yoo SW, Ko YT. 2016. Nanodelivery systems based on mucoadhesive polymer coated solid lipid nanoparticles to improve the oral intake of food curcumin. *Food Res. Int.* 84:113–19

Rao CV, Rivenson A, Simi B, Reddy BS. 1995. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Res.* 55:259–66

Ravindranath V, Chandrasekhara N. 1980. Absorption and tissue distribution of curcumin in rats. *Toxicology* 16:259–65

Ravindranath V, Chandrasekhara N. 1982. Metabolism of curcumn-studies with [^{3}H] curcumin. *Toxicology* 22:337–44

Righeschi C, Bergonzi MC, Isacchi B, Bazzicalupi C, Gratteri P, Bilia AR. 2016. Enhanced curcumin permeability by SLN formulation: the PAMPA approach. *Lwt-Food Sci. Technol.* 66:475–83

Roberts CK, Sindhu KK. 2009. Oxidative stress and metabolic syndrome. *Life Sci.* 84:705–12

Schneider C, Gordon ON, Edwards RL, Luis PB. 2015. Degradation of curcumin: from mechanism to biological implications. *J. Agric. Food Chem.* 63:7606–14

Shewan HM, Stokes JR. 2013. Review of techniques to manufacture micro-hydrogel particles for the food industry and their applications. *J. Food Eng.* 119:781–92

Shin GH, Chung SK, Kim JT, Joung HJ, Park HJ. 2013. Preparation of chitosan-coated nanoliposomes for improving the mucoadhesive property of curcumin using the ethanol injection method. *J. Agric. Food Chem.* 61:11119–26

Shishodia S, Sethi G, Aggarwal BB. 2005. Curcumin: getting back to the roots. *Ann. N. Y. Acad. Sci.* 1056:206–17

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* 64:353–56

Singh S, Aggarwal BB. 1995. Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane) [corrected]. *J. Biol. Chem.* 270:24995–5000

Subramanian AP, Jaganathan SK, Manikandan A, Pandiaraj KN, Gomathi N, Supriyanto E. 2016. Recent trends in nano-based drug delivery systems for efficient delivery of phytochemicals in chemotherapy. *RSC Adv.* 6:48294–314

Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M, et al. 2002. Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology* 123:1912–22

Takahashi M, Uechi S, Takara K, Asikin Y, Wada K. 2009. Evaluation of an oral carrier system in rats: bioavailability and antioxidant properties of liposome-encapsulated curcumin. *J. Agric. Food Chem.* 57:9141–46

Tamjidi F, Shahedi M, Varshosaz J, Nasirpour A. 2013. Nanostructured lipid carriers (NLC): a potential delivery system for bioactive food molecules. *Innovative Food Sci. Emerg. Technol.* 19:29–43

Tang JL, Ji HY, Ren JM, Li MT, Zheng NN, Wu LH. 2017. Solid lipid nanoparticles with TPGS and Brij 78: a co-delivery vehicle of curcumin and piperine for reversing P-glycoprotein-mediated multidrug resistance *in vitro*. *Oncol. Lett.* 13:389–95

Taylor TM, Davidson PM, Bruce BD, Weiss J. 2005. Liposomal nanocapsules in food science and agriculture. *Crit. Rev. Food Sci. Nutr.* 45:587–605

Teng Z, Li Y, Wang Q. 2014. Insight into curcumin-loaded beta-lactoglobulin nanoparticles: incorporation, particle disintegration, and releasing profiles. *J. Agric. Food Chem.* 62:8837–47

Ting YW, Jiang Y, Ho CT, Huang QR. 2014. Common delivery systems for enhancing in vivo bioavailability and biological efficacy of nutraceuticals. *J. Funct. Foods* 7:112–28

Tønnesen HH, Karlsen J. 1985. Studies on curcumin and curcuminoids. *Z. Für Lebensmittel-Untersuchung Und Forschung* 180:402–4

Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, et al. 2008. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. *Cancer Epidemiol. Biomark. Prev.* 17:1411–17

Vecchione R, Quagliariello V, Calabria D, Calcagno V, De Luca E, et al. 2016. Curcumin bioavailability from oil in water nano-emulsions: in vitro and in vivo study on the dimensional, compositional and interactional dependence. *J. Control. Release* 233:88–100

Venkataranganna MV, Rafiq M, Gopumadhavan S, Peer G, Babu UV, Mitra SK. 2007. NCB-02 (standardized curcumin preparation) protects dinitrochlorobenzene-induced colitis through down-regulation of NFκ-B and iNOS. *World J. Gastroenterol.* 13:1103–7

Wang S, Su R, Nie SF, Sun M, Zhang J, et al. 2014. Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals. *J. Nutr. Biochem.* 25:363–76

Wang W, Sukamtoh E, Xiao H, Zhang G. 2015. Curcumin inhibits lymphangiogenesis in vitro and in vivo. *Mol. Nutr. Food Res.* 59:2345–54

Wang YH, Yuan Y, Yang XQ, Wang JM, Guo J, Lin Y. 2016. Comparison of the colloidal stability, bioaccessibility and antioxidant activity of corn protein hydrolysate and sodium caseinate stabilized curcumin nanoparticles. *J. Food Sci. Technology-Mysore* 53:2923–32

Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, et al. 1997. Stability of curcumin in buffer solutions and characterization of its degradation products. *J. Pharm. Biomed. Anal.* 15:1867–76

Watson JL, Hill R, Lee PW, Giacomantonio CA, Hoskin DW. 2008. Curcumin induces apoptosis in HCT-116 human colon cancer cells in a p21-independent manner. *Exp. Mol. Pathol.* 84:230–33

Weiss J, Decker EA, McClements DJ, Kristbergsson K, Helgason T, Awad T. 2008. Solid lipid nanoparticles as delivery systems for bioactive food components. *Food Biophys.* 3:146–54

Wu XM, Xu JH, Huang XW, Wen CX. 2011. Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability. *Drug Dev. Ind. Pharm.* 37:15–23

Xu W, Jin WP, Zhang CL, Li ZS, Lin LF, et al. 2014. Curcumin loaded and protective system based on complex of κ-carrageenan and lysozyme. *Food Res. Int.* 59:61–66

Yada RY, Buck N, Canady R, DeMerlis C, Duncan T, et al. 2014. Engineered nanoscale food ingredients: evaluation of current knowledge on material characteristics relevant to uptake from the gastrointestinal tract. *Compr. Rev. Food Sci. Food Safety* 13:730–44

Yadav VR, Suresh S, Devi K, Yadav S. 2009. Novel formulation of solid lipid microparticles of curcumin for anti-angiogenic and anti-inflammatory activity for optimization of therapy of inflammatory bowel disease. *J. Pharm. Pharmacol.* 61:311–21

Ye FY, Lei DD, Wang SM, Zhao GH. 2017. Polymeric micelles of octenylsuccinated corn dextrin as vehicles to solubilize curcumin. *Lwt-Food Sci. Technol.* 75:187–94

Yen FL, Wu TH, Tzeng CW, Lin LT, Lin CC. 2010. Curcumin nanoparticles improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities. *J. Agric. Food Chem.* 58:7376–82

Yu HL, Huang QR. 2011. Investigation of the absorption mechanism of solubilized curcumin using Caco-2 cell monolayers. *J. Agric. Food Chem.* 59:9120–26

Yu HL, Huang QR. 2012. Improving the oral bioavailability of curcumin using novel organogel-based nanoemulsions. *J. Agric. Food Chem.* 60:5373–79

Zhang DD, Hannink M. 2003. Distinct cysteine residues in Keap1 are required for Keap1-dependent ubiquitination of Nrf2 and for stabilization of Nrf2 by chemopreventive agents and oxidative stress. *Mol. Cell Biol.* 23:8137–51

Zhang ZP, Zhang RJ, Zou L, Chen L, Ahmed Y, et al. 2016. Encapsulation of curcumin in polysaccharide-based hydrogel beads: impact of bead type on lipid digestion and curcumin bioaccessibility. *Food Hydrocolloids* 58:160–70

Zhu J, Sanidad KZ, Sukamtoh E, Zhang G. 2017. Potential roles of chemical degradation in the biological activities of curcumin. *Food Funct.* 8:907–14

Zou L, Liu W, Liu CM, Xiao H, McClements DJ. 2015a. Designing excipient emulsions to increase nutraceutical bioavailability: emulsifier type influences curcumin stability and bioaccessibility by altering gastrointestinal fate. *Food Funct.* 6:2475–86

Zou L, Liu W, Liu CM, Xiao H, McClements DJ. 2015b. Utilizing food matrix effects to enhance nutraceutical bioavailability: increase of curcumin bioaccessibility using excipient emulsions. *J. Agric. Food Chem.* 63:2052–62

Zou L, Zheng B, Liu W, Liu C, Xiao H, McClements DJ. 2015c. Enhancing nutraceutical bioavailability using excipient emulsions: influence of lipid droplet size on solubility and bioaccessibility of powdered curcumin. *J. Funct. Foods* 15:72–83

Zou L, Zheng B, Zhang R, Zhang Z, Liu W, et al. 2016a. Influence of lipid phase composition of excipient emulsions on curcumin solubility, stability, and bioaccessibility. *Food Biophys*. 11:213–25

Zou L, Zheng BJ, Zhang RJ, Zhang ZP, Liu W, et al. 2016b. Food-grade nanoparticles for encapsulation, protection and delivery of curcumin: comparison of lipid, protein, and phospholipid nanoparticles under simulated gastrointestinal conditions. *RSC Adv*. 6:3126–36

Zou Y, Zhong JJ, Pan RT, Wan ZL, Guo J, et al. 2017. Zein/tannic acid complex nanoparticles-stabilised emulsion as a novel delivery system for controlled release of curcumin. *Int. J. Food Sci. Technol.* 52:1221–28