Properties and Biological Effects of Curcumin in Food Product Development

Introduction

Curcuma longa L., commonly known as turmeric, belongs to the family of Zingiberaceae. [Citation1,Citation2] Curcuma longa L. has been used as a condiment since Ayurvedic times. This plant usually grows in tropical, subtropical, and south-eastern regions[Citation3] and contains a large variety of phytochemicals, which display pharmacological properties and have been exploited for health-promoting purposes.[Citation4–10] One example of a widely studied phytochemical is curcumin, [Citation11;Citation12] which can be obtained from turmeric. This phytochemical serves as a coloring agent and spice in food production. Apart from curcumin, other phytochemicals present in turmeric include methoxylcurcumin, cyclocurcumin, and dimethoxylcurcumin.[Citation11] Compared with studies on curcumin, those on these phytochemicals are much less, partly owing to the comparatively less effective health-promoting function of these compounds compared with curcumin.

Curcumin shows strong dyeing capacity and has an E number of E100.[Citation13] Depending on the food type, the maximal usage level of curcumin is in the range of 20–500 mg/kg food.[Citation13] In beverages, the maximum usage level can be as high as 200 mg/L.[Citation13] The accepted daily intake, as allocated by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives, is 0–3 mg/kg body weight/day.[Citation14] In addition to its use as a coloring and flavoring agent, it has been widely exploited for use in food preservation.[Citation15] Over the years, curcumin has been widely adopted as a condiment to add color and flavor to Persian and Thai dishes, and as an important ingredient in curry powder in India. When curcumin is used as a coloring agent, it exists in several forms: water-soluble curcumin, water-insoluble curcumin powder, and dispersed curcumin oil. Technologies for the production of curcumin products are currently mature. Because curcumin can be processed easily, it is widely used in confectioneries, cakes, canned foods, beverages, wine, fruit juices, pasta, and cooking dishes. It has also been used as a compound seasoning.

In fact, over the years, curcumin has been mainly used as a natural coloring agent during food production. However, this phytochemical has the potential to be repositioned as a functional agent, where its pharmacological properties could add value to the food product generated. This is partially supported by the fact that curcumin has been adopted as a wound-healing agent for millennia and has been used to treat diverse diseases in oriental medicine.[Citation16] In addition, taking advantage of the health benefits of curcumin in food products is in line with the concept of functional food development, in which foods are no longer only an entity of nutrients, but also a mediator of health benefits. In addition, curcumin can be developed as a nutraceutical in diverse forms, ranging from capsules and pills to tablets. Regarding the versatility of its use in the food industry as well as its well-supported health benefits, it is anticipated that with further understanding of the physiological and pharmacological activities of this phytochemical, curcumin will play an increasingly important role in food product development. The objective of this article is to present the latest research on curcumin as a functional food additive. We hope that this article will shed light on clearer directions for future research and for the more effective use of curcumin in the food industry.

Chemical properties of curcumin

The molecular weight of curcumin is 368.37 g mol−1, which is relatively low among polyphenols. The availability of this agent is especially high in the roots and stems of turmeric.[Citation17] Structurally, curcumin consists of two methoxyl groups, two hydroxyl

groups and two aromatic rings. [Citation18] [Citation19] It is a diferuloyl methane in which two o-methoxy phenolic OH groups are attached to the heptadiene-dione moiety. Owing to the presence of three ionizable protons, curcumin has three protonation constants.[Citation20] The three pKa values of curcumin, viz. 8.54, 9.3, and 10.69, are thought to be linked to the equilibria for deprotonation of the enolic proton and the two phenolic protons, respectively.[Citation21] Under ambient conditions, curcumin exists as powder with a distinctive smell. It gives a light-yellow color under acidic conditions and a reddish-brown color under alkaline conditions. It can also change color in the presence of Fe ions. Common physical properties of curcumin are presented in Table 1.[Citation22–27]

Table 1. Properties of curcumin.

Biochemically, curcumin performs a variety of functions, ranging from ion chelation to antioxidation,[Citation28–32] via its metabolic derivatives. The antioxidant capacity of curcumin is determined largely by the keto-enol-enolate equilibrium of its heptadiene-dione moiety,[Citation33] although the phenolic OH group or the CH2 group of the β-diketone moiety of curcumin has also been thought to play a role.[Citation20] However, the evidence supporting the latter has been contradictory. While some studies have reported, based on observations made via pulse radiolysis and diverse biochemical methods, that the phenolic OH group is responsible for the antioxidant activity of curcumin, [Citation34] [Citation35] other studies have attributed the antioxidant activity to the methylene CH2 group.[Citation36] Such discrepancy was later clarified by Indira Priyadarsini et al.,[Citation20] who compared the antioxidant activity of curcumin and dimethoxy curcumin (in which the two phenolic OH groups of curcumin were blocked, while the β-diketo structure was kept intact). By examining the extent of radiation-induced lipid peroxidation in an N2O-purged microsomal solution (pH 7.4) in the absence and presence of either curcumin or dimethoxy curcumin, dimethoxy curcumin has been found to show less antioxidant capacity. This demonstrates that the locking of phenolic OH groups can lead to a reduction in the ability of curcumin to inhibit oxidation reactions. This antioxidant property not only enables curcumin to exhibit health-promoting effects, but also allows curcumin to serve as an antioxidant to protect food products from oxidative deterioration.[Citation37]

Biological effects of curcumin for functional food development

Curcumin has been reported to display therapeutic effects in various disorders, ranging from pain disorders and liver diseases to skin diseases. [Citation2] [Citation38] For example, curcumin was shown to influence cell cycle regulation, apoptosis, tumorigenesis, metastasis, and gene expression. [Citation39] [Citation40] Administration of curcumin (440–2200 mg daily) to human subjects with advanced colorectal cancer for 4 months was confirmed to be safe.[Citation41] Concomitant administration of curcumin with luteinizing hormone analogs via the intravenous route was also confirmed to inhibit the proliferation of cancer cells and reduce the size of the tumors in mice.[Citation42] The ability of curcumin to accelerate apoptosis of cancer cells is partially attributed to its ability to inhibit the activity of extracellular signal-regulated kinases and downregulate epidermal growth factor receptor expression.[Citation43] In addition, curcumin increases the number of IFN-γ-secreting CD8+ T cells in the body, leading to a delay in tumor growth and an increase in the survival time of mice with lung cancer.[Citation44] In fact, curcumin shows a wide range of physiological properties, [Citation4] [Citation45] [Citation46] among them, its antioxidant capacity and anti-microbial ability are the two properties that have particularly attracted extensive research interest in food product development.

Antioxidant properties

Curcumin inhibits the oxidation of nutrients, such as proteins and lipids. [Citation47] [Citation48] It also acts against the oxidation of phenolic substances,[Citation49] and scavenges free radicals. Using ethyl linoleate as a model of polyunsaturated lipids, the antioxidant mechanism of curcumin in polyunsaturated lipids is thought to involve an oxidative coupling reaction at the 3'-position of curcumin with the lipid, followed by a subsequent intramolecular Diels-Alder reaction.[Citation50] Oxidation is, in fact, one of the important issues to be addressed during food preservation. This is especially true for food products (such as fishery products and fish oils) that are rich in polyunsaturated fatty acids (PUFAs).[Citation51] Oxidation of PUFAs cannot only deteriorate the sensory attributes of a food product by giving off-flavors but can also lead to a loss of nutritional value.[Citation52] The oxidation reaction is initiated by removing a hydrogen atom from an unsaturated fatty acid, leading to the formation of an alkyl radical.[Citation53] This initiation reaction can be elicited in the presence of singlet state oxygen,[Citation54] which can be generated once a food product is exposed to temperature changes or UV irradiation.[Citation54] In addition, upon reaction with O2, a peroxyl radical can be generated from an alkyl radical. It can then be further converted into a new alkyl radical and lipid hydroperoxide.[Citation55] Apart from the free radicals mentioned above, lipid oxidation produces a series of volatile compounds (such as pentanal, hexanal, 3-hydroxy−2-butanone, 2-hexenal, nonenone, 2-nonenal, dimethyl disulfide, dimethyl trisulfide, butanoic acid, and methanethiol) that can produce off-odors. [Citation53] [Citation54] Due to the capacity of curcumin to act against the oxidation of lipids and other nutrients in food products, it serves as a functional agent in food preservation.[Citation56]

Apart from acting against oxidation in food products, curcumin can serve as an antioxidant in cells. [Citation57] [Citation58] Reactive oxygen species in the body can cause oxidative damage to lipids, proteins, and nucleic acids.[Citation59] An earlier study has found that, owing to the presence of the unique phenolic hydroxyl structure, curcumin and its derivatives inhibit 2'-azodiazodihydrochloride (AAPH)- and Cu2+-induced peroxidation of low-density lipoproteins (LDL).[Citation60] Using fruit flies as a model, curcumin has been shown to prolong lifespan and enhance sports performance.[Citation61] Finally, superoxide dismutase (SOD) plays an important role in scavenging free radicals in cells to reduce oxidative stress. Curcumin increases the expression of SOD−1 and SOD−2 to act against attacks caused by free radicals.[Citation62] In addition, curcumin upregulates heme oxygenase−1 expression and protects endothelial cells against oxidative stress.[Citation63] While pristine curcumin serves as an antioxidant, curcumin forms complexes with transition metals, with the complexes generated acting as superoxide dismutase mimics to scavenge free radicals.[Citation64] These results confirm the potential use of curcumin as a functional ingredient to promote health during food product development.

Besides curcumin per se, derivatives of curcumin have shown strong antioxidant properties. This has been reported by an earlier study, in which Sahu and coworkers have developed derivatives of curcumin and evaluated their antioxidant properties.[Citation65] The results suggest that curcumin derivatives show in vitro antioxidant activity superior to curcumin when tested against superoxide and nitric oxide radicals. Moreover, curcumin derivatives have been found to show higher anticancer efficacy against cancer cell lines.[Citation65] In addition, Lal and colleagues have also synthesized curcumin derivatives (curcumin 3, 4-dihydropyrimidinones/thiones/imines) and have assessed the antioxidant and anti-inflammatory properties of the derivatives.[Citation66] The findings suggest that curcumin derivatives give a higher level of antioxidant and anti-inflammatory activity than curcumin

itself.[Citation66] More recently, Zhang and coworkers have discovered that a curcumin derivative, namely Cur20, has similar antioxidant properties and significantly higher stability than curcumin.[Citation67] In addition, zebrafish screening experiments have revealed that, compared to curcumin, Cur20 gives a substantially greater impact on inhibiting angiogenesis.[Citation67] Preclinical trials on rats have corroborated the effect of Cur20 on angiogenesis, providing further evidence for its usefulness in treating ischemia-related disorders (including vascular dementia).[Citation67] All these have indicated the potential of not only curcumin but also its derivatives in combating oxidative stress.

Antimicrobial properties

Curcumin has inhibitory effects on a wide range of microorganisms, from fungi to bacteria.[Citation68–73] Its antibacterial effect arises from its ability to interfere with bacterial metabolism and inhibit DNA replication to weaken bacterial activity.[Citation72] Owing to its amphiphilic nature, curcumin destroys the cell membrane and exhibits broad-spectrum antibacterial properties,[Citation74] thereby enabling its potential use in food safety applications. The possibility of this can be exemplified in the case of Staphylococcus aureus. Curcumin has been found to inhibit this bacterium partly by functioning as a potent inhibitor of sortase A, with an IC50 value of 13.8 ± 0.7 μg/mL.[Citation75] Sortase A plays an important role in enabling bacterial cells to adhere to host tissues. Inhibiting the activity of sortase A in Staphylococcus aureus renders the bacterial cell defective in establishing infections, although the viability of the bacterial cells is not significantly affected. [Citation76] [Citation77] As Staphylococcus aureus is one of the major bacteria causing gastroenteritis resulting from the consumption of contaminated foods,[Citation78] the inhibitory action of curcumin renders it applicable for use in preventing food-borne Staphylococcus aureus infection.

Bacillus subtilis, as well as the closely related species Bacillus pumilus and Bacillus licheniformis, are other groups of bacteria that play a role in the etiology of food poisoning.[Citation79] Curcumin has been found to induce filamentation in Bacillus subtilis 168.[Citation80] It also inhibits the formation of cytokinetic Z-rings in bacteria.[Citation80] This activity is largely attributed to the capacity of curcumin to inhibit the assembly of FtsZ protofilaments and increase the GTPase activity of FtsZ.[Citation80] In the in vitro context, curcumin has been shown to bind to FtsZ.[Citation80] All these factors allow curcumin to be used to inhibit the proliferation of bacteria for food preservation. In addition to its antibacterial properties, curcumin exhibits antifungal activity. Fungal diseases are the leading cause of pre-harvest losses in crop production.[Citation81] Curcumin has been shown to have fungicidal activity against Botrytis cineria, Phytophthora infestans, Puccinia recondita, and Rhizoctonia solani.[Citation81] Compared with fluconazole, curcumin exhibits a stronger inhibitory effect on the growth of Paracoccidioides brasiliensis.[Citation82] Curcumin is thought to mediate antifungal action partly by downregulating desaturase activity, causing a reduction in the production of ergosterol in fungal cells. This leads to oxidative stress and cell death.[Citation83]

Anticancer and anti-inflammatory properties

Curcumin inhibits carcinogenesis by inhibiting angiogenesis and tumor progression as evidenced in vitro and in vivo.[Citation84] An earlier study has reported that the incidence of noninvasive adenocarcinomas is considerably reduced by including curcumin in the diet during the progression phase.[Citation85] Recently, Kim and coworkers have discovered that curcumin displays better cytotoxic activity on A549 and H460 cells (as well as on their subtypes that are resistant to paclitaxel and cisplatin).[Citation86] Sueki and colleagues have found that curcumin can enhance the anticancer capacity of 5-aminolevulinic acid-mediated

photodynamic therapy (5-ALA-PDT) in the Caco−2 cancer cell line.[Citation87] Rayane Ganassin and coworkers have also observed that curcumin induces immunogenic cell death (ICD) in colorectal cancer CT26 cells. The findings have indicated that apoptosis occurs in curcumin-treated cells.[Citation88] X-box binding protein 1 (XBP1) expression has been found to be upregulated in CT26 cells after treatment with curcumin, indicating the effect of curcumin in inducing endoplasmic reticulum stress. This finding confirms that curcumin is an ICD inducer and may be adopted to stimulate the immune system to combat tumours.

Curcumin possesses anti-inflammatory capacity, too.[Citation89] Agents possessing such capacity usually block or inhibit the action of inflammatory agents, or induce the production of anti-inflammatory mediators. Curcumin can modulate inflammatory signalling channels and block the synthesis of inflammatory mediators.[Citation90] The ability of curcumin to suppress inflammatory gene expression is attributed to its effect in repressing the activities of nuclear factor κB (NFκB) and activator protein 1 (AP1).[Citation91] Both NFκB and AP1 are required for the lipopolysaccharide (LPS)-induced proinflammatory response. Recently, curcumin has been found to show anti-inflammatory effects in lipoteichoic acid (LTA)-stimulated microglial cells, possibly via blocking NF-κB and p38 MAPK activation and by inducing the production of Nrf1 and HO−1.[Citation92] As far as the immune response of a host is concerned, CD4+ T helper (Th) cells are an essential component; however, they may play a role in the development of inflammatory and autoimmune illnesses under specific circumstances. Curcumin can make T-regulatory cells work better, while inhibiting Th1 and Th17 cells.[Citation93] However, the effect of curcumin on Th9 and Th22 remains ill-elucidated, highlighting the need for additional research in this area. In addition, microglia become active when the brain is injured and releases cytokines and mediators (such as nitric oxide and prostaglandins) to cause inflammation.[Citation94] Curcumin inhibits the production of cyclooxygenase 2 and inducible nitric oxide synthase, which are enzymes that mediate inflammation.[Citation95] Curcumin can also inhibit the production of intercellular adhesion molecule 1 (ICAM−1) and monocyte chemoattractant protein 1 (MCP−1).[Citation95] Curcumin has been demonstrated to inhibit the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) system by stimulating Src homology 2 domain-containing protein tyrosine phosphatase 2, which is a specific inhibitor of the JAK function.[Citation95]

Metabolic fate of curcumin

Curcumin can be metabolized in both enzymatic and non-enzymatic manners. [Citation96] [Citation97] After oral ingestion, curcumin is further metabolized by conjugation and reduction (Figure 1),[Citation98] generating di-, tetra-, hexa-, and octahydrocurcumin via successive reduction of heptadienone. NADPH-dependent curcumin reductase (CurA) is produced by intestinal Escherichia coli. It can effectively degrade curcumin in the intestinal environment. [Citation99] [Citation100] After entering systemic circulation, curcumin is converted into tetra- and hexahydrocurcumin under the action of alcohol dehydrogenase in the liver. Microsomal enzymes also convert curcumin into di- and octahydrocurcumin. [Citation101] [Citation102] During curcumin metabolism, a large variety of metabolites are formed, including tetrahydrocurcumin and hexahydrocurcumin.[Citation103] However, these metabolites often exhibit weaker biological functions than curcumin, although exceptions have been reported. [Citation104] [Citation105] In plasma, curcumin also exists in the form of β-d-methylglucoside complexes and sulfates. [Citation103][Citation106] Apart from enzymatic degradation, curcumin also undergoes non-enzymatic degradation via autooxidation.[Citation96] This process is initiated by O2, which functions as the initial electron acceptor.[Citation98] During oxidative transformation, hydrogen abstraction from one of the phenolic hydroxyl groups of curcumin occurs, resulting in the formation of a phenoxyl

radical.[Citation107] This process occurs first as proton loss, followed by electron transfer from a phenolate anion to molecular oxygen. [Citation108] The major product of auto-oxidation is bicyclopentadione, which is formed by oxygenation and double cyclization of the heptadienedione chain linking the two methoxyphenol rings of curcumin (Figure 2).[Citation98] In addition to bicyclopentadione, various other products may be generated. These include dihydroxy cyclopentadione, hemiacetal cyclopentadione, ketohydroxy cyclopentadione, spiroepoxide cyclopentadione, vinylether cyclopentadione, cyclobutyl cyclopentadione, and diguaiacol.[Citation98]

Figure 1. Metabolic and degradation pathways of curcumin: (a) reduction; (b) conjugation; (c) oxidation; (d) cleavage.

Figure 2. The process of formation of bicyclopentadione during autoxidation of curcumin. Reproduced from Ref. [Citation98] with permission from American Chemical Society.

The chemical stability of curcumin is affected by the pH and composition of the surrounding medium.[Citation109] In general, the rate of decomposition of curcumin is higher when the surrounding medium is at a neutral pH. In addition, when curcumin is placed in a serum-free medium (pH 7.2) for 30 min at 37°C, around 90% of curcumin undergoes decomposition.[Citation109] However, if curcumin is added to a serum-containing medium, only 50% of curcumin is decomposed even after 8 h of incubation.[Citation109] This shows that the presence of serum enhances the stability of curcumin. Trans−6-(4’-hydroxy−3’−methoxyphenyl)−2,4-dioxo−5-hexenal is a major degradation product of curcumin, although compounds such as ferulic acid, feruloyl methane, and vanillin can be produced.[Citation110] Moreover, curcumin is sometimes consumed in the form of turmeric rhizome extract, in which curcuminoids (such as demethoxycurcumin and bisdemethoxycurcumin) are present. These curcuminoids have been found to enhance the chemical stability of curcumin in vitro,[Citation110] although their possible role in stabilizing curcumin in vivo is yet to be fully confirmed. The rate of curcumin metabolism is also affected by the physiological environment, in which albumin can improve the chemical stability of curcumin and make it less susceptible to autooxidation.[Citation109] After absorption into the body, curcumin undergoes glucuronidation at the phenolic hydroxyl groups.[Citation98] This blocks the hydroxyl groups required for the onset of autooxidation, thereby leading to an increase in the chemical stability of curcumin. In addition, oxidative transformation of curcumin can be stimulated by oxidative stress at inflammatory sites[Citation98] and by peroxidases, which use curcumin as a reducing co-substrate.[Citation107]

Strategies to enhance the bioavailability of curcumin in functional food development

Despite its health-promoting effects and potential use in functional food development as depicted in preceding sections, applications of curcumin have limitations. Curcumin generally has poor chemical stability and a low absorption rate. These problems partly lead to a reduction in oral bioavailability of curcumin. Apart from its poor oral bioavailability, curcumin shows poor aqueous solubility, dispersibility, and high susceptibility to degradation (caused by heat, light, and oxygen) during food processing.[Citation13] These factors all severely limit the application potential of curcumin in food product development. Over the years, various strategies have been adopted to formulate curcumin (Table 2).[Citation111–127] For example, electrohydrodynamic atomization has previously been adopted to generate curcumin-encapsulated zein nanoparticles.[Citation128] Compared with unmodified curcumin, those nanoparticles have exhibited better dispersibility and coloring ability in semi-skimmed milk, thereby exhibiting high potential to be used as a coloring ingredient in beverages.[Citation128]

Apart from this, curcumin nanoemulsions have been developed by using sodium caseinate as an emulsifier.[Citation129] These nanoemulsions have been found to be stable throughout a wide range of processing conditions,[Citation129] with ice cream being one of the suitable food systems for delivering curcumin nanoemulsions.[Citation129] Further research is needed to explore possible applications of these emulsions in food product development. Recently, the possible use of different curcumin formulations (including curcumin powder, water-dispersible curcumin, and nanoencapsulated curcumin) as yogurt colorants has been tested. Among these formulations, curcumin powder has been found to show the highest antioxidant, anti-inflammatory, and cytotoxic effects.[Citation130] Compared to free curcumin, curcumin in curcumin formulations shows high stability.[Citation130] Once it is added into a yogurt, it does not change the nutritional value or fatty acid profile of the yogurt, but shows better colour homogeneity and dispersibility than free curcumin.[Citation130]

Table 2. Examples of formulated curcumin reported for enhanced bioavailability.

Curcumin has also been formulated as an organogel-based nanoemulsion in which Tween 20 has been selected as the emulsifier. Compared with unformulated curcumin, the generated curcumin-containing nanoemulsion has led to a 9-fold increase in the oral bioavailability of curcumin in mice.[Citation131] In addition, using ultrasonication, curcumin-containing nanoemulsions consisting of lecithin, Tween 80, and medium-chain triglycerides have been generated.[Citation132] Compared with native curcumin whose water dispersibility is around 0.39 ± 0.05 μg/mL, the water dispersibility of formulated curcumin has been reported to be increased by 1,400 times.[Citation132] To further enhance the stability of the nanoemulsion droplets, the droplets have been coated with chitosan. After incorporating the coating, rough and irregular structures have been observed on the smooth surface of the nanoemulsion droplets (Figure 3). Owing to its protective effect, the coating enables formulated curcumin to be more resistant to thermal and UV irradiation treatments.[Citation132] A similar observation of the effect of nanoemulsions to stabilize curcumin has been made by Wang et al.,[Citation133] who have reported the success of incorporating curcumin into oil-in-water emulsions to maintain the stability of curcumin at pH 5.0–5.5 for seven days. More recently, upon formulation of curcumin into nanoemulsions consisting of Tween 80, lecithin, ethyl oleate, and water, degradation of curcumin at pH 5.9 has been prevented during a storage period of two months.[Citation134] All these results confirm the possibility of enhancing the practical potential of curcumin upon formulation for applications in food product development.

Figure 3. Transmission electron microscopy images of (a) uncoated nanoemulsion droplets, as well as those coated with (b) low molecular weight chitosan, (c) medium molecular weight chitosan and (d) high molecular weight chitosan. Scale bar = 100 nm. Reproduced from Ref. [Citation132] with permission from Elsevier B.V.

Nanoemulsions can be converted from a liquid state into a dried particulate form using various techniques to further enhance the ease of handling. A good example of these techniques is freeze-drying, which has been applied for microencapsulation of curcumin to enhance the resistance of curcumin against acidity and heat and to improve the stability of curcumin in carbonated beverages.[Citation135] Another technique is spray drying, which protects chemically unstable compounds inside a matrix formed by the wall material.[Citation136] Because the wall material can function as a barrier to protect the compounds from external environmental influences, this enhances the stability of the compounds.[Citation136] The possible use of spray drying in microencapsulation of curcumin has been partially demonstrated by an earlier study,[Citation137] in which curcumin-loaded nanocarriers

clustered into hollow porous microspheres consisting of acacia gum and xanthan gum have been generated using the spray drying technique. Using hamsters as a model, the nanocarriers have been found to adhere more preferentially to the small intestine (Figure 4), thereby promoting intestinal absorption while reducing curcumin degradation in the stomach. In another study, curcumin microcapsules have been produced via spray drying from a whey protein blend, with maltodextrin and acacia gum serving as wall materials.[Citation138] By increasing the inlet air drying temperature, the free radical scavenging activity of curcumin has been found to be enhanced, with the bulk density and moisture content of the microcapsules having been reduced.[Citation138]

Figure 4. Scanning electron microscopy images of the curcumin-loaded nanocarriers taken at different time points [(a, b) 0 h, (c, d) 6 h, (e, f) 24 h, and (g, h) 72 h] in the (a, c, e, g) stomach and (b, d, f, h) small intestine. Reproduced from Ref. [Citation137] with permission from Elsevier B.V.

In fact, after storage at 37°C and compared with native curcumin, unencapsulated curcumin has been found to undergo a more significant color change.[Citation139] This is partly attributed to the fact that microencapsulation of curcumin reduces the degradation rate of curcumin into vanillin, thereby reducing the extent of the subsequent Maillard reaction and color change.[Citation139] The possible application of spray drying to formulate curcumin has already been exploited in functional food products. This is exemplified by the case of curcumin-enriched milk cream powder.[Citation140] This powder has been generated first by microfluidization, followed by spray drying, in which either sodium caseinate or acacia gum has been used as the wall material. Compared with the spread made from acacia-gum-based curcumin-enriched milk cream powder, the one generated using the powder with sodium caseinate as the wall material has been found to give a brighter yellow color and better taste.[Citation140] This reveals the role of the design of the process of microencapsulation in determining the properties of formulated curcumin and, hence, the quality of the generated food product.

Factors to be considered in the application and processing of curcumin

Encapsulation techniques enhance the bioavailability of curcumin, but various factors play a role in influencing its effective use in practice. A good example of this is the route of administration. The possible impact of the route of administration on the bioavailability of curcumin has been demonstrated in an earlier study,[Citation141] which has shown that even after oral administration of curcumin at a dose of 1 g/kg, the serum level of curcumin in Sprague-Dawley rats has still been difficult to detect. Another study has also reported that after oral administration of curcumin at a dose of 1 g/kg to mice, the concentration of curcumin in the plasma has been found to be only as low as 0.22 μg/mL .[Citation103] Compared with oral administration, intraperitoneal injection can lead to a higher plasma level of curcumin, with the detected plasma level being 2.25 μg/mL after administration of curcumin at a 0.1 g/kg dose.[Citation103] Intravenous administration also improves the bioavailability of curcumin. While oral administration of curcumin at a dose of 500 mg/kg to rats gives the maximum concentration (Cmax) of 0.06 ± 0.01 μg/mL,[Citation142] with the time to reach the maximum concentration (Tmax) being 41.7 ± 5.4 min,[Citation142] intravenous injection of curcumin at a lower dose (10 mg/kg) can give a higher maximum serum level (0.36 ± 0.0525 μg/mL).[Citation142] Because the serum level of curcumin may be linked to the biological effect brought about by curcumin consumption, it is expected that changing the route of administration may help improve the bioavailability and, hence, the health-promoting effect of curcumin. This approach may be useful for treatment development. However, it has little

relevance in the development of curcumin-based functional food products because the oral route is the major route of food consumption.

When curcumin undergoes encapsulation, proper selection of encapsulating materials is important. This has been demonstrated in a recent study,[Citation143] which has used various polymers [including acacia gum, sodium alginate, and a chitosan derivative (generated by carboxylation of chitosan, with a deacetylation degree of 96.5%) as wall materials during spray-drying-mediated microencapsulation of curcumin. Based on the differential volume distribution, the average size of those microparticles generated from sodium alginate, modified chitosan and acacia gum is 11.7, 29.8, and 8.6 μm, respectively.[Citation143] This demonstrates the impact of the selection of wall materials on the size of the generated microparticles. In addition, different wall materials produce microparticles with different surface morphologies (Figure 5). Compared with the rough-surface microparticles produced using sodium alginate and acacia gum, those generated from modified chitosan have a smooth surface.[Citation143] These variations may partly explain the remarkable difference in the release sustainability of the generated curcumin-containing microparticles, with the time needed to achieve total release of curcumin from microparticles produced from modified chitosan, acacia gum, and sodium alginate being 35 min, 4 h, and 2 h, respectively.[Citation143] More recently, curcumin-containing emulsions stabilized with gWPI-COS nanoparticles have been reported to exhibit higher stability (and viscoelasticity) when compared with those stabilized with whey protein isolate (WPI), glycosylated whey protein isolate (gWPI), and WPI-chitooligosaccharide (COS) nanoparticles (Figure 6).[Citation144] These results demonstrate the important role played by the encapsulating material in determining the physical properties of formulated curcumin.

Figure 5. Scanning electron microscopy images of the microparticles, (a, c, e) without or (b, d, f) with being loaded with curcumin, generated from (a-b) sodium alginate, (c-d) modified chitosan, and (e-f) acacia gum. Scale bar = 3 μm. Reproduced from Ref. [Citation143] with permission from Elsevier B.V.

Figure 6. Confocal laser scanning microscopy images of emulsions stabilized by (a) WPI, (b) gWPI, (c) WPI-COS nanoparticles, and (d) gWPI-COS nanoparticles. Reproduced from Ref. [Citation144] with permission from Elsevier B.V.

In addition to the encapsulating material, the encapsulation method should be considered. This has been demonstrated in an earlier study,[Citation135] which has examined the effect of spray-drying and freeze-drying methods on the microencapsulation efficiency, stability, and various physicochemical properties of curcumin in a model beverage. Compared with spray drying, freeze-drying has been found to generally yield a higher microencapsulation efficiency and to more effectively retain the activity of curcumin.[Citation135] This is partly attributed to the fact that the processing conditions involved in freeze drying are much milder than those in spray drying.[Citation135] However, curcumin-containing microparticles generated by spray drying are smaller than those generated by freeze drying.[Citation135] In addition, spray-dried microparticles are more spherical in shape and have a smoother surface, whereas those produced by freeze-drying have a rougher surface on which more cracks can be observed. Importantly, while spray drying provides microparticles that exhibit a unimodal size distribution, freeze-drying enables the generation of microparticles with a bimodal distribution pattern.[Citation135] The comparatively small and uniform size of the spray-dried sample is due to the process of atomization. This process is absent in freeze-drying, in which the size of the generated microparticles relies largely on the grinding procedure and hence is more

polydisperse.[Citation135] Because variations in the microencapsulation efficiency, stability, and physicochemical properties (including size, size distribution, and surface morphology) may affect the functioning of formulated curcumin, proper selection of an encapsulation method is crucial to success in functional food development.

Concluding remarks and future outlook

Curcumin is a polyphenol with multiple biological effects (including antioxidant and antimicrobial activities). It has therefore been exploited not only in health promotion[Citation145–149] but also in food product development.[Citation150–152] Since the turn of the last century, advances in microencapsulation technologies have enhanced the oral bioavailability and stability of curcumin. This significantly improves the practical potential of curcumin for food product development. Despite the advances discussed above, some areas still require research to further enhance the effective use of curcumin in food applications. One of these areas is the adverse effects and long-term safety of curcumin. Although curcumin has been approved for use as a food additive,[Citation13] various adverse effects have been reported in both preclinical and clinical trials. For example, topical administration of a medicament containing curcumin has been found to cause allergic contact dermatitis[Citation153] and contact urticaria.[Citation154] Incubation of human sperms with curcumin at a dose of 30–300 μg/mL has also led to a loss of sperm mobility.[Citation155] Recently, the effects of turmeric supplements on healthy individuals, aged 21–38 years, have been examined.[Citation156] These individuals have been administered turmeric at a dose of 2.8 g for 4 weeks. Results have shown that turmeric intake increases urine oxalate excretion, raising the concern that consuming turmeric improperly can increase the urinary oxalate level and hence the risk of kidney stone formation.[Citation156] In another study, 15 individuals have been administered with curcumin at a dose of 0.45–3.6 g per day for 1–4 months.[Citation157] Some of them have experienced nausea and diarrhoea.[Citation157] The serum levels of alkaline phosphatase and lactate dehydrogenase have also been found to be increased.[Citation157] More recently, a 55-year-old female with a history of turmeric usage has been diagnosed with acute autoimmune hepatitis. After she has discontinued her long-term use of turmeric, her liver function has, however, become normal. All cases reported above have raised safety concerns regarding the use of curcumin in routine food product development.[Citation158] Other adverse effects caused by the use of curcumin are presented in Table 3.[Citation159–168] Further studies on the safety of enriching or fortifying food products with curcumin are needed. Moreover, current investigations of the toxicity of curcumin are confined to short-term studies. The long-term tolerance of human subjects with different physiological conditions (e.g., elderly people, adolescents, children, and those with chronic diseases) to different doses of curcumin is yet to be fully elucidated. Clarifying the safety profile of curcumin will help develop safer curcumin-based functional foods for different populations of consumers.

Table 3. Side effects caused by administration of different curcumin-based formulations.

Another area worth further study is the development of more effective strategies to predict the interactions between curcumin and food components. Food matrices are highly complex and heterogeneous.[Citation169] This situation is compounded by the fact that some of the food components may even change chemically during different life stages (ranging from food processing and storage to transportation) of a food product.[Citation170] These components may also potentially interact with curcumin, leading to changes in its bioactivity and stability. To date, elucidation of the possible chemical reactions between curcumin and the food components relies largely on experimental observations.[Citation171–173] Regarding the high

complexity of food matrices and the variations in compositions from product to product, studying possible interactions between curcumin and each of the food components is sometimes not practical. Further understanding of the structure-activity relationship and chemical properties of curcumin may facilitate the prediction of possible interactions between curcumin and food ingredients, streamlining the composition of food products, and enabling the development of more effective curcumin-based functional foods. Although there is still much to do to enhance the effectiveness and safety of curcumin-based food products, regarding its diverse health-promoting effects, along with the increasing sophistication in bioactive agent encapsulation[Citation174–177] and food technologies,[Citation178–181] this phytochemical will have great potential for applications in functional food development in the coming decades.

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No potential conflict of interest was reported by the author(s).

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