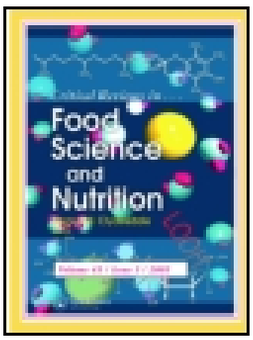

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REVIEW

Bidirectional interactions between dietary curcumin and gut microbiota

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ABSTRACT

Curcumin is a polyphenolic compound with a long history of use as an herbal remedy, dietary spice, and food-coloring agent. Despite curcumin possesses a wide range of biological and pharmacological activities, it exhibits extremely poor bioavailability, which makes its pharmacology intriguing and also hinders its clinical application. In recent years, there is ample evidence supporting the associations between the alteration of gut microbiota and many diseases. Interestingly, after oral administration, curcumin shows its preferential distribution and accumulation in the intestine. In view of the above aspects, we reviewed the updated knowledge regarding the bidirectional interactions between curcumin and gut microbiota from two perspectives: (1) gut microbiota regulation by curcumin and (2) curcumin biotransformation by digestive microbiota. Besides the study deals with 3 potential pharmacological implications: (1) identification of metabolites being more active and bioavaliable than parent curcumin; (2) assessment of contribution of gut microbiota regulation of curcumin to its pharmacological effects and (3) development of gut microbiota regulation-based disease prevention/treatment strategy for curcumin in view of its clinical safety. This review is important to deepen our understanding of the mechanisms of action of curcumin and to provide future directions about how to use this natural compound to combat human diseases.

KEYWORDS

Curcumin; Gut microbiota; Bioavailability; Interactions; Microbial biotransformation

Introduction

Curcumin is a polyphenolic compound isolated from the rhizome of the plants of the Zingiberaceae and Araceae families, and is the main active component of an Asian spice named turmeric, which has a long history of use as an herbal remedy, dietary spice, and food-coloring agent in East Asia (Ammon and Wahl 1991; Hatcher et al. 2008; Gupta et al. 2013).

The chemical structure of curcumin (1E,6E-1,7-Bis(4-hydroxi-3-methoxyphenyl)hepta-1,6-diene-3,5-diene, Figure 1) was firstly established in 1910 and confirmed by synthesis in 1913 (Miłobędzka et al. 1910; Lampe and Milobedzka 1913). Curcumin is one of the most intensively studied natural compound as evidenced by the a total number of above 10,966 citations from 1,049 till November 2017 in the literature publications, including a gradual increment in the last decade as showed by the PubMed database searched by term "curcumin" (Figure 1).

The tremendous attentions attracted by curcumin worldwide mainly arises from its wide spectrum of biological and pharmacological activities and its profound medicinal value, which includes antioxidant, antiinflammatory, antiviral, antibacterial, and beneficial effects against several types of cancers, cardiovascular diseases, diabetes, liver, and neurodegenerative diseases (Goel et al. 2008; Aggarwal and Sung 2009; De et al. 2009; Aggarwal et al. 2013; Shehzad et al. 2013; Seo et al. 2008; Aggarwal et al. 2003; Shen and Ji 2007; Kunnumakkara et al. 2017; Goozee et al. 2016; Tang and Taghibiglou 2017). In addition, curcumin has good clinical safety as evaluated by many clinical trials in humans (Lao et al. 2006; Cheng et al. 2001; Klickovic et al. 2014; Sharma et al. 2004). Several clinical studies indicated the curcumin was well tolerated even at doses as high as 12 g per day (Lao et al. 2006; Shoba et al. 1998).

In spite of its various pharmacological activities, many clinical trials indicated that curcumin possesses extremely poor bioavailability mainly arising from its low solubility and stability, and rapid metabolism (Aggarwal and Sung 2009; Anand et al. 2007; Mirzaei et al. 2017; Heger et al. 2014). For example, a phase II trial of curcumin on pancreatic cancer indicated that with a dose of 8 g per day via oral administration, the plasmatic level of free curcumin was negligible and those of glucuronated- and sulfated-curcumin metabolites were found to be only in the range of ng/ml (Dhillon et al. 2008). In a similar clinical trial with an oral dose of 3.6 g of curcumin, a plasma level as low as 11.1 nmol L^{-1} was detected an hour of after dosing (Sharma et al. 2004). In addition, curcumin has low stability and can degrade readily under conditions like aqueous phosphate buffer or serum-free medium at 37 °C (Wang et al. 1997;

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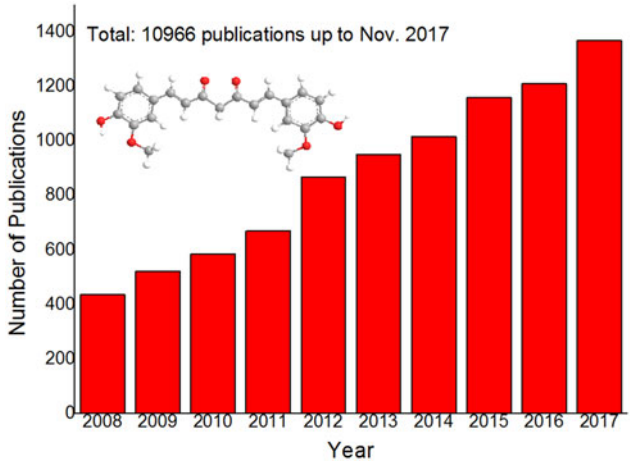

Figure 1. Increasing publications included in the Pubmed database searched by term "curcumin" in the past 10 years. A total of 10,966 publications were deposited in the PubMed database since 1949 till November 2017. The number of publications in each year increased steadily in recent years, indicating the tremendous attentions attracted by curcumin due to its diverse biological and pharmacological activities.

Shen and Ji 2012; Jankun et al. 2016; Lin et al. 2000). The paradox between the poor bioavailability of curcumin and its diverse pharmacological effects not only mystifies its pharmacology but also severely hampers its further clinical applications.

The human gut tract contains tens of trillions of microorganisms, which are estimated to include more than 1,000 bacterial species. The gut microbial community is essential for human physiology and metabolism and also for the maintenance of general health (Savage 1977; Zhernakova et al. 2016; Qin et al. 2010; Falony et al. 2016; Arboleya et al. 2012). In recent years, there are dramatically increasing studies indicating that alterations in the composition of gut microbiota are linked to a wide range of disorders, including liver, obesity, diabetes, cancers, inflammatory bowel, psoriasis, depression, and neurodegenerative diseases (Arnold et al. 2016; Harris et al. 2012; Doulberis et al. 2017; Dubinkina et al. 2017; Karlsson et al. 2013; Cammarota et al. 2015; Tang et al. 2017; Scheperjans et al. 2015; Shen et al. 2017). Thus, gut microbiota has been widely considered as a promising therapeutic target for these gut microbiota-associated diseases (Woodhouse et al. 2017; Brunkwall and Orho-Melander 2017; Maruvada et al. 2017; Wiest et al. 2017).

Of interest, in contrast with the extremely poor bioavailability in plasma and tissues, it was reported that after either oral or intraperitoneal administration, curcumin showed its preferential distribution and accumulation in the intestine, and could achieve biologically active levels (Anand et al. 2007; Ravindranath and Chandrasekhara 1980; Pan et al. 1999). In this sense, 30 min after oral administration of curcumin to rats (400 mg), 90% of curcumin accumulated in the stomach and small intestine (Ravindranath and Chandrasekhara 1980). Likewise, after intraperitoneal administration of curcumin (0.1 $g \cdot kg^{-1}$) to mice, the level of curcumin in the intestines was 177.04 $\mu g g^{-1}$ 1 hour later, which was much higher than those in other organs (Pan et al. 1999). The increased bioavailability of curcumin in the gastrointestinal tract may open a new avenue to elucidate its intriguing pharmacology.

These factors discussed above make necessary to understand comprehensively the interactions between curcumin and gut microbiota. Thus, the aim of this study was to review the current reports concerning the bidirectional interactions between curcumin and gut microbiota: (1) gut microbiota regulation by curcumin and (2) curcumin biotransformation by gut microbiota. Both will be critical to elucidate its pharmacology and direct its potential therapeutic use in gut microbiota-associated diseases.

Gut microbiota regulation by curcumin

After oral or intraperitoneal administration curcumin preferentially distributes in the intestine, and thus it is rational to infer that curcumin may exert regulative effect on the gut microbiota community, including microbial richness, diversity, and composition, which should be involved in its pharmacological effects (Shen and Ji 2016). The importance of the regulative effect of curcumin on gut microbiota has gained increasing attention very recently, as reflected by the fact that several related studies on this issue have been published in the past few years.

In this context, our group investigated the regulative effects of curcumin administration by oral delivery on the gut microbiota of C57BL/6 mice using high-throughput 16S rDNA sequencing. The results indicated that curcumin administration tended to decrease the microbial richness and diversity but without significant differences between the control and curcumin groups. However, curcumin administration exerted significant effect on the abundance of several representative bacterial families in gut microbial communities like *Prevotellaceae*, *Bacteroidaceae,* and *Rikenellaceae* (Shen et al. 2017).

In view of the proved association between the alteration of gut microbiota and the development of nonalcoholic fatty liver disease, Feng et al. investigated the involvement of gut microbiota regulation in the curcumin-mediated attenuation of hepatic steatosis in rats (Feng et al. 2017). They revealed that curcumin dramatically regulated the gut microbial composition. The altered operational taxonomic units (OTUs) by curcumin administration were associated with hepatic steatosis related parameters. Thus, the effect of curcumin on hepatic steatosis may arise in part from stain-specific impacts on hepatic steatosis associated phylotypes of gut microbiota (Feng et al. 2017).

Besides Ohno et al. studied the effects of a nanoparticle curcumin on experimental colitis in mice and found that nanoparticle curcumin increased the abundance of butyrate-producing bacteria and fecal butyrate level (Ohno et al. 2017). Thus, these authors concluded that nanoparticle curcumin administration suppressed the development of colitis potentially through modulating structure of gut microbial (Ohno et al. 2017). In this sense, a similar study by McFadden et al. explored the modulative effects of curcumin administration on colonic microbiota during colitis (McFadden et al. 2015). These authors found that curcumin

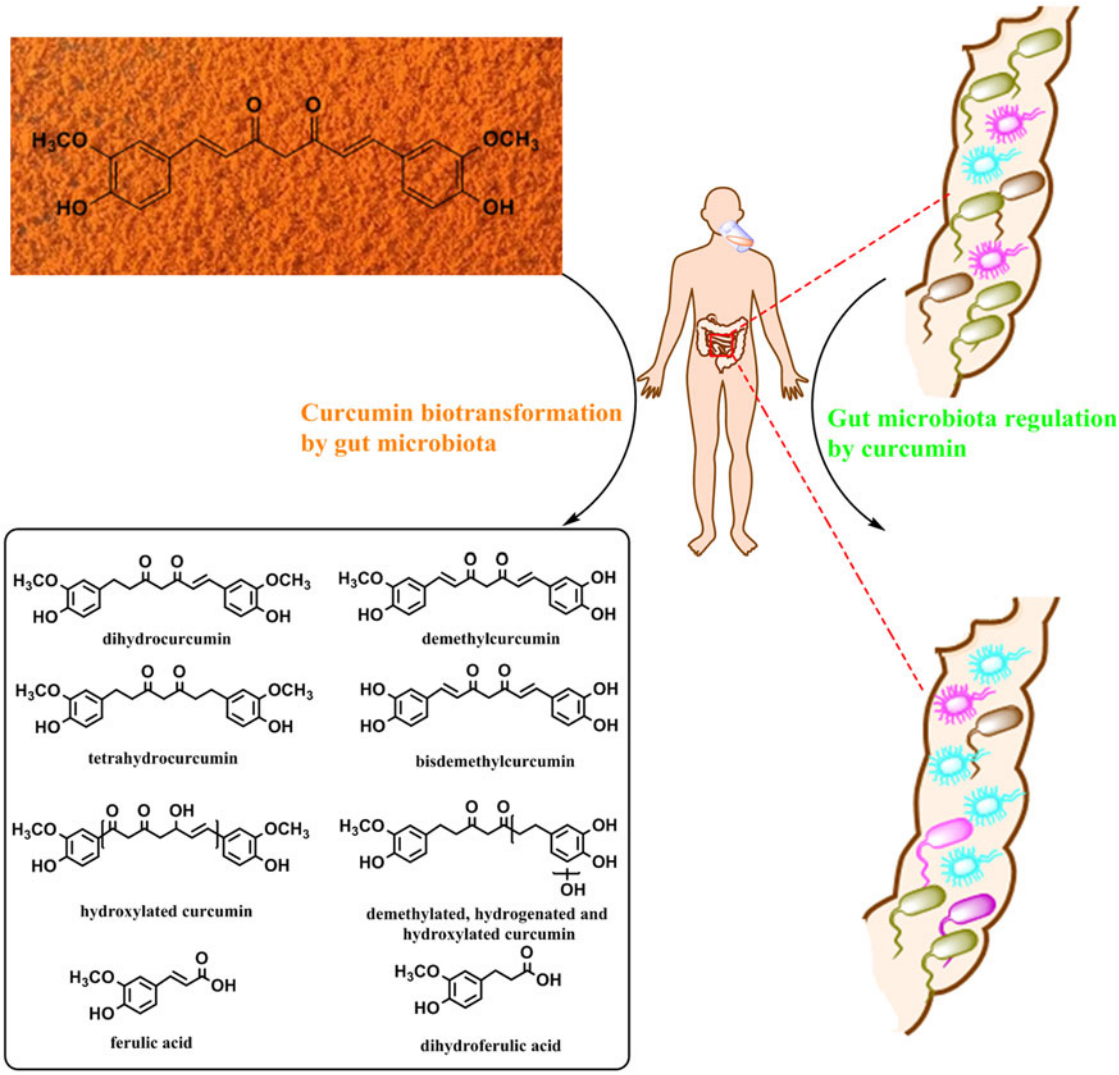

Figure 2. Schematic illustration of the bidirectional interactions between curcumin and gut microbiota. Current available evidence indicated that the interactions were reciprocal. On the one hand, curcumin is biotransformed by gut microbiota to various metabolites through pathways including demethylation, hydroxylation demethoxylation, and breakdown many of which are reported to be more bioactive and bioavaliable than parent curcumin. On the other hand, gut microbiota can be regulated by curcumin administration resulting in the alterations of microbial richness, diversity and composition, which may exert indirect health benefits.

could increase microbiota richness, prevent alpha diversity decrease, increase the proportion of *Lactobacillales* order, and decrease the proportion of *Coriobacterales* order. All these findings suggested that the benefits of curcumin on tumorigenesis were related to the maintenance of a more diverse colonic microbial ecology (McFadden et al. 2015).

Likewise, Zhang et al. explored the effects of curcumin administration on gut microbiota of ovariectomized rats using 16S rDNA sequencing (Zhang et al. 2017). These authors found that curcumin administration caused significant weight loss in ovariectomized rats, probably related to the gut microbiota modulation produced by this compound. Specially, curcumin promoted a significant increase in the number of species of seven different bacterial genus (*Serratia, Anaerotruncus, Shewanella, Pseudomonas, Papillibacter, Exiguobacterium*, and *Helicobacter*). Thus, curcumin could partially reverse changes in the diversity of gut microbiota in rats caused by estrogen deficiency induced by ovariectomy (Zhang et al. 2017).

In addition, the beneficial effects of curcumin administration have also been reported to act through improving intestinal barrier function in metabolic diseases. In recent years, the association between bacterial endotoxin lipopolysaccharide (LPS) and metabolic diseases has been reported in many studies (Pendyala et al. 2012; Cani et al. 2007; Creely et al. 2007; Genth-Zotz et al. 2002). Thereby Ghosh et al. demonstrated that curcumin supplementation could significantly attenuate the Western-diet-induced increase level of LPS in plasma. Their study suggested oral supplementation with curcumin was a potential therapeutic strategy for intestinal barrier function improvement and metabolic diseases prevention (Ghosh et al. 2014). In this sense, a recent similar study found that curcumin administration improved intestinal barrier function, by modulating intracellular signaling and the organization of tight junctions (Wang et al. 2017). All these studies suggest that curcumin may prevent metabolic diseases through a potential action mechanism involved in the regulation of the intestinal barrier function.

Curcumin biotransformation by gut microbiota

On the other hand, curcumin undergoes biotransformation by gut microbiota in the digestive tract, so it is interesting to detect and identify the biotransformation products of this natural compound. The studies concerning the biotransformation of curcumin were performed using two models: fecal slurries and single bacterial strain.

Biotransformation by fecal slurries

Tan et al. investigated the biotransformation of three curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) by human fecal microbiota using a model in vitro (Tan et al. 2015). Three main metabolites, including tetrahydrocurcumin, dihydroferulic acid and 1-(4-Hydroxy-3-methoxyphenyl)-2-propanol, were detected through the use of ultra high pressure liquid chromatography (UHPLC), coupled with a linear ion trap mass spectrometer after 24 h of fermentation (Figure 2) (Tan et al. 2015). Besides, Lou et al. employed ultra performance liquid chromatography coupled with quadrupole time of flight mass spectrometry (UPLC-Q-TOF MS)-with automated data analysis software to identify curcumin metabolites produced by human intestinal flora. A total of 23 metabolites were registered and several novel human gut microbiota curcumin metabolic pathways, via demethylation, reduction, hydroxylation, and acetylation, or the combination of these, were revealed (Lou et al. 2015).

Biotransformation by single bacterial strain

As to the biotransformation by a single strain of gut microbiota, Burapan et al. reported their findings of demethylation as an important metabolism pathway of curcuminoids (a mixture of curcumin (1), demethoxycurcumin (2), and bisdemethoxycurcumin (3)), by the human intestinal bacterium *Blautia sp.* MRG-PMF1 (Burapan et al. 2017). It was found that curcumin was converted to two new metabolites, demethylcurcumin and bisdemethylcurcumin through the methyl aryl ether cleavage reaction. Furthermore, Tan et al. studied the biotransformation of curcuminoids by *Escherichia fergusonii* (ATCC 35469) and two *Escherichia coli* strains (ATCC 8739 and DH10B) (Tan et al. 2014). Three metabolites, including dihydrocurcumin, tetrahydrocurcumin, and ferulic acid, were detected in fermentation cultures with in all the strains used. In addition, a curcumin adduct, curcumin-L-cysteine, was also identified. Likewise, a recent work explored the biotransformation of curcumin by a strain of *Bacillus megaterium* DCMB-002 isolated from mice feces (An et al. 2017). We identified seven metabolites by tracing HPLC coupled with quadrupole time-of-flight tandem mass spectra, generated through pathways of demethylation, reduction, hydroxylation, and demethoxylation, six of which were reported for the first time. Jazayeri et al. reported that six biologically relevant bacterial strains (*Bifidobacteria longum BB536*, *Bifidobacteria pseudocatenulatum G4*, *Escherichia coli K-12*, *Enterococcus faecalis JCM 5803*, *Lactobacillus acidophilus*, and *Lactobacillus casei*) were capable of degrading curcumin, with at least 56% reduction, measured at loss of the parent compound (Jazayeri et al. 2009). There are several studies regarding the microbial transformation of curcumin by a single strain from soil or yeast, with varying metabolites (Zhang et al. 2013; Zhang et al. 2010; Maehara et al., 2011).

To describe the enzymology of the metabolic pathways utilized by specific microbial species and taxa, only limited information is known so far. Hassaninasab et al. reported the purification and characterization of a unique curcumin-converting enzyme (Hassaninasab et al. 2011). The enzyme was identified as NADPH-dependent curcumin/dihydrocurcumin reductase, from *Escherichia coli* in human feces. The enzyme had a molecular mass of about 82 kDa and consisted of two identical subunits, which could reduce the double bonds of curcumin through two steps to generate dihydrocurcumin and tetrahydrocurcumin.

Conclusions and future directions

The interactions between curcumin and human gut microbiota in two main ways (Figure 2): (1) gut microbiota modulation by curcumin and (2) curcumin biotransformation by gut microbiota provide a novel understanding of its pharmacology and also useful clues to direct future studies.

Firstly, they can explain the controversy about the poor bioavailability of curcumin but its diverse pharmacological effects, not yet solved. On the one hand, the preferential distribution and accumulation of curcumin in the intestine after administration lays the foundation of the modulation of the gut microbiota composition, which may exert indirect beneficial effects on a wide variety of diseases. On the other hand, curcumin is transformed into various bioactive metabolites by gut microbiota, which may be responsible for various pharmacological activities.

Secondly, it is possible to identify more bioavailable and bioactive molecules from the biotransformed metabolites of parent curcumin. Despite the metabolites varied in chemical structures and metabolizing pathways, depending on the model chosen, many of them possess stronger pharmacological activities and better bioavailability than parent curcumin (An et al. 2017; Teymouri et al. 2018; Pinkaew et al. 2016). For instance, Tamvakopoulos et al. reported that dimethoxycurcumin had stronger *in vivo* stability and was more active killing cancer cells by apoptosis in comparison with parent curcumin (Tamvakopoulos et al. 2007). Likewise Khanna et al. reported that demethylated curcuminoid exhibited promising neuroprotective and antiinflammatory properties (Khanna et al. 2009). Similarly, Pinkaew et al. found that Di-O-Demethylcurcumin exerted a neuroprotective effect against amyloid-β peptides-induced neurotoxicity in culture neuroblastoma cells, through the suppression of nuclear factor κB and activating nuclear factor erythroid-2 (Pinkaew et al. 2016). All these findings suggest the great potential of these curcumin metabolites transformed by gut microbiota as promising agents to combat neurodegenerative diseases.

In addition, in view of the low stability of curcumin under physiological conditions, it has been hypothesized that the degradation products, e.g., feruic acid and vanillin, should make important contributions to the putative pharmacological activities observed for curcumin (Shen and Ji 2012; Jankun et al. 2016; Ji and Shen 2014; Esatbeyoglu et al. 2015). In this sense, further experiments supported that the degradation products generated by boiling and roasting parent curcumin, possess significant biological activities (Shen et al. 2016; Esatbeyoglu et al. 2015). Thus, the metabolites transformed by gut microbiota and its degradation products should be considered as an important source to identify biologically active molecules. Additionally, more studies delving into the enzymology of the metabolic pathways utilized by gut microbiota are needed to obtain more bioavaliable and bioactive metabolites of curcumin.

Thirdly, the line of evidence discussed above pave the way for future studies to develop gut microbiota-based prevention/therapy along with curcumin, for many diseases. More clinical studies are strongly encouraged to explore the effectiveness of this strategy, especially in view of the good clinical safety profile of curcumin.

In conclusion, the current knowledge concerning the bidirectional interactions between curcumin and gut microbiota is of value to explain the paradox between bioavailability and bioactivity of curcumin and also provide a new avenue for curcumin to treat human diseases.

Disclosure statement

No potential conflict of interest was reported by the authors.

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