Enhanced bioavailability and relative distribution of free (unconjugated) curcuminoids following the oral administration of a food-grade formulation with fenugreek dietary fibre: A randomised double-blind crossover study

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ABSTRACT

Despite the various reports on enhanced bioavailable formulations of curcumin, systemic oral bioavailability of unconjugated curcuminoids remains a challenge. Considering the differences in plasma bioactivity and membrane permeability of free curcuminoids over conjugated metabolites, herein we report a randomised double-blinded crossover study (n = 50) to investigate the relative bioavailability and pharmacokinetics of free curcuminoids following the oral administration of high (1000 mg) and low (250 mg) doses of a food-grade formulation of curcumin with fenugreek dietary fibre as curcumagalactomannosides (CGM), which was reported to exhibit improved blood-brain – barrier permeability in rats. CGM administration provided over 45.5-fold enhancement in free curcuminoids bioavailability when compared to unformulated standard curcumin. Further investigations with and without enzymatic hydrolysis of plasma collected over 5 h post-administration of CGM at 1000 mg dose revealed higher free curcuminoids in plasma (74 ± 8%) as compared to conjugated curcuminoids (26 ± 12%) indicating a significant distribution of free curcuminoids over conjugated curcumin metabolites.
Improved blood–brain-barrier permeability and tissue distribution following the oral administration of a food-grade formulation of curcumin with fenugreek fibre

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ABSTRACT

The delivery of significant concentrations of biologically active free curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin) at the target tissues has always been regarded as a major limitation for the efficacy of curcumin. Herein we report the blood–brain-barrier permeability, tissue distribution and enhanced bioavailability of free curcuminoids following the oral administration of a food grade curcumin formulation in comparison with the standardized native curcumin, for the first time. UPLC-ESI-MS/MS analyses of post-administration tissue samples of Wistar rats (200 mg/kg body weight) demonstrated significant (p < 0.001) enhancement in plasma bioavailability (25-fold), in vivo stability and blood–brain-barrier permeability as evidenced from the tissue distribution of free curcuminoids at, (ng/g), brain (343 ± 64.7), heart (391.7 ± 102.5), liver (445.5 ± 83), kidney (240.1 ± 47.2), and spleen (229.7 ± 42.2), with extended elimination half-life of 3 to 4 h. Standard curcumin, on the other hand, detected only 1.4 ± 0.8 ng/g of curcumin in the brain tissues.

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1. Introduction

Curcuminoids, the yellow pigment molecules of the kitchen spice turmeric (Curcuma longa L.), have shown to possess a wide spectrum of health beneficial pharmacological activities and safety profile suitable for the plausible development as a therapeutic agent and/or functional food ingredient for the prevention, control and/or treatment of a variety of pro-inflammatory diseases (Gupta, Patchva, & Aggarwal, 2013; Hamaguchi, Ono, & Yamada, 2010; Hasima & Aggarwal, 2012; Nishikawa, Tsutsumi, & Kitani, 2013). Chemically, curcumin is characterized as a bis-α,β-unsaturated β-diketone polyphenol, [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], and its commercially available natural form (commonly referred to as ‘standard curcumin’) is a mixture of three curcuminoids: curcumin (72 to 78%), demethoxycurcumin, (DMC, 12 to 18%) and bisdemethoxycurcumin, (BDMC, 3 to 8%) with purity of ≥95%. The significant pleiotropic effect emanating from its ability to interact and modulate multiple molecular...
Enhanced bioavailability and safety of curcumagalactomannosides as a dietary ingredient

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In spite of the various bioavailable formulations of curcumin for pharma and dietary supplement applications, food grade formulations suitable as a dietary ingredient, and capable of providing significant levels of plasma curcumin, are limited. The present contribution describes the safety and oral bioavailability of a novel water soluble formulation of curcumin, curcumagalactomannosides (CGM), when used as a dietary ingredient in selected food items. CGM was prepared using a food grade hydrocolloid (galactomannans) derived from the kitchen spice fenugreek (Trigonella foenum gracum), without using any synthetic excipients. The safety of the formulation was assessed through acute and subchronic toxicity studies on Wistar rats and genotoxicity studies. The efficacy of CGM as a bioavailable dietary ingredient was assessed by successfully preparing various food items and by measuring the post-blood plasma curcumin levels at various time intervals after the consumption of food items. High performance liquid chromatography coupled with a photodiode array detector (HPLC-PDA) and electrospray ionization tandem mass spectrometer (ESI-MS/MS) was employed for the quantification of plasma curcuminoids. It was observed that CGM is safe and suitable for further development and clinical studies, with a no observable adverse effect level (NOAEL) up to 2.0 g kg⁻¹ per day b.wt. CGM was found to offer seven to ten times higher bioavailability of curcumin in humans, when incorporated into various food/beverage items at 100 mg CGM per serving size, as compared to the standard unformulated curcumin.

1. Introduction

Curcuma longa L. (Turmeric) is a popular kitchen spice that has been widely used in Indian curries and medicinal preparations for thousands of years. Modern scientific research has identified many bioactive compounds in turmeric rhizomes, in which curcumin or diferuloylmethane, [1,7-bis-[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione], a hydrophobic polyphenolic compound, has been characterized as the most active component responsible for numerous health beneficial pharmacological effects.1,2 Observational studies have already delineated the dietary intake of turmeric with a reduced incidence of chronic diseases such as Cancer and Alzheimer’s in the subcontinent of India.3,4 With more than 3000 preclinical investigations on various aspects of cancer, curcumin stands as one of the best studied natural products to date; a significant promising candidate capable of selectively modulating multiple cell signaling pathways.1-4 Considering the multi-targeted mechanism of action of this promiscuous natural agent of immense therapeutic value, curcumin has emerged as an ‘yellow gold’.2 Though some food/beverage products containing curcumin are available today, the number of branded food products containing physiologically relevant amounts of curcumin per serving is limited due to the very low solubility and stability of curcuminoids in water and oil.2,6 The solubility of curcumin in aqueous buffer at pH 5.0 has been reported to be as low as 11 ng mL⁻¹.6 In addition, the poor systemic oral bioavailability of curcumin (due to its extremely low aqueous solubility, high hydrolytic instability and rapid enzymatic in vivo degradation) has also been a major limitation against the development of curcumin as a functional food ingredient or therapeutic agent.2,6,7

While the uptake and distribution of curcumin in the body is essential for its biological activity, curcumin offers only negligible quantities in plasma due to the poor absorption, permeability and rapid metabolism.2,7 The consumption of even 10 to 12 g of curcumin as capsules was reported to provide only less than 50 ng mL⁻¹ of curcumin in human plasma.8 Several attempts to overcome the problem of poor bioavailability of curcuminoids, comprising the use of adjuvants to inhibit in vivo enzymatic degradation, the formation of nanoparticles, and the formulation of phospholipid complexes and lipo-
An enhanced bioavailable formulation of curcumin using fenugreek-derived soluble dietary fibre

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ABSTRACT

Poor intestinal absorption has been regarded as a major limiting factor for the therapeutic use of curcumin, the primary active constituent of turmeric. Herein, we investigated the bioavailability of a novel formulation of curcumin-impregnated soluble dietary fibre dispersions (BR213 curcumagalactomannosides) comprising an extensive gel forming and non-digestible soluble galactomannan fibre derived from the spice fenugreek. The dispersions were prepared as microgranulates of mean particle size 150 ± 20 \(\mu\)m by an ultrasound mediated gel-phase dispersion technique. In vitro release studies at pH 1.2 and 6.8 showed slow and prolonged release of colloidal curcumin from the amorphous microgranulates of curcumin-impregnated soluble fibre. Enhanced bioavailability of the new formulation was further demonstrated in animals (Wistar rats) and human volunteers in comparison with unformulated curcumin. It was observed that the relative absorption of curcumin from the novel fibre formulation, as evident from the area under curve calculations, was 20 times higher in animals and 15.8 times higher in humans when supplemented orally. Maximum absorption was also found to be prolonged as compared to the unformulated curcumin.

1. Introduction

Turmeric (Curcuma longa L.), belonging to the family of Zingiberaceae, is a perennial herb native to India where its rhizome is used as a yellow colorant curry spice and traditional medicine. The active principle in turmeric was identified as a group of polyphenolic compounds, namely curcumin (74–78\%), demethoxycurcumin (15–18\%) and bisdemethoxycurcumin (4–6\%) commonly referred to as ‘curcumin’ (Aggarwal, Kumar, Aggarwal, & Shishodia, 2004, chap. 23). Numerous pre-clinical and clinical evaluations have confirmed many interesting bioactivities of curcumin in various disease states, including thrombosis (Srivastava, Dikshit, Srimal, & Dhawan, 1985), myocardial infarction (Nirmala & Puvanakrishnan, 1996), arthritis (Funk et al., 2006), rheumatism (Deodhar, Sethi, & Srimaal, 1980), Alzheimer’s disease (Yang et al., 2005), Crohn’s disease (Holt, Katz, & Kirshoff, 2005), diabetes (Arun & Nalini, 2002) and in various types of cancer (Aggarwal, Kumar, & Bharti, 2003; Dorai & Aggarwal, 2004; Hsu & Cheng, 2007; Kunnumakkara, Anand, & Aggarwal, 2008; Ruby, Kuttan, Babu, Rajasekharan, & Kuttan, 1995). Curcumin is hepato- and nephroprotective (Kiso, Suzuki, Watanabe, Oshima, & Hikino, 1983; Venkatesan, Punithavath, & Arumugam, 2000) with a strong capacity to reduce proliferation of a variety of malignant cells, to induce apoptosis and to suppress tumour initiation, promotion and metastasis (Dorai & Aggarwal, 2004; Kunnumakkara et al., 2008). Curcumin has shown to act mainly by down-regulating the transcription factors like NF-\(\kappa\)B, which leads to...