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The oral bioavailability of curcuminoids in healthy humans is markedly enhanced by micellar solubilisation but not further improved by simultaneous ingestion of sesamin, ferulic acid, naringenin and xanthohumol

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ABSTRACT

Curcuminoids (curcumin, demethoxycurcumin and bis-demethoxycurcumin) are poorly absorbed and rapidly metabolised and excreted. We investigated in healthy young and aged women and men if co-administration of adjuvants (sesamin, ferulic acid, naringenin, and xanthohumol) alone or in combination with micellar solubilisation improves the bioavailability of curcuminoids. A single oral dose of 98 mg curcuminoids was administered as native curcuminoids (NC), native curcuminoids plus phytochemicals (NCP), curcuminoid micelles (MC) or curcuminoid plus phytochemical micelles (MCP). Total curcuminoids were quantified in blood samples collected over 24 h. Based on the area under the curve, NCP, MC, and MCP increased the bioavailability of the major curcuminoid curcumin 8-, 88-, and 73-fold, respectively, compared to NC. No sex or age differences were observed. Thus, simultaneous ingestion of phytochemicals does modestly increase curcuminoid bioavailability, but does not enhance the large increase in bioavailability observed with micellar curcuminoids.

1. Introduction

Curcuminoids are lipophilic polyphenols present in the rhizome of the plant turmeric (*Curcuma longa Linn.*). Dried and ground turmeric contains 3–5% curcuminoids of which curcumin makes up ca. 75–80%, demethoxycurcumin (DMC) 15–20% and bis-demethoxycurcumin (BDMC) 4–8% (all by weight) (Anand, Kunnumakkara, Newman, & Aggarwal, 2007). In addition to its use as a food additive (E100) and spice, curcumin possesses numerous health beneficial effects and has been traditionally used in Ayurvedic medicine for the treatment of respiratory

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Abbreviations: AUC, area under the plasma concentration–time curve; BDMC, bis-demethoxycurcumin; C_{max}, maximum plasma concentration; DMC, demethoxycurcumin; NC, native curcuminoids; NCP, native curcuminoids and phytochemicals; MC, micellar curcuminoids; MCP, micellar curcuminoids and phytochemicals; T_{max}, time to reach the maximum plasma concentration

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and liver disorders, anorexia, rheumatism, diabetic wounds, runny nose, cough and sinusitis (Araujo & Leon, 2001). In cell culture, animal and human studies, curcuminoids exert anti-carcinogenic, anti-inflammatory and antioxidative activities (Goel, Kunnumakkara, & Aggarwal, 2008) and may therefore be useful in the prevention and treatment of disorders such as cancer, arteriosclerosis, diabetes mellitus and Alzheimer's disease (Aggarwal & Sung, 2009).

The oral bioavailability of curcuminoids, however, is low. Due to their hydrophobicity and thus poor solubility in the chyme as well as their instability at physiological and alkaline pH (Wang et al., 1997), only a small fraction of ingested curcuminoids is absorbed. In the intestine and liver, curcuminoids undergo rapid metabolism by reductases to di-, tetra-, hexa- and octahydrocurcuminoids. The reduced metabolites are conjugated predominantly with glucuronic acid and to a lesser extent sulphate to hydrophilic derivatives that facilitate their biliary and urinary excretion (Hoehle, Pfeiffer, & Metzler, 2007; Hoehle, Pfeiffer, Solyom, & Metzler, 2006; Ireson et al., 2002). The bioavailability of curcuminoids is further limited by the activity of transport proteins in the luminal membrane of enterocytes that transfer the intracellular conjugates back to the intestinal lumen. In rats and humans, only negligible amounts of orally ingested curcumin are excreted as urinary metabolites (Schiborr et al., 2014; Wahlström & Blennow, 1978), while the majority is eliminated unchanged with faeces (Wahlström & Blennow, 1978). Different strategies to increase the uptake and systemic availability of curcumin and consequently its biological activity have been investigated. One such strategy is the inhibition of curcumin metabolism with adjuvants that interfere with metabolising enzymes. In eight healthy human volunteers, the concomitant ingestion of curcumin (2 g) and piperine (20 mg) resulted in a 20-fold higher area under the plasma concentration–time curve (AUC) in comparison with curcumin alone (Shoba et al., 1998).

Other phytochemicals may also have the potential to alter curcuminoid metabolism and bioavailability. For example, ferulic acid, because of its structural similarity with curcumin (also known as diferuloylmethane), might competitively inhibit xenobiotic enzymes involved in the biotransformation of curcuminoids. Naringenin inhibits phase II enzymes, such as the UDP-glucuronosyltransferase (UGT) 1A1, conjugating curcuminoids with glucuronic acid (Williams et al., 2002) and membrane transporters exporting glucuronidated metabolites out of intestinal cells (Brand et al., 2006). Sesamin is metabolised by and modulates the activities of phase I and II enzymes, including UGT and catechol-O-methyltransferases (Yasuda et al., 2011), and in our previous animal and human studies significantly inhibited the metabolism and pharmacokinetics of vitamin E (Frank et al., 2006, 2008; Grebenstein, Schumacher, Graeve, & Frank, 2014; Kamal-Eldin et al., 2000; Ross et al., 2004). Xanthohumol is conjugated by UGT and sulphotransferases (Ruefer, Gerhauser, Frank, Becker, & Kulling, 2005) and might thus competitively inhibit the metabolism of curcuminoids by these enzymes.

Another frequently employed strategy is the administration of curcumin in the form of novel delivery systems, such as nanoparticles, liposomes, or micelles, designed to enhance its solubility and stability in the gastrointestinal tract (Kurita & Makino, 2013). The hitherto largest increase in curcumin bioavailability reported in the literature was achieved with 410 mg micellar curcumin in our recent human trial involving 23 healthy subjects, in which 185-fold larger AUC and a 455-fold higher maximum total curcumin plasma concentration (C_{max}) were observed (Schiborr et al., 2014).

In the present trial, we therefore aimed to investigate if the combination of the two strategies "co-administration of adjuvants" and "micellar solubilisation" results in synergistic enhancement of the bioavailability of curcuminoids. To this end, native or micellar curcuminoids were administered simultaneously with or without a mixture of the adjuvants sesamin, naringenin, ferulic acid, and xanthohumol, in a single-blind, crossover, human study and their pharmacokinetics followed for 24 h. The sex and age differences in the pharmacokinetics and the safety of these strategies were further examined. Both strategies, if successful, may enhance the health-beneficial potential of curcuminoids and thus spur their use as ingredients in dietary supplements and functional foods.

2. Materials and methods

2.1. *Curcumin formulations*

The native curcumin powder used for the preparation of all formulations was from Jupiter Leys (Cochin, Kerala State, India) and contained 82% curcumin, 16% demethoxycurcumin (DMC), and 2% bis-demethoxycurcumin (BDMC). The phytochemical mixture (formulations containing adjuvants) contained curcumin, sesamin (99% pure, CAS # 607-80-7), ferulic acid (≥98% pure, CAS # 1135-24-6), naringenin (≥98% pure, CAS # 480-41-1) from Intatrade Chemicals GmbH (Friedersdorf, Germany), and xanthohumol (>85% pure, CAS # 6754-58-1) from Simon H. Steiner Hopfen GmbH (Mainburg, Germany) in the ratio 2:2:1:1:1 (by weight). Silicon dioxide was used as filler in the preparations with native curcumin. The micelles consisted of 7% curcuminoid powder (equal to 6% curcumin) and 93% Tween-80 (Kolb, Hedingen, Switzerland) and were produced by AQUANOVA AG (Darmstadt, Germany). Micelles with phytochemicals consisted of 95.1% Tween-80, 1.4% curcumin, 1.4% sesamin, and 0.7% naringenin, 0.7% ferulic acid and 0.7% xanthohumol. The single dose administered with each of the formulations was 98 mg total curcuminoids and 80.36 mg curcumin, 15.68 mg DMC and 1.96 mg BDMC. Placebo capsules (see 2.2) contained micelles composed of 7% medium-chain triacylglycerols and 93% Tween-80 (AQUANOVA). All (powder and liquid) formulations were filled into LiCaps® capsules (Capsugel France SAS, Colmar Cedex, France).

2.2. *Subjects and study design*

The study protocol was reviewed and approved by the ethics committee of the State Medical Society of Baden-Württemberg (Germany) and the trial registered (NCT01982734) at ClinicalTrials.gov. Exclusion criteria included use of medications (with exception of contraceptives), pregnancy, lactation, chronic diseases, drug or alcohol abuse, smoking, use of dietary supplements, >5 h physical activity per week, or hypersensitivity to curcuminoids. Twenty-three healthy human subjects