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Curcumin - A promising nutritional strategy for chronic kidney disease patients

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ABSTRACT

Many studies have been conducted to identify therapeutic strategies to modulate inflammation and oxidative stress, complications that contribute to the increased morbidity and cardiovascular mortality in patients with chronic kidney disease (CKD). Among several non-pharmacological strategies, the use of bioactive compounds has emerged as a potential approach to reduce these complications in CKD patients. In this context, turmeric/curcumin may have positive consequences in terms of cardiovascular and nephroprotection because of its antibacterial, antiviral, anti-inflammatory and anti-oxidative effects. The aim of this review is to discuss the role of curcumin as a nutritional strategy to reduce cardiovascular risk factors as inflammation and oxidative stress in CKD patients.

1. Introduction

Chronic kidney disease (CKD) patients have many complications associated with protein energy wasting, ageing, inflamed adipose tissue, systemic inflammation and oxidative stress, which are closely related to the progression of renal failure and cardiovascular disease (CVD). Bioactive compounds present in some foods have been considered non-pharmacological nutritional strategies to combat oxidative stress and to modulate chronic inflammation in these patients (Correa et al., 2013; Pakfetrat, Akmali, Malekmakan, Dabaghimanesh, & Khorsand, 2015; Stenvinkel & Haase, 2017).

Curcumin, a natural phenolic compound extracted from the root of turmeric, used in traditional medicine in China and even more so in India, has been extensively studied because of its anti-proliferative and anti-inflammatory activities and it is thought to be a promising agent with potential applications such as in cancer prevention, cardiovascular, gastrointestinal disorders and diabetes (Hajavi et al., 2017; Khajehdehi, 2012; Ravindran, Nirmal Babu, & Sivaraman, 2007; Tapia et al., 2013). Curcumin is designated by the United States Food and Drug Administration as a food additive that is generally recognized as safe (GRAS), and it used as a supplement and sold in several forms as capsules, tablets, and energy drinks (Gupta, Patchva, & Aggarwal, 2013). There are several hypotheses that can explain the anti-inflammatory effect of curcumin as downregulation of transcription factors like cyclooxygenase-2 (COX-2), Signal transducer and activator of transcription 3 (STAT3) and IκB kinase β (IKKβ) (inhibitor of nuclear factor kappa-B - NF-kB). Curcumin seems able to decrease cytokines synthesis, improve nitric oxide (NO) bioavailability and scavenging of reactive oxygen species (ROS) that promote inflammation and oxidative stress, which are common complications in several chronic diseases, including CKD (Campbell & Fleenor, 2017; Serafini, Catanzaro, Rosini, Racchi, & Lanni, 2017; Shehzad, Qureshi, Anwar, & Lee, 2017).

However, although these actions of curcumin are promising, most studies about curcumin in CKD are still experimental and there are only few studies on turmeric supplementation in CKD patients and therefore information on the dose and time of supplementation are still uncertain. This review describes briefly the mechanisms of action of curcumin as well as discusses its use as a nutritional strategy to reduce oxidative

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stress and inflammation in CKD.

2. Chronic kidney disease

The definition and classification of CKD have evolved over time, but current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per $1 \cdot 73\ m^2$, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause (Webster, Nagler, Morton, & Masson, 2016).

There is a strong relationship between CKD and CVD, which could be explained by a typical clustering of several risk factors in CKD, such as hypertension, proteinuria, volume overload, activation of the renin-angiotensin system, and other autocrine and paracrine mechanisms (García-Trejo et al., 2016).

Moreover, in CKD patients nuclear factor erythroid-derived 2 (Nrf2) is downregulated coupled to an upregulation of NF-kB expression. Given the contribution of the impaired Nrf2 system in the pathogenesis of oxidative stress and inflammation, this adds to the imbalance between ROS production and insufficient endogenous antioxidant defense mechanisms in CKD. These common findings are considered to play a critical role in the progression of CKD and related complications, mainly the increased risk of developing CVD, which is the major cause of death in these patients (Antunovic et al., 2017; Esgalhado, Stenvinkel, & Mafra, 2017).

Many studies have been conducted in an attempt to identify therapeutics strategies to modulate inflammation and oxidative stress in CKD (Machowska, Carrero, Lindholm, & Stenvinkel, 2016). In this context, turmeric/curcumin has been linked to nephroprotection and protection against CVD because of its capacity to interact with several signaling pathways, and by exercising anti-inflammatory and anti-oxidant effects.

3. Bioavailability of curcumin

The main dietary source of curcumin is the turmeric, a member of the Zingiberaceae family. Curcumin is responsible for the bright yellow color of the turmeric root and its chemical name is 1,7-bis (4-hydroxy 3-methoxyphenyl)-1,6-heptadiene-3,5-dione (1E-6E) (Ravindran et al., 2007). Turmeric is usually used as a spice, giving flavor and natural coloring to food and its average intake by Asians varies from 0.5 to 1.5 g/day/person, which does not produce toxic symptoms (Chattopadhyay, Biswas, Bandyopadhyay, & Banerjee, 2004; Jurenka, 2009).

Since archaic times, curcumin is widely used by Chinese and Indian medicine and after many studies concluded that curcumin is an active polyphenol; numerous citations in the literature have been reported (Tyagi, Prasad, Yuan, Li, & Aggarwal, 2015). Curcumin is commercially available as capsules containing powder, extracts and curcuma-based dye. In animal studies, curcumin seems to have effects at doses of 100 and 200 mg/kg body weight in Wistar rats (Eigner & Scholz, 1999). Doses of up to 300 mg/kg were also used and no adverse effects were observed (Chainani-Wu, 2003). Animal and human studies have demonstrated that high doses of curcumin are required for significant pharmacological effects and, rats as well as humans have showed that even at high doses, curcumin is safe (Aggarwal, Chacko, & Kuruvilla, 2016; Mirzaei et al., 2017; Satyajit & Nahar, 2007). Clinical trials in humans indicate that using 1–2.5 g of curcumin per day appears to be safe. However, its bioavailability is low and the levels in plasma and target tissues are low (Bharti, Donato, & Aggarwal, 2003).

Thus a major problem associated with the use of curcumin is its low bioavailability because of slow intestinal absorption, rapid metabolism and conjugation to hydrophilic molecules in the liver with biliary excretion, poor solubility in water and clearance of the body. In addition, curcumin is not a chemically stable molecule and it is sensitive to alkaline pH, oxygen and irradiation (Aggarwal et al., 2016; Metzler, Pefeiffer, Shulz, & Dempe, 2013; Panahi et al., 2017). Thus, several strategies have been tested to improve its bioavailability such as use of liposomes or nanoparticles, chitosan, formation of self-micro emulsifying drug delivery systems, complexation with phospholipids or essential oils and, solid-lipid micro particles based technique utilizing bovine serum albumin, synthesis of structural analogues of curcumin. More recently, intranasal administration also been identified as nanotechnology to increase the bioavailability of curcumin (Aggarwal et al., 2016).

In 2011, Cuomo et al. (2011) observed that the bioavailability of curcumin could be improved with the lecithin formulation. Zhang, Tang, Xu, and Li (2013) improved the curcumin bioavailability using a curcumin-phytosome-chitosan complex microspheres, which was based on the combination of polymeric and lipid base. This system increased absorption and delayed elimination of curcumin. Purpura et al. (2017) improved the solubility, dispersibility and absorption of curcumin in healthy humans using cyclodextrins from the cyclic oligosaccharide family. Vecchione et al. (2016) showed that unformulated curcumin had no anti-inflammatory activity. However, when administered together with piperine (a pungent alkaloid found in black pepper), the curcumin given to rats (0.8 mg of curcumin per kg of rat and even at low doses as 0.2 mg of curcumin per kg), showed anti-inflammatory activities based on the reduction of several cytokines and serum lipopolysaccharides (LPS) levels. Chakraborty, Bhattacharjee, and Kamath (2017) observed that Wistar albino rats treated with a combination of curcumin (50 mg/kg) with piperine (20 mg/kg) presented better cardioprotection when compared to curcumin alone (200 mg/kg). In another study, it was observed that piperine could be used for the inhibition of UDP-glucuronyl transferase enzymes and sulfotransferases expression, which contribute to a lower absorption of curcumin and are responsible for the biotransformation of curcumin into O-glucuronide curcumin and O-sulfate curcumin (Zeng et al., 2017).

Currently, studies are lacking that could help to define specific curcumin dose requirements for CKD patients. Thus, the doses used to study the action of curcumin in CKD are usually the same as for the non-CKD population. In animal studies, doses are often between 60 and 150 mg/kg/day (Aparicio-Trejo et al., 2017; Chiu, Khan, Farhangkhoee, & Chakrabarti, 2009; Correa et al., 2013). In most studies in humans, turmeric doses used vary from 824 to 1500 mg/day (Khajehdehi et al., 2011; Moreillon et al.,2013; Pakfetrat et al., 2015; Shelmadine et al., 2017). The results obtained in these studies are summarized in Table 1.

There are no reports in the literature on the use of components that can improve the absorption and bioavailability of curcumin in CKD. Until such studies are performed one may need to accept that the strategies already studied for other conditions can be used also in CKD (Chakraborty et al., 2017; Vecchione et al., 2016; Zeng et al., 2017).

3.1. Curcumin metabolism

The metabolism of curcumin, both in phase I and in phase II, has been studied mainly *in vivo* and *in vitro* models. The phase I studies of metabolism of curcumin is described as a process of successive reduction of three double bonds of the heptadiene-3,5-dione system. The enzymes responsible for the reduction process are present in hepatocytes and enterocytes. These processes are dependent on the enzyme alcohol dehydrogenase or occur through the NADPH-cytochrome P450 reductase (Metzler et al., 2013).

The autoxidation of curcumin is initiated by H-abstraction from a phenolic hydroxyl followed by formation of a phenoxyl radical in a sequential proton loss electron transfer (SPLET) process. Once the initial radical is formed, the transformation of curcumin proceeds as a radical chain reaction resulting in stable incorporation of two oxygen atoms, one of which comes from O_2 and one from H_2O, and two cyclization reactions to form the final bicyclopentadione product (Luis et al., 2017). However, there are no studies published to date demonstrating exactly the enzymes involved in the phase I metabolism of

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