JOURNAL OF FUNCTIONAL FOODS 18 (2015) 898–909

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jff

Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials

Amirhossein Sahebkar [a,b,1], *Maria-Corina Serban* [c,1], *Sorin Ursoniu* [c], *Maciej Banach* [d,*]

[a] *Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[b] *Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia*
[c] *Department of Functional Sciences, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania*
[d] *Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland*

ARTICLE INFO

Article history:
Received 17 September 2014
Received in revised form 26 December 2014
Accepted 9 January 2015
Available online 30 January 2015

Keywords:
Superoxide dismutase
SOD
Curcumin supplementation
Curcuma longa
Oxidative stress
Curcuminoids

ABSTRACT

The aim of the meta-analysis was to evaluate the efficacy of purified curcuminoids supplementation on plasma activities of superoxide dismutase (SOD), catalase and glutathione (GSH) and lipid peroxides as parameters of oxidative stress. Seven randomized controlled trials were finally selected for the meta-analysis. There was a significant increase of serum SOD activities after curcuminoids supplementation (weighted mean difference [WMD]: 1.15 U/mL, 95% confidence interval [CI]: 0.49–1.82, $p = 0.0007$). In a subgroup analysis, no significant effects was observed in the subset of studies administering curcuminoids for <6 weeks (WMD: 0.75 U/mL, 95%CI: –0.56–2.05, $p = 0.26$), but a significant increase of SOD activities was found with supplementation duration ≥6 weeks (WMD: 1.46 U/mL, 95%CI: 0.60–2.32, $p = 0.0009$). The curcuminoids significantly reduced serum lipid peroxides (WMD: –6.35 nmol/mL, 95%CI: –11.06 to –1.64, $p = 0.008$), increased GSH concentrations (WMD: 5.39 μg/mL, 95%CI: 1.17–9.60, $p = 0.01$), and catalase activity (WMD: 51.78 U/mL, 95%CI: 15.71–87.85, $p = 0.005$). This meta-analysis showed a significant effect of curcuminoids in elevating serum SOD and catalase activities, GSH concentrations, and reduction of serum lipid peroxides.

1. Introduction

Oxidative stress is a state of imbalance between the production of reactive oxygen intermediates and the capacity of biological antioxidant defense mechanisms in favor of the former (Davies, 1995). It has been shown that oxidative stress is implicated in the pathogenesis of over 100 human disorders (Davies, 1995; Kedziora-Kornatowska et al., 2010). Superoxide anion is a biologically important reactive oxygen intermediate, with known capacity to produce other toxic species (e.g. hydrogen peroxide, peroxynitrite and peroxynitrite

* *Corresponding author.* Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland. Tel.: +48 42 639 37 71; fax: +48 42 639 37 71.
E-mail address: maciejbanach@aol.co.uk (M. Banach).

[1] Both authors contributed equally to this meta-analysis.

Abbreviations: ARE, antioxidant response element; BMI, body mass index; CI, confidence interval; CMA, comprehensive meta-analysis; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; GSH, glutathione; LDL-C, low-density lipoprotein cholesterol; PLGA, polylactic-co-glycolic acid; PRISMA, preferred reporting items for systematic reviews and meta-analysis; SOD, superoxide dismutase; SDs, standard deviations; WMD, weighed mean difference

http://dx.doi.org/10.1016/j.jff.2015.01.005
1756-4646/

degradation products) leading to oxidative stress (Fridovich, 1995). The best known physiological neutralizer of superoxide radicals is the enzyme superoxide dismutase (SOD), which converts superoxide to hydrogen peroxide, the latter being subsequently converted to H_2O through the action of glutathione peroxidase and catalase (Kowalski, Banach, Barylski, Irzmanski, & Pawlicki, 2008; Yilmaz, 2012). Some available studies have shown protective effects of exogenous SOD administration against a range of abnormalities, most importantly cancer and cardiovascular disease (CVD) (Carillon, Rouanet, Cristol, & Brion, 2013). Aside from direct chelating activity, exogenous administration of SOD has been shown to promote endogenous expression of antioxidant and anti-inflammatory elements (Nelson, Bose, Grunwald, Myhill, & McCord, 2006; Rosenfeld et al., 1996; Skarpanska-Stejnborn et al., 2011). It has been hypothesized that SOD administration can increase the nuclear-factor-E2-related factor (Nrf2)-antioxidant response element (ARE) interaction and down-regulate NF-κB expression (Carillon et al., 2013).

These positive effects have attracted increasing attention to the administration of SOD as a powerful antioxidant and anti-inflammatory drug for human diseases (Carillon et al., 2013; Davies, 1995; Rosenfeld et al., 1996). However, oral delivery of SOD like many other proteins is hampered by extremely low bioavailability which is the consequence of problems such as low intestinal permeability, lack of hydrophobicity and rapid hydrolysis by proteases in the gastrointestinal tract (Giri & Misra, 1984; Park, Kwon, & Park, 2011; Zidenberg-Cherr, Keen, Lonnerdal, & Hurley, 1983). On the other hand, parenteral routes of administration (e.g. subcutaneous, intravenous or intramuscular) are limited by the problem of low compliance. Moreover, even if SOD is safely delivered into the blood circulation, its half-life would be very short owing to rapid elimination and preferential accumulation in the renal tissue (Huber, Menander-Huber, Saifer, & Williams, 1980; Swart et al., 1999).

Aside from formulation development attempts to encapsulate SOD for oral delivery, a promising strategy to take advantage of beneficial effects of SOD is to use SOD mimetic agents with non-peptide structures (Marchiani, Rozzo, Fadda, Delogu, & Ruzza, 2014). One such agent is curcumin, a polyphenolic compound that is the pigment of the famous spice turmeric, and which has been extensively investigated with respect to its medicinal properties (Lin, 2007; Marchiani et al., 2014). Curcumin has a unique structure with phenolic hydroxyl- and methoxy-groups, which are responsible for radical scavenging activity, and a central methylenic moiety capable of H-atom donation and breaking chain oxidation reaction (Lin, 2007; Marchiani et al., 2014). This phytochemical possesses numerous pharmacological properties including protective effects against cancer (Panahi, Beiraghdar et al., 2014; Panahi, Saadat, Beiraghdar, & Sahebkar, 2014; Zlotogorski et al., 2013), inflammatory disorders (Panahi, Saadat et al., 2014; (Panahi, Sahebkar, Parvin, & Saadat, 2012; Sahebkar, 2014a; Sahebkar et al., 2013), depression and anxiety (Panahi, Badeli, Karami, & Sahebkar, 2014), atherogenic dyslipidemia (Mohammadi et al., 2013; Sahebkar, 2014b, 2014c), metabolic syndrome (Panahi, Khalili, Hosseini, Abbasinazari, & Sahebkar, 2014; Panahi, Saadat et al., 2014; Sahebkar, 2013b), Alzheimer's and Parkinson's diseases (Darvesh et al., 2012), some dermatologic disorders (Nguyen & Friedman, 2013; Panahi, Sahebkar, Amiri et al., 2012), osteoarthritis (Panahi, Rahimnia et al., 2014; Rahimnia, Panahi, Sharafi, Alishiri, & Sahebkar, 2014), and some pulmonary disorders (Panahi, Ghanei, Bashiri, Hajihashemi, & Sahebkar, 2014; Panahi, Ghanei, Hajhashemi, & Sahebkar, 2014). Antioxidant and anti-inflammatory properties are the two important mechanisms that underlie most of the pharmacological effects of curcumin (Lin, 2007; Marchiani et al., 2014). Moreover, curcumin has been shown to improve systemic markers of oxidative stress, and there is evidence that it can increase serum activities of SOD (Banach et al., 2014; Menon & Sudheer, 2007; Panahi, Sahebkar, Amiri et al., 2012); however, clinical data have not been fully conclusive (DiSilvestro, Joseph, Zhao, & Bomser, 2012; Mohajer et al., 2014). Therefore, the aim of this systematic review and meta-analysis was to assess the impact of curcuminoids supplementation on plasma activities of SOD, catalase, GSH, and lipid peroxides as parameters of oxidative stress.

2. Methods

2.1. Search strategy

This study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). PUBMED, Cochrane Library, Scopus, and EMBASE databases were searched using the following search terms in titles and abstracts (also in combination with Medical Subject Headings [MESH] terms): (superoxide dismutase or SOD) and (curcumin or curcuminoids or *Curcuma*). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature search was limited to randomized controlled trials (RCTs) carried out from January 1, 1970 to September 1, 2014. Selected articles were hand searched to identify further relevant studies. Two reviewers (AS and CS) evaluated each article separately. Disagreements were resolved by agreement and discussion with a third party (MB). Uncontrolled studies or those with results that did not consider the main objectives of the meta-analysis were omitted.

2.2. Study selection

2.2.1. Inclusion criteria

Original studies were included if they met the following inclusion criteria: (1) being a randomized clinical controlled trial in either parallel or cross-over design, (2) investigating the impact of purified curcuminoids on plasma/serum activities of SOD, (3) presentation of sufficient information on serum SOD activities at baseline and at the end of study in both curcuminoids and control groups.

2.2.2. Exclusion criteria

The studies were excluded if: (1) they had a non-randomized or uncontrolled design, (2) non-standardized curcuminoids-containing extracts were used, (3) no numerical values were