JOURNAL OF FUNCTIONAL FOODS 6 (2014) 615–622

Available at www.sciencedirect.com

ScienceDirect

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

Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial

Yunes Panahi[a], *Alireza Saadat*[b], *Fatemeh Beiraghdar*[c], *Seyyedeh Mehrabeh Hosseini Nouzari*[a], *Hamid R. Jalalian*[b], *Amirhossein Sahebkar*[d,*]

[a]*Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[b]*Department of Internal Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[c]*Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran*
[d]*Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

ARTICLE INFO

Article history:
Received 17 November 2013
Received in revised form
6 December 2013
Accepted 10 December 2013
Available online 4 January 2014

Keywords:
Curcumin
Carcinogenesis
Antioxidant
Glutathione
Superoxide dismutase
Catalase

ABSTRACT

The present study investigated the impact of a bioavailability-enhanced preparation of curcuminoids on the biomarkers of systemic oxidative stress in patients with solid tumors receiving standard chemotherapy regimens. In a randomized double blind placebo-controlled trial, eighty subjects were allocated to bioavailability-enhanced curcuminoids (900 mg/day equivalent to 180 mg/day of curcuminoids; $n = 40$) or matched placebo ($n = 40$) for a period of 8 weeks. Serum activities of superoxide dismutase (SOD) and catalase (CAT) as well as concentrations of reduced glutathione (GSH) and thiobarbituric acid reactive species (TBARS) (as malondialdehyde equivalents) were evaluated at baseline and at the end of treatment period. Health-related quality of life (QoL) score was also calculated for each patient using the University of Washington index. Supplementation with curcuminoids was associated with a significantly greater elevation in the activities of SOD and CAT, and concentrations of GSH compared to the control group ($p < 0.001$). In contrast, serum TBARS were significantly reduced by curcuminoids ($p < 0.001$). Comparison of QoL scores also revealed a beneficial effect of curcuminoids versus placebo ($p < 0.001$). Likewise, the ratio of subjects with improved QoL at the end of study was significantly higher in the curcuminoids versus the placebo group ($p = 0.003$). Supplementation with bioavailability-enhanced curcuminoids in patients with solid tumors under concurrent chemotherapy is associated with a significant improvement of systemic oxidative stress and QoL.

1. Introduction

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the capacity of biological antioxidant defense mechanisms to scavenge or detoxify these species (Sies, 1986). A persistent state of oxidative stress triggers chronic inflammation and underlies the pathogenesis of a wide variety of disorders including different types of cancer (Reuter et al., 2010). The carcinogenic effects of ROS are mainly due to the oxidation of vital biomolecules

* *Corresponding author.* Address: Biotechnology Research Center, Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, P.O. Box: 91779-48564, Iran. Tel.: +98 5118002288; fax: +98 5118002287.
E-mail addresses: sahebkara@mums.ac.ir, amir_saheb2000@yahoo.com (A. Sahebkar).
1756-4646/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jff.2013.12.008

e.g. DNA, RNA, lipids and proteins, and impairment of several signaling pathways (Reuter et al., 2010; Sosa et al., 2013). Aside from pro-oxidant species that are produced during the process of carcinogenesis, a considerable oxidative burden is generated by chemotherapy agents such as anthracyclines and platinum-based drugs, which causes several adverse events such as cardio-, nephro-, oto- and neuro-toxicities (Alberts & Noel, 1995; Taguchi et al,, 2005). Given the detrimental effects of oxidative stress on the quality of life (QoL) and outcomes of cancer patients, antioxidant therapy is regarded as a potential therapeutic option to counteract damaging effects of free radicals (Fuchs-Tarlovsky, 2013).

Curcuminoids, comprising curcumin, demethoxycurcumin and bisdemethoxycurcumin, are bioactive polyphenols derived from dried ground rhizomes of *Curcuma longa* L. (turmeric). Numerous pharmacological activities and health benefits have been reported for curcuminoids (Basnet & Skalko-Basnet, 2011; Darvesha et al., 2012; Gupta et al., 2011; Gupta et al., 2013a,b; Hasima & Aggarwal, 2012; Hu et al., 2013; KunnumakkarA et al., 2009; Mohammadi et al., 2013; Nishikawa et al., 2013; Panahi et al., 2012a,b; Ravindran et al., 2009; Sahebkar, 2010; Sahebkar, 2013a,b; Sahebkar et al., 2013; Shehzad et al., 2013a; Shigeshiro et al., 2013; Steward & Gescher, 2008). Among these activities are chemopreventive and anti-tumor properties that are the consequence of interaction of curcuminoids with multiple molecular targets and modulation of several signaling pathways involved in tumor initiation, promotion and progression (Basnet & Skalko-Basnet, 2011; Shehzad et al., 2013a; Steward & Gescher, 2008). Curcuminoids induce pro-apoptotic proteins (p53 and caspases) but down-regulate anti-apoptotic ones (BCL-2 and BCL-X_L), reduce the expression of pro-inflammatory cytokines (e.g. tumor necrosis factor-α (TNFα), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), IL-2, IL-6, IL-8 and IL-12) via suppression of the NF-κB pathway, inhibit the expression of cyclooxygenase-2 and matrix metalloproteinases (MMPs), and suppress cell proliferation via down-regulating cyclin D1, β-catenin and Akt (Shehzad et al., 2010). Along with the above-mentioned effects, curcuminoids are effective in counterbalancing oxidative damage via re-inforcing biological antioxidant defense mechanisms such as induction of pro-oxidant-detoxifying enzymes and activation of Nrf2-HO-1 axis (Panahi et al., 2012b; Sahebkar et al., 2013b; Yin et al., 2012), and scavenging of free radicals (Ak & Gülçin, 2008). The antioxidant effects of curcuminoids and established anti-inflammatory properties of these phytochemicals (Shehzad et al., 2013b) make them promising candidates for cancer therapy (Gupta et al., 2013a,b; Shehzad et al., 2013a). In addition to their multimodal anti-cancer actions, curcuminoids have an excellent safety profile and are well tolerated even at very high doses (Cheng et al., 2001). However, effectiveness of supplementation with curcuminoids in cancer patients needs to be verified by randomized controlled trials. Therefore, the present study set out to investigate the impact of supplementation with a bioavailability-enhanced curcuminoid preparation on the biomarkers of systemic oxidative stress in patients with solid tumors receiving standard chemotherapy.

2. Methods

2.1. Subjects

This study was conducted in the Oncology Clinic of the Baqiyatallah Hospital, Tehran, Iran. Inclusion and exclusion criteria are summarized in Table 1.

2.2. Design

This study was designed as a randomized double-blind placebo-controlled trial. Subjects who met the inclusion criteria were allocated to either curcuminoids (180 mg/day) ($n = 40$) or matched placebo ($n = 40$) for a period of 8 weeks. All patients were receiving standard chemotherapy treatment that was continued during the trial. Curcuminoids were administered in the phytosomal form (Meriva®; Indena S.p.A, Pescana, Italy). The selection of dose was based on the previous clinical trials with Meriva® and the manufacturer's guide for the optimal dose of this product (Allegri et al., 2010; Ledda, et al., 2012; Mazzolani, 2012; Mazzolani & Togni, 2013). Meriva® is a patented formulation of curcuminoids which takes the advantage of complexation of curcuminoids with soy phosphatidylcholine (lecithin) in a 1:2 weight ratio, in order to address the problem of low systemic absorption (Cuomo et al., 2011; Marczylo et al., 2007). The complex also contains 2 parts of microcrystalline cellulose in order to increase the flowability of the powder. The final content of curcuminoids in Meriva® is 20%. Meriva® that is prepared based on the phytosome technology which includes dispersion of curcuminoid-containing extract in the lecithin matrix, followed by solvent evaporation.

Table 1 – Inclusion and exclusion criteria of the study.

Inclusion criteria
Men and women aged 25–65 y
Presence of solid tumors documented by clinical, paraclinical and histopathological evidence
Exclusion criteria
History of hypersensitivity to herbal preparations
Not taking the study medication for more than two weeks
Intolerance to chemotherapy
Exacerbation of disease to an uncontrollable level
Occurrence of severe adverse events during treatment