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Adjuvant Therapy with Bioavailability-Boosted Curcuminoids Suppresses Systemic Inflammation and Improves Quality of Life in Patients with Solid Tumors: A Randomized Double-Blind Placebo-Controlled Trial

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Curcuminoids are bioactive polyphenolics with potent antiinflammatory properties. Although several lines of *in vitro* and preclinical evidence suggest potent anticancer effects of curcuminoids, clinical findings have not been conclusive. The present randomized double-blind placebo-controlled trial aimed to evaluate the efficacy of curcuminoids as adjuvant therapy in cancer patients. Eighty subjects with solid tumors who were under standard chemotherapy regimens were randomly assigned to a bioavailability-boosted curcuminoids preparation (180 mg/day; $n = 40$) or matched placebo ($n = 40$) for a period of 8 weeks. Efficacy measures were changes in the health-related quality of life (QoL) score (evaluated using the University of Washington index) and serum levels of a panel of mediators implicated in systemic inflammation including interleukins 6 (IL-6) and 8 (IL-8), TNF-α, transforming growth factor-β (TGFβ), high-sensitivity C-reactive protein (hs-CRP), calcitonin gene-related peptide (CGRP), substance P and monocyte chemotactic protein-1 (MCP-1). Curcuminoid supplementation was associated with a significantly greater improvement in QoL compared with placebo ($p < 0.001$). Consistently, the magnitude of reductions in TNF-α ($p < 0.001$), TGFβ ($p < 0.001$), IL-6 ($p = 0.061$), substance P ($p = 0.005$), hs-CRP ($p < 0.001$), CGRP ($p < 0.001$) and MCP-1 ($p < 0.001$) were all significantly greater in the curcuminoids versus placebo group. In contrast, the extent of reduction in serum IL-8 was significantly greater with placebo versus curcuminoids ($p = 0.012$). Quality of life variations were associated with changes in serum TGFβ levels in both correlation and regression analyses. Adjuvant therapy with a bioavailable curcuminoid preparation can significantly improve QoL and suppress systemic inflammation in patients with solid tumors who are under treatment with standard chemotherapy protocols. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: curcumin; cancer; quality of life; inflammation; cytokine; randomized controlled trial.

INTRODUCTION

Chronic inflammation is known as a key inducer of several types of cancers for a long time. Inflammation, secondary to either microbial infection or irritation, also drives tumor progression and exacerbation of symptoms in different tissues by influencing the survival, proliferation, invasion, angiogenesis and metastasis of tumor cells and their resistance to chemotherapy and radiotherapy (Eiro and Vizoso, 2012; Hussain and Harris, 2007; Moore *et al.,* 2010). In most organs, cancer is preceded by an inflammatory disease, for example, hepatocellular carcinoma following hepatitis, colorectal cancer following ulcerative colitis and prostate cancer following prostatitis. The inter-relationship between cancer and inflammation is mediated by a panel of cytokines and other inflammatory molecules and involves both innate and adaptive immunity (Germano *et al.,* 2008; Klampfer, 2011). In this context, the NF-κB pathway is of particular importance and has been shown to be over-activated in cancer patients (Karin, 2006; Naugler and Karin, 2008). Different downstream effectors of NF-κB have been shown to promote tumor formation and progression through a variety of mechanisms including inhibition of apoptotic elimination of preneoplastic and malignant cells, recruitment of additional inflammatory cells to the tumor site and perturbation of cellular microenvironment in favor of tumor growth (Karin, 2006; Naugler and Karin, 2008). Measurement of systemic inflammatory response also predicts survival in many cancers (McMillan *et al.,* 2001) and limits patients' response to anticancer therapies (Moore *et al.,* 2010). Owing to all the aforementioned effects of inflammation, antiinflammatory agents are receiving increasing attention in cancer therapy. The most extensively studied antiinflammatory agents in cancer therapy are corticosteroids, cyclooxygenase II

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(COX-II) inhibitors, non-steroidal antiinflammatory drugs and natural products.

Curcuminoids are bioactive ingredients of the spice turmeric derived from the rhizomes of *Curcuma longa* L. (Zingiberaceae). Curcumin (bis-α,β-unsaturated b-diketone; diferuloylmethane) is the main curcuminoid that constitutes around 2–5% of turmeric content and, most frequently, 70–75% of total curcuminoids of the plant. Being structurally a polyphenol, curcumin is endowed with numerous health benefits against different disorders (Gupta *et al.,* 2013; Panahi *et al.,* 2012a; Panahi *et al.,* 2012b; Sahebkar, 2010, 2013a, 2013b; Sahebkar *et al.,* 2013; Shehzad *et al.,* 2010). Such a variety of pharmacological activities is due to the ability of this molecule to interact with different biological targets and signaling pathways (Mohammadi *et al.,* 2013; Sahebkar, 2013b). Of particular interest are the anti-apoptotic, anti-metastatic, anti-angiogenic, antiinflammatory, anti-oxidant and anti-proliferative properties that make curcumin a wonderful drug candidate for various types of cancer (Basnet and Skalko-Basnet, 2011; Shehzad *et al.,* 2010). Central to the antiinflammatory effects of curcumin is inhibition of the NF-κB pathway as a master switch in regulating inflammatory response (Shakibaei *et al.,* 2007). Curcumin achieves this inhibition via blocking the phosphorylation and degradation of IκBα by IκK, thereby preventing relocation of NF-κB into the nucleus (Jobin *et al.,* 1999). This effect of curcumin leads to the down-regulation of a panel of pro-inflammatory cytokines that are casually related to tumor formation and promotion (Jobin *et al.,* 1999; Shakibaei *et al.,* 2007). Moreover, curcumin may abrogate inflammation via NF-κB-independent mechanisms such as direct inhibition of 5-lipoxygenase, COX-II, mitogen-activated protein kinase and inducible nitric oxide synthase pathways (Strimpakos and Sharma, 2008; Zhou *et al.,* 2011).

In spite of encouraging findings in cell culture and preclinical studies, the number of published randomized controlled trials investigating the efficacy of curcuminoids as an anticancer agent has been few. Findings from phase I/II trials have implied only a modest efficacy of curcuminoids despite administering large doses (Cheng *et al.,* 2001; Dhillon *et al.,* 2008; Sharma *et al.,* 2004; Sharma *et al.,* 2001). Yet, most of these studies did not apply a strategy to overcome the extremely low bioavailability of curcuminoids, which is the main factor limiting treatment response to these phytochemicals. The present study aimed to further resolve the clinical efficacy of curcuminoid therapy in patients with solid tumors using a bioavailability-boosted formulation.

METHODS

Subjects. This study was designed as a randomized double-blind placebo-controlled trial and conducted at the Oncology Clinic of the Baqiyatallah Hospital, Tehran, Iran. Included subjects were men and women aged 25–65 years with histologically documented solid tumors. Exclusion criteria were history of hypersensitivity to herbal preparations, not taking the study medication for more than 2 weeks, intolerance to chemotherapy, exacerbation of disease to an uncontrollable level and occurrence of severe adverse events during treatment.

Included subjects were randomized to receive either curcuminoids (180 mg/day) (curcuminoids group; $n = 47$) or matched placebo (placebo group; $n = 49$) for a period of 8 weeks. All patients were under treatment with standard chemotherapy regimens of the respective cancer, and chemotherapy was maintained during the trial. Patients were visited every 2 weeks and asked about their compliance and regularity of consuming study medication as well as any experienced adverse effect. Drug was dispensed at each 2-week visit. A phytosomal preparation of curcuminoids (Meriva®; Indena S.p.A, Italy) was used for the present study. This is a delivery system containing curcuminoids complexed with phosphatidylcholine and has been shown to have a boosted pharmacokinetic profile in both rat (Marczylo *et al.,* 2007) and human (Cuomo *et al.,* 2011). The overall content of curcuminoids in Meriva® is 20%. Therefore, each patient was asked to take three 300 mg Meriva® capsules (one capsule TID) per day.

Patients were visited by a board-certified oncologist at baseline and at the end of treatment duration. The study protocol was approved by the Ethics Committee of the Baqiyatallah University of Medical Sciences, and written informed consent was obtained from all participants.

Biochemical analyses. Fasted blood samples were collected at baseline and at the end of trial. Collected samples were centrifuged at 750 g for 10 min to obtain serum. Serum samples were then kept at −80 °C until analysis. Biochemical parameters that were assessed in each sample were IL-6, IL-8, calcitonin gene-related peptide (CGRP), TNF-α, monocyte chemotactic protein-1 (MCP-1), transforming growth factor-β (TGFβ), substance P and high-sensitivity C-reactive protein (hs-CRP). Measurements were conducted using commercial enzyme immunoassay kits. Serum hs-CRP was determined using an immunoturbidimetric assay.

Quality of life assessment. Assessment of health-related quality of life (QoL) was performed using the University of Washington QoL index (UW-QoL) version 4 (Millsopp *et al.,* 2006). UW-QoL is a simple and validated scale that consists of 12 domain items, three global items and a rating of the most important domains as perceived by the patient over the past 7 days. Response to each of the 12 domains is given a score between 0 (worst QoL) and 100 (best QoL). A composite score is also calculated as the arithmetic mean of all domain scores.

Statistical analysis. Statistical analyses were performed using the SPSS software version 11.5 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean ±SD or number (%). Within-group comparisons were performed using paired samples *t*-test (in case of normal distribution of data) or Wilcoxon signed-ranks test (in case of non-normal distribution of data). Between-group comparisons were made using independent samples *t*-test (in case of normal distribution of data) or Mann–Whitney *U*-test (in case of non-normal distribution of data). Categorical variables were compared using chi-square test. Bivariate correlations between changes in the evaluated parameters during the course of study were assessed using Pearson's (in case of normal distribution of data) or

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Spearman's rank (in case of non-normal distribution of data) correlation coefficients. The impact of putative moderators (i.e., changes in serum levels of IL-6, IL-8, TNF-α, TGFβ, MCP-1, hs-CRP, CGRP and substance P) on QoL change was evaluated using stepwise multiple linear regression analysis. A two-sided p-value of <0.05 was considered to be statistically significant.

RESULTS

Eighty subjects completed the trial including 40 subjects in each group. Drop outs were due to loss to follow-up and not returning for the final visit and blood sampling (Fig. 1). There was no significant difference in drop-out rate between the study groups ($p > 0.05$). The groups were matched regarding baseline characteristics including age, weight, gender, smoking habit and history of radiotherapy ($p > 0.05$). The predominant types of cancer in both groups were colorectal cancer, gastric cancer and breast cancer. The frequency of these cancers was comparable between the groups ($p > 0.05$) (Table 1). Treatment with curcuminoids was safe and well tolerated. Eight subjects reported mild gastrointestinal side effects from curcuminoids. None of the drop outs was due to adverse reactions.

The predominant types of cancer in both curcuminoids and placebo groups were colorectal, breast and gastric cancer. Chemotherapy regimens that were commonly used for these cancers were docetaxel-cisplatin-5-FU (gastric cancer and breast cancer), topotecan-cyclophosphamide-etoposide (breast cancer), cyclophosphamide-methotrexate-5-FU (breast cancer) and 5-FU-based regimens (colorectal cancer).

Effect of curcuminoids on quality of life and biochemical parameters

The primary efficacy measure, QoL, was increased in both curcuminoids and placebo groups by the end of trial ($p < 0.001$). There were significant reductions in serum concentrations of TNF-α ($p < 0.001$ in the curcuminoids group and $p = 0.039$ in the placebo group), TGFβ ($p < 0.001$ in both groups), IL-6 ($p < 0.001$ in both groups), IL-8 ($p = 0.001$ in the curcuminoids group and $p < 0.001$ in the placebo group), hs-CRP ($p < 0.001$ in the curcuminoids group and $p = 0.039$ in the placebo group), CGRP ($p < 0.001$ in both groups) and MCP-1 ($p < 0.001$ in the curcuminoids group and $p = 0.031$ in the placebo group) in both studied groups. Serum substance P levels were only reduced in the curcuminoids group ($p < 0.001$) whilst remaining statistically unchanged in the placebo group ($p > 0.05$) (Table 2).

Between-group comparisons revealed that curcuminoids supplementation is associated with a greater improvement in the QoL compared with placebo ($p < 0.001$). Consistently, the magnitude of reductions in TNF-α ($p < 0.001$), TGFβ ($p < 0.001$), IL-6, substance P ($p = 0.005$), hs-CRP ($p < 0.001$), CGRP ($p < 0.001$) and MCP-1 ($p < 0.001$) were all significantly greater in the curcuminoids versus

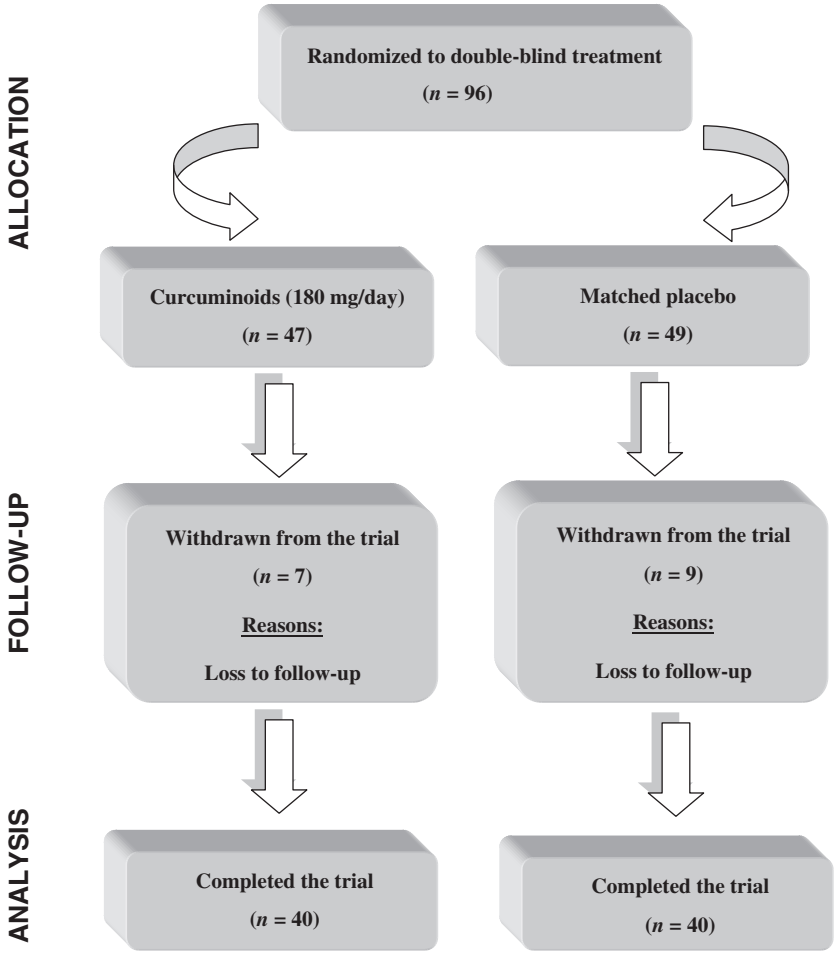

Figure 1. Flowchart of the trial.

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Table 1. Demographic characteristics of study groups

	Curcuminoids	Placebo	*p*-value
n	40	40	
Age (years)	59.58 ± 14.63	58.33 ± 16.10	0.724
Female (%)	32.5%	42.5%	0.609
Weight (kg)	68.89 ± 12.73	67.38 ± 13.85	0.630
Smoking (%)	13.5%	15.4%	0.817
Radiotherapy (%)	12.1%	22.2%	0.269
Type of cancer			
Colorectal	22.8%	30.0%	0.808%
Gastric	22.8%	16.7%	
Breast	14.2%	20.0%	
Sarcoma	2.9%	10.0%	
Lymphoma	8.6%	6.7%	
Lung	8.6%	6.7%	
Prostate	—	3.3%	
Bladder	2.9%	3.3%	
Esophagus	5.7%	3.3%	
Ovary	2.9%	—	
Testicles	5.7%	—	
Hepatocellular carcinoma	2.9%	—	

placebo group. In contrast, the extent of reduction in serum IL-8 was significantly greater with placebo versus curcuminoids ($p = 0.012$) (Table 3).

Mean difference in QoL scores was not significantly different between subgroups receiving and not receiving concurrent radiotherapy in each group ($p > 0.05$). Likewise, changes in QoL did not significantly differ in each group after stratification for the type of cancer ($p > 0.05$). Consistent with the overall analysis, comparison of changes in QoL scores between subgroups of patients with similar type of cancer in the study groups indicated a significantly greater effect of curcuminoids versus placebo (Table 4). The same findings were also found after stratification for concurrent radiotherapy (Table 4)

Bivariate correlations

In bivariate correlation analysis, changes in the QoL score were positively correlated with changes in hs-CRP ($p = 0.081$) and TGFβ ($p = 0.023$) and negatively correlated with changes in IL-6 ($p = 0.001$) in the curcumin group. In the placebo group, a positive correlation was found between changes in QoL and MCP-1 ($p = 0.045$), and negative correlations were found between changes in QoL with TNF-α ($p = 0.020$) and IL-8 ($p < 0.001$). A full description of significant and marginally significant bivariate correlations between changes in the

Table 3. Comparison of changes in the evaluated biochemical parameters between curcuminoids and placebo groups

Parameter	Curcuminoids	Placebo	*p*-value
QoL	34.23 ± 8.23	5.62 ± 5.02	<0.001
TNF-α (pg/mL)	−12.32 ± 3.97	−1.72 ± 5.00	<0.001
TGFβ (pg/mL)	−25.95 ± 8.61	−7.28 ± 5.98	<0.001
IL-6 (pg/mL)	−0.93 ± 2.31	−0.26 ± 0.37	0.061
IL-8 (pg/mL)	−1.86 ± 3.16	−4.85 ± 6.41	0.012
Substance P (pg/mL)	−1.12 ± 1.85	−0.04 ± 1.36	0.005
hs-CRP (mg/L)	−2.33 ± 2.19	−0.62 ± 1.80	<0.001
CGRP (pg/mL)	−13.91 ± 4.67	−5.46 ± 7.94	<0.001
MCP-1 (pg/mL)	−13.33 ± 8.75	2.05 ± 5.73	<0.001

QoL, quality of life; TGFβ, transforming growth factor-β; IL-6, interleukin 6; IL-8, interleukin 8; hs-CRP, high-sensitivity C-reactive protein; CGRP, calcitonin gene-related peptide; MCP-1, monocyte chemotactic protein-1.

Table 4. Comparison of changes in the quality of life score between different subgroups of curcuminoids and placebo groups stratified according to the type of cancer and receiving concurrent radiotherapy

Parameter	Curcuminoids	Placebo	*p*-value
Type of cancer			
Colorectal	35.00 ± 5.73	4.62 ± 5.85	<0.001
Breast	38.80 ± 3.56	4.67 ± 4.76	<0.001
Gastric	27.71 ± 13.07	5.40 ± 5.77	0.005
Other*	35.44 ± 6.64	6.31 ± 4.53	<0.001
Concurrent radiotherapy			
Yes	35.25 ± 8.66	3.43 ± 4.89	<0.001
No	33.41 ± 8.63	6.04 ± 5.22	<0.001

*Includes sarcoma, lymphoma, hepatocellular carcinoma and cancers of lung, prostate, bladder, esophagus, ovary and testicles.

Table 2. Impact of curcuminoids on the evaluated biochemical parameters at baseline and at the end of 8-week supplementation period

	Curcuminoids			Placebo		
Parameter	Pre-trial	Post-trial	*p*-value	Pre-trial	Post-trial	*p*-value
QoL	41.67 ± 5.98	75.90 ± 3.51	<0.001	69.69 ± 3.66	75.31 ± 4.08	<0.001
TNF-α (pg/mL)	28.03 ± 2.67	15.74 ± 2.71	<0.001	27.05 ± 4.13	25.33 ± 3.05	0.039
TGFβ (pg/mL)	42.82 ± 5.71	16.87 ± 6.97	<0.001	40.49 ± 4.14	33.21 ± 4.32	<0.001
IL-6 (pg/mL)	1.55 ± 2.30	0.61 ± 0.20	<0.001	1.57 ± 0.48	1.31 ± 0.44	<0.001
IL-8 (pg/mL)	21.64 ± 2.43	19.78 ± 2.31	0.001	26.23 ± 4.36	21.38 ± 3.98	<0.001
Substance P (pg/mL)	6.02 ± 1.45	4.89 ± 1.18	0.001	4.76 ± 1.23	4.72 ± 1.66	0.843
hs-CRP (mg/L)	6.96 ± 1.88	4.63 ± 2.18	<0.001	8.54 ± 1.64	7.92 ± 1.72	0.039
CGRP (pg/mL)	34.08 ± 9.11	20.17 ± 6.97	<0.001	41.64 ± 3.88	36.18 ± 7.03	<0.001
MCP-1 (pg/mL)	134.23 ± 8.38	120.90 ± 8.22	<0.001	121.77 ± 6.43	123.82 ± 7.47	0.031

QoL, quality of life; TGFβ, transforming growth factor-β; IL-6, interleukin 6; IL-8, interleukin 8; hs-CRP, high-sensitivity C-reactive protein; CGRP, calcitonin gene-related peptide; MCP-1, monocyte chemotactic protein-1.

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evaluated parameters during the course of study is summarized in Table 5.

Linear regression analysis

Stepwise linear regression analysis was used to assess the impact of changes in individual moderators on the changes in the primary efficacy measure, that is, QoL. Changes in QoL were entered into the model as the dependent variable. Predictor variables included changes in serum levels of TNF-α, TGFβ, IL-6, IL-8, substance P, hs-CRP, CGRP and MCP-1 concentrations. Changes in serum levels of TGFβ ($\beta = 0.37$, 95% confidence interval (CI): 0.05–0.63, $p = 0.02$) and IL-8 ($\beta = -0.68$, 95% CI: −0.72 to −0.34, $p < 0.001$) were found as significant predictor of QoL changes in the curcuminoids and placebo group, respectively. When a combined analysis was conducted on the study population regardless of grouping, changes in TNF-α ($\beta = -0.48$, 95% CI: −1.52 to −0.71, $p < 0.001$), MCP-1 ($\beta = -0.27$, 95% CI: −0.69 to −0.13, $p = 0.005$) and CGRP ($\beta = -0.20$, 95% CI: −0.76 to −0.08, $p = 0.016$) were found to predict QoL changes.

DISCUSSION

The present study aimed to evaluate the impact of adjuvant therapy with a bioavailability-boosted curcuminoids formulation on the QoL of patients with diagnosed solid tumors. We also aimed to look at the changes in the serum levels of a number of mediators of inflammation following curcuminoids supplementation and assess the potential relationship between biochemical alterations and changes in the overall QoL score. Interestingly, curcuminoids supplementation was found to improve QoL of patients by dramatic rates. Moreover, such an improvement was accompanied by a reducing effect on circulating levels of several inflammatory mediators.

Table 5. Bivariate correlations between changes in the evaluated parameters in curcuminoids and placebo groups

Variable # 1	Variable # 2	*r*	*p*
Curcuminoids			
QoL	IL-6	−0.531	0.001
QoL	hs-CRP	0.283	0.081
QoL	TGFβ	0.363	0.023
hs-CRP	IL-6	−0.348	0.030
CGRP	IL-6	0.273	0.092
TNF-α	TGFβ	0.351	0.031
TNF-α	IL-8	0.279	0.090
MCP-1	IL-6	0.298	0.065
MCP-1	Substance P	0.309	0.055
TGFβ	IL-6	−0.711	<0.001
Placebo			
QoL	MCP-1	0.323	0.045
QoL	TNF-α	−0.371	0.020
QoL	IL-8	−0.682	<0.001
hs-CRP	CGRP	0.357	0.026
hs-CRP	TGFβ	0.303	0.060
IL-6	Substance P	−0.385	0.015
IL-8	Substance P	−0.274	0.092
IL-8	TNF-α	0.538	<0.001

QoL, quality of life; TGFβ, transforming growth factor-β; IL-6, interleukin 6; IL-8, interleukin 8; hs-CRP, high-sensitivity C-reactive protein; CGRP, calcitonin gene-related peptide; MCP-1, monocyte chemotactic protein-1.

The causal relationship between inflammation with neoplastic transformation and tumorigenesis is supported by a large body of evidence (Eiro and Vizoso, 2012; Hussain and Harris, 2007; Moore *et al.,* 2010). An inflammatory milieu often underlies aberrations in proto-oncogenes and tumor suppressor genes and contributes to tumor formation and promotion (Eiro and Vizoso, 2012). NF-κB is a key transcription factor that can be considered at the crossroad of inflammation and cancer. Hence, inhibition of NF-κB pathway and its downstream pro-inflammatory, anti-apoptotic, angiogenic and metastatic products is an attractive and viable option to fight cancer (Yamamoto and Gaynor 2001).

Curcumin is one of the strongest inhibitors of the NF-κB pathway and is known to modulate several biomarkers of inflammation, oxidative stress, apoptosis and tumor growth in cancer patients (Usharani *et al.,* 2008; Hu *et al.,* 2010; Aggarwal *et al.*, 2013; Gupta *et al.,* 2013). There is clinical evidence indicating that supplementation with curcuminoids is associated with a reduction of TNF-α, prostaglandin E2, M_1G (a biomarker of DNA adduct formation), glutathione S-transferase, Bcl-2 and p53 whilst increasing Bax in colorectal cancer (Garcea *et al.,* 2005; Sharma *et al.,* 2004; Sharma *et al.,* 2001; Yamamoto and Gaynor ,2001); reduction of IL-6, IL-8, IL-10, NF-κB, COX-II, STAT-3 and malonedialdehyde (MDA) whilst increasing reduced glutathione in pancreatic cancer (Durgaprasad *et al.,* 2005; Ide *et al.,* 2010); reduction of NF-κB, COX-II and STAT-3 in multiple myeloma (Golombick *et al.,* 2009); reduction of MDA and 8-hydroxydeoxyguanosine whilst increasing vitamins C and E in patients with cancer lesions (Rai *et al.,* 2010); reduction of plasma free radicals in a mixed population of cancer patients (Golombick *et al.,* 2013); and reduction of IκKβ and IL-8 in head and neck cancer (Gupta *et al.,* 2013; Kim *et al.,* 2011). Notwithstanding these biochemical improvements, the efficacy of curcuminoids in reducing clinical outcomes has been controversial. Belcaro *et al.* (2013) reported a significant effect of 4-month treatment with Meriva® in improving QoL and reducing the burden side effects associated with chemotherapy or radiotherapy in 160 cancer patients. Combination therapy with curcuminoids (480 mg) and quercetin (20 mg) for 6 months was reported to reduce both the size and number of colorectal polyps in a small study in five patients with familial adenomatous polyposis (Cruz-Correa *et al.,* 2006). In another non-randomized open-label study in 41 smokers with aberrant crypt foci on colonoscopy, 30-day curcuminoids supplementation reduced the number of foci at a daily dose of 4 g but not 2 g (Carroll *et al.,* 2011). In a phase I dose escalation trial in nine patients with advanced metastatic breast cancer, combination of curcuminoids (500–8000 mg/day) and docetaxel was associated with a partial response in about 50% of subjects (Bayet-Robert *et al.,* 2010). A phase I/II uncontrolled trial investigated the efficacy of curcuminoids (at ranging doses up to 8 g/day) as adjunct to gemcitabine-based chemotherapy in 21 gemcitabine-resistant patients. The median survival rate was found to be only 19%, and no patient

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experienced either complete or partial therapeutic response (Kanai *et al.,* 2011). Another similar study evaluated the activity and feasibility of gemcitabine in combination with curcuminoids (4000–8000 mg/day) in patients with advanced pancreatic cancer. Again, the proportion of patients achieving a partial response (9%) was in minority, and most patients (55%) had tumor progression (Epelbaum *et al.,* 2010). Chainani-Wu *et al.* investigated the efficacy of curcuminoids (2000 mg/day) in alleviating the symptoms of oral lichen planus in a randomized double-blind placebo-controlled trial. However, the trial was terminated prematurely because of the lack of significant difference in clinical signs between curcuminoids and placebo groups (Chainani-Wu *et al.,* 2007). The efficacy of curcuminoids was also investigated by two phase I trials by Sharma *et al.*, each recruiting 15 subjects with advanced colorectal cancer refractory to standard chemotherapy. The results of these trials indicated radiologically stable disease in only a minor proportion of study patients [5/15 in (Sharma *et al.,* 2001) and 2/15 in (Sharma *et al.,* 2004)].

The mild-to-modest therapeutic response to curcuminoids in different types of cancer contradicts the remarkable anti-tumor properties of these phytochemicals in cell culture and preclinical studies (Gupta *et al.,* 2013; Shehzad *et al.,* 2013). A plausible explanation for this inconsistency is the poor bioavailability of curcuminoids in human, which is generally regarded as the main obstacle for their clinical application (Anand *et al.,* 2007). Almost all of the studies described earlier used crude curcuminoids that have inherently low systemic bioavailability. To meet the bioavailability limitation, several strategies have been tested including liposomal encapsulation, synthesis of structural analogs, formulation into polymeric microparticles and nanoparticles, co-administration with piperine and complexation with phosphatidylcholine (lecithin) (Anand *et al.,* 2007). Among these methods, the last two approaches have been studied more extensively, and the clinical results have turned out to be promising. However, the relevance of co-administration with piperine may be argued because of the strong inhibitory effects of piperine on enzymes involved in both phase I and II drug metabolism (Bhardwaj *et al.,* 2002; Srinivasan, 2007). This will increase the risk of drug interactions, which is especially important for patients taking chemotherapy cocktail regimens (Burgos-Moron *et al.,* 2010; Mancuso and Barone, 2009). Unlike piperine, co-administration of curcuminoids with phosphatidylcholine does not introduce additional risk of drug interactions but enhances the bioavailability via preserving from hydrolytic degradation and increasing intestinal absorption (Barry *et al.,* 2009; Semalty *et al.,* 2010). The present study took advantage of such an optimized formulation (Meriva®), and as referred earlier, almost all evaluated parameters (including the QoL index) were significantly improved with a curcuminoids dosage as low as 180 mg/day. In a robust human pharmacokinetic study, Cuomo and colleagues showed that the absorption of curcuminoids with Meriva® is about 30 folds higher compared with unformulated curcuminoids, and this ranges from 20-fold increase in the absorption of monomolecular curcumin to 50- to 60-fold increase for demethoxycurcumin and bisdemethoxycurcumin (Cuomo *et al.,* 2011).

In summary, findings from the present randomized double-blind placebo-controlled trial supported the clinical efficacy of adjuvant therapy with curcuminoids (in the bioavailable phosphatidylcholine complex formulation) in improving the QoL of patients with solid tumors. This finding was accompanied by a significant reduction in serum levels of inflammatory mediators and biomarkers (IL-6, TNF-α, MCP-1, CGRP, substance P and hs-CRP) revealing suppression of systemic inflammation by curcuminoids. Although the duration of the present trial was relatively short, the findings clearly support a clinically relevant effect. A limitation of the present study was that baseline values for QoL and some of the biochemical parameters were not matched between the curcuminoids and placebo groups, and this might have confounded the results. That subjects in the curcuminoids group had a significantly lower QoL score at baseline (vs. placebo group) reflects a more impaired health status, and the possibility of greater treatment responses in such patients compared with those in the placebo group (with less advanced stage of disease based on the QoL score) cannot be excluded. Further studies are encouraged to employ other useful QoL questionnaires (e.g., FACT-G) and assess the impact of adjuvant therapy with bioavailability-boosted curcuminoids on tumor response, long-term outcomes and the survival rate of patients with solid tumors and other types of cancer. Although Meriva® has been shown by previous studies to have a better pharmacokinetic profile compared with unformulated curcuminoids, it would be still helpful to include an additional group receiving unformulated curcuminoids in order to determine the extent of improvement in treatment response by Meriva®. With the current knowledge, administration of bioavailability-boosted curcuminoids preparations in cancer patients is recommended as these phytochemicals have been repeatedly reported to be safe and well tolerated even at doses higher than that used in the present trial (Chainani-Wu 2003; Cheng *et al.,* 2001; Sharma *et al.,* 2001).

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Conflict of Interest

The authors have declared that there is no conflict of interest.

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