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The Effects of Curcumin and Curcumin–Phospholipid Complex on the Serum Pro-oxidant–Antioxidant Balance in Subjects with Metabolic Syndrome

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Metabolic syndrome (MetS) is defined by a clustering of metabolic and anthropometric abnormalities and is associated by an increased risk of cardiovascular disease. We have investigated the effect of curcumin supplementation on the serum pro-oxidant–antioxidant balance (PAB) in patients with MetS. This double-blind, randomized, placebo-controlled trial was conducted over 6 weeks. Subjects (n = 120) were randomly allocated to one of three groups (curcumin, phospholipidated curcumin, and placebo). The curcumin group received 1 g/day of simple curcumin, the phospholipidated curcumin group received 1 g/day of phospholipidated curcumin (containing 200 mg of pure curcumin), and the control group received 1 g/day of placebo. Serum PAB was measured before and after the intervention (at baseline and at 6 weeks). Data analyses were performed using SPSS software (version 16.0). Serum PAB increased significantly in the curcumin group ($p < 0.001$), but in the phospholipidated curcumin group, elevation of PAB level was not significant ($p = 0.053$). The results of our study did not suggest any improvement of PAB following supplementation with curcumin in MetS subjects. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: metabolic syndrome; curcumin; pro-oxidant–antioxidant balance.

INTRODUCTION

Metabolic syndrome (MetS) is a multifaceted condition with high healthcare cost in numerous societies of the world. The elements defining MetS, include hyperglycemia, high blood pressure, low level of high-density lipoprotein cholesterol, visceral obesity, and elevated triglycerides (Reaven, 1988). Type II diabetes and cardiovascular disease are consequents of MetS (Alberti *et al*., 2009). The prevalence of MetS in Iran is 42% and 24% in women and men, respectively (Azizi *et al*., 2010), whereas the prevalence rate of this syndrome in industrialized countries is 20–30% (Cameron *et al*., 2004; Hildrum *et al*., 2007).

Several studies on the physiopathology of MetS have shown that abnormalities of oxidation are characteristics of MetS (Hopps *et al*., 2010). Oxidative stress including conditions that balance between the composing of oxidants and antioxidants has been disrupted. These conditions usually are connected to increased formation of reactive oxygen species (ROS), also supposing that these species have a key role in pathogenesis and occurrence of cardiovascular disease and related outcomes (Rahsepar *et al*., 2012). Reactive oxygen species is a by-product of oxygen metabolism that has a series of features such as strong reactant, short-term stability, and ubiquitous elements that bind to the proximate molecules at the site of composition. Reactive oxygen species include the superoxide radical, hydrogen peroxide, hydroxyl radical, and reactive nitrogen species, such as nitric oxide and the peroxynitrite radical, which are oxygen by-products that have critical roles in vascular biology (Roberts and Sindhu, 2009). Increased ROS formation is associated to oxidative stress. Oxidative stress is an imbalance between the production of pro-oxidants and antioxidant species in favor of pro-oxidants (Sadeghnia *et al*., 2013; Sahebkar *et al*., 2013). It plays

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an important role in the initiation and progression of atherosclerosis (Alamdari *et al*., 2008), as well as in the pathogenesis of cardiovascular disease and its related disorders (Ashok and Ali, 1999).

Herbal derivatives (phytochemicals) are used as a complementary treatment for some conditions (Wongcharoen and Phrommintikul, 2009; Bachmeier *et al*., 2010). It has been reported that carotenoids have antioxidant effects in a time-dependent and dose-dependent manner and cause a reduction in cardiovascular disease risk. The beneficial effects of carotenoid-rich products in improving the risk of certain diseases can be attributed to carotenoids such as β-carotene, lutein, lycopene, zeaxanthin, crocin, and curcumin, owing to their antioxidant effects (Alamdari *et al*., 2008). The antiinflammatory activity of curcumin is exerted by the suppression of several cell signaling pathways including nuclear factor κB, signal transducer and activator of transcription 3, nuclear factor (erythroid-derived 2)-like 2, ROS, and cyclooxygenase 2 (Kunnumakkara *et al*., 2017).

Curcuma longa L. (turmeric) belongs to the Zingiberaceae family. Curcumin is a yellow pigment of turmeric (Prasad *et al*., 2014). Turmeric has been used as a medication in traditional medicine for many years (Priyadarsini, 2014). Curcumin has a variety of pharmacological activities including anticancer, antioxidant, antidepressant, antimicrobial, and antiinflammatory properties (Maheshwari *et al*., 2006; Esmaily *et al*., 2015; Kunnumakkara *et al*., 2017; Milani *et al*., 2017). The antioxidant role of curcumin has been marked by some of its biological activities such as inhibition of lipid peroxidation and scavenging of superoxide and hydroxyl radical (Ruby *et al*., 1995). Evidence from numerous papers has shown that curcumin has poor absorption, biodistribution, metabolism, and bioavailability. Thus, continuous research on curcumin found some possible ways to overcome these problems. To increase bioavailability, longer circulation, better permeability, and resistance to metabolic processes of curcumin, several formulations have been prepared, which include nanoparticles, liposomes, micelles, and phospholipid complexes (Prasad *et al*., 2014).

With regard to the importance of pro-oxidant–antioxidant balance (PAB) in the physiopathology of MetS (Alamdari *et al*., 2008) and the role of curcumin as an antioxidant, we investigated the effect of curcumin supplementation in a simple and modified formula on serum PAB levels in patients with MetS in this study.

MATERIAL AND METHODS

Subjects. Generally, 120 subjects who met inclusion criteria, such as age of 18 to 65 years, no consumption of nutritional supplements and drugs in the past 3–6 months, consent for participation in this research, and MetS (on the basis of the International Diabetic Federation criterion, 2005), were admitted by a nutritional clinic of Ghaem Hospital in Mashhad, Iran. The Ethics Committee at Mashhad University of Medical Sciences approved the study protocol (code: 930165), and the study has been registered in the Iranian Registry of Clinical Trials (IRCT) with a registration number IRCT2014052014521N3.

Subjects with systemic disease and lactating or pregnant women were excluded from this study. Subjects were provided with written sheets and oral description about the study. Information about demographic data, medical and drug history, family history, smoking, and job was collected thru questionnaires. All participants provided written informed consent, and the protocol satisfied the Mashhad University of Medical Sciences Ethics Committee requirements.

Data analysis was on an intention-to-treat basis. The current study was a substudy from another original research with a registration number IRCT2014052014521N3, which is under consideration for publication. The sample size was determined in the original work according to the changes of triglyceride levels based on our previous study (Mohammadi *et al*., 2013). It was determined to be 35 subjects per group (considering $\alpha = 0.05$ and $\beta = 0.02$).

Study design. This study was designed as a 6-week double-blind, randomized, placebo-controlled trial. Participants were randomly divided into three groups by a computer-generated code such that each group has 40 persons. The intervention groups were composed of two separate subgroups, with one of them receiving capsules of curcumin with a dose of 1 g/day (two 500-mg capsules per day) and the other subgroup receiving capsules of phospholipidated curcumin with a dose of 1 g/day (twice a day), and the control group received 1 g/day (twice a day) of placebo capsules (lactose: the inert substance) for 6 weeks. Exclusion criteria were (1) a history of systemic disease such as lupus and rheumatoid arthritis, kidney disease, pregnancy, and lactation and (2) use of any supplements or drugs for decreasing blood pressure, glucose, and lipid during the previous 6 months. In this period, nutritional recommendations (based on the American Heart Association guidelines) have been provided for all participants. Diet compositions of participants assessed by using the NUTRITIONIST 4 software (First Databank, San Bruno, CA). Patients' adherence to this study has been assessed by counting capsules. Moreover, adherence was monitored during this study by biweekly visits; participants who did not consume their capsules regularly or had intolerance to the consumption of capsules were excluded from the study.

Blood samples. Blood samples at baseline and at the end of the study (after 12-h fasting at night) were collected. The samples that have hemolysis were excluded from analysis. After separation processes, the aliquots were frozen at −80 °C until analysis time. Fasting blood sugar, lipid profile, and serum PAB level were determined for each patient at baseline and the end of the study.

A method used for measuring PAB was developed by Alamdari *et al*. (2008) previously. This method is based on two different reactions (oxidation and reduction) that occur at the same time. This method has been implemented by using 3,3′,5,5′-tetramethylbenzidine (TMB) and two different types of reactions (the first is an enzymatic reaction in which the TMB chromogen is oxidized to a color cation by peroxides, and the other

is a chemical reaction in which the TMB cation is reduced to a colorless compound by antioxidants) and gives us a redox stress index.

Study intervention. Subjects were given blinded bottles containing 500-mg capsules of curcumin and phospholipidated curcumin and were asked to take two capsules per day. Phospholipidated curcumin contained a complex of curcumin and soy phosphatidylcholine in a 1:2 weight ratio and two parts of microcrystalline cellulose to improve flowability, with an overall content of curcumin in the final product of around 20% (Belcaro *et al*., 2010; Semalty *et al*., 2010). The shape, weight, and color of placebo capsules were the same as the original intervention (curcumin).

Statistical analysis. All statistical analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL). The normality of data was assessed by the Kolmogorov–Smirnov test. Data were reported as mean ± standard deviation or median and interquartile range. The comparisons between groups were computed by analysis of variance (for normal variables) or Kruskal–Wallis test (for nonnormal variables). The Wilcoxon signed ranks test (for

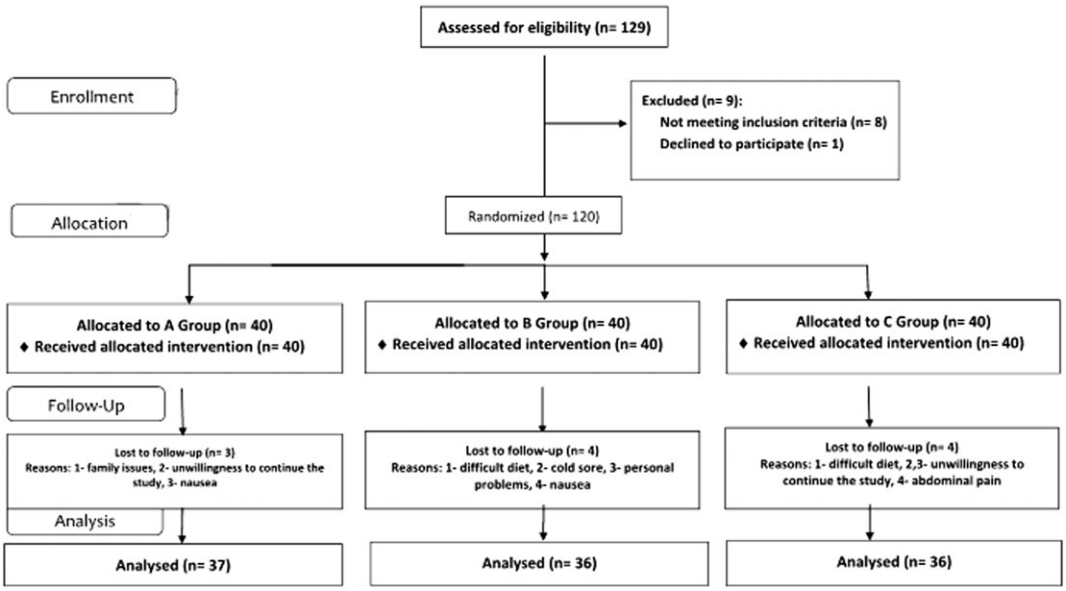

Figure 1. Summary of the study design, randomization, and clinical outcomes of the 6-week treatment (A, curcumin–phospholipid complex group; B, curcumin group; C, placebo group).

Table 1. Baseline features of studied groups

Variables	Phospholipidated curcumin	Curcumin	Placebo	*p*-value
Women (*n*)	25	31	30	0.280
Men (*n*)	15	9	10	
Age (years)	40.05 ± 10.48	37.52 ± 9.47	38.59 ± 10.28	0.534
Weight (kg)	84.06 ± 14.67	80.61 ± 11.71	82.12 ± 12.68	0.803
BMI (kg/m^2)	30.66 ± 5.06	30.67 ± 3.57	31.22 ± 4.67	0.828
WC (cm)	103.00 ± 10.24	99.94 ± 9.37	102.49 ± 9.41	0.341
Fat (%)	34.51 ± 8.07	35.42 ± 6.12	35.21 ± 7.86	0.848
HDL-C (mg/dL)	52.23 ± 12.91	53.33 ± 10.55	51.91 ± 10.62	0.844
LDL-C (mg/dL)	152.99 ± 38.84	165.90 ± 38.76	153.78 ± 40.40	0.262
TC (mg/dL)	241.28 ± 51.96	254.12 ± 43.64	242.12 ± 46.83	0.405
TG (mg/dL)	153.50 (102.50–217.00)	150.00 (108.25–234.25)	158.0 (128.5–216.25)	0.935
FBG (mg/dL)	95.97 ± 19.97	98.72 ± 27.17	92.82 ± 16.62	0.479
SBP (mmHg)	120.82 ± 10.24	119.74 ± 11.87	120.26 ± 11.50	0.914
DBP (mmHg)	83.48 ± 9.17	81.26 ± 10.06	81.70 ± 10.76	0.589
Current smoking, % (*n*)	15.4 (6)	26.3 (10)	13.9 (5)	0.318

Values expressed as mean ± standard deviation. Between-group comparisons were assessed by analysis of variance and chi-square tests for quantitative and qualitative variables, respectively. BMI, body mass index; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC; total cholesterol, TG; triglyceride; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Effect of curcumin on PAB and comparison of PAB between groups

Studied group		PAB (HK, arbitrary unit)		*p*-value		
		Before	After	Wilcoxon test	Kruskal–Wallis test	Mann–Whitney test
Phospholipidated curcumin		91.62 (48.36–120.14)	98.32 (66.45–141.50)	0.053	—	—
Curcumin		92.29 (66.10–126.02)	142.14 (98.05–184.41)	<0.001	—	—
Placebo		122.94 (66.44–159.96)	110.43 (87.89–128.36)	0.128	—	—
Change in PAB at baseline and after intervention	Phospholipidated curcumin	20.25 (−12.02 to 53.06)		—	<0.0001	0.096[a]
	Curcumin	46.90 (4.23 to 64.64)		—		0.007[b]
	Placebo	−18.11 (−43.39 to 23.66)		—		0.0001[c]

Data were expressed as median and interquartile range. PAB, pro-oxidant–antioxidant balance.
[a]Curcumin versus phospholipidated curcumin.
[b]Phospholipidated curcumin versus placebo.
[c]Curcumin versus placebo.

nonnormal variables) was used for comparison within groups. The statistical significance for all data was $p < 0.05$.

RESULTS

Baseline features of studied groups

In the period of this study, 11 patients were excluded from the study because of various reasons such as difficulty of diet ($n = 2$), family issues ($n = 1$), unwillingness to continue the study ($n = 3$), personal problems ($n = 1$), nausea ($n = 2$), cold sore ($n = 1$), and abdominal pain ($n = 1$). Fig. 1 shows the detailed information.

A comparison of baseline features between the three groups in this study is shown in Table 1. Data showed that the baseline features of the three groups in this study have no significant differences ($p > 0.05$).

Effect of curcumin on pro-oxidant–antioxidant balance

Pro-oxidant–antioxidant balance levels increased significantly in the curcumin group ($p < 0.001$), but in the phospholipidated curcumin group, elevation of PAB levels was not significant ($p = 0.053$). In the placebo group, the PAB levels were decreased, but this reduction was not significant statistically ($p = 0.128$). There was a significant difference in the change of PAB at baseline and after intervention between the study groups ($p < 0.001$). All these changes are shown in Table 2 and Fig. 2.

Food analysis of participants

Food intakes of participants were evaluated before and after the intervention. The changes in the intakes of micronutrients and macronutrients at baseline and after the intervention had no significant difference between the three groups. These results are shown in Table 3.

DISCUSSION

The results of the present study indicated that using curcumin and phospholipid curcumin supplementation for 6 weeks in patients with MetS cannot improve PAB levels. To our knowledge, the present study is the first one to investigate the effect of curcumin and phospholipid curcumin on PAB in patients with MetS.

Obesity and MetS account for the altered oxidant/antioxidant status and inflammation, suggesting that these conditions are the cause of atherosclerosis (Hopps *et al*., 2010). Alamdari *et al*. (2008) showed that PAB values may be considered as a cardiovascular risk marker. The PAB, along with other risk factors, can help in the prediction of the risk for cardiovascular events (Alamdari *et al*., 2009).

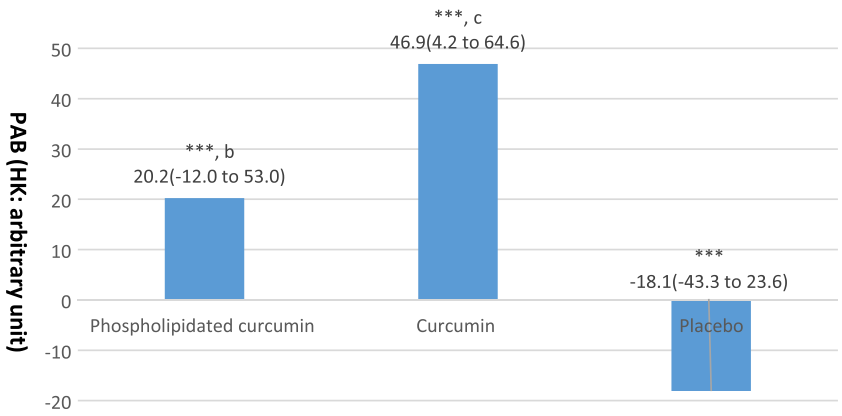

Figure 2. Change in pro-oxidant–antioxidant balance (PAB) at baseline and after intervention. Data were expressed as median and interquartile range. There was a significant difference in change of PAB at baseline and after intervention between the study groups (***$p < 0.001$). a = Curcumin versus phospholipidated curcumin ($p > 0.05$); b = phospholipidated curcumin versus placebo ($p < 0.01$); c = curcumin versus placebo ($p < 0.001$). Kruskal–Wallis and Mann–Whitney tests were applied. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3. Changes in food analysis of participants at baseline and after intervention

	Phospholipidated curcumin	Curcumin	Placebo	*p*-value
Macronutrients				
Calorie (kcal)	−290.21 ± 740.31	−15.56 ± 841.15	−293.08 ± 657.67	0.288
Protein (g)	−11.28 ± 37.78	2.79 ± 44.19	−5.29 ± 26.10	0.361
Carbohydrate (g)	−30.91 ± 104.66	−26.00 ± 107.20	−36.87 ± 100.43	0.926
Fat (g)	−10.03 ± 38.43	7.80 ± 41.90	−13.56 ± 28.90	0.073
Cholesterol (mg)	−42.41 ± 191.14	17.10 ± 170.09	−42.11 ± 203.77	0.402
Saturated fatty acid (g)	−4.17 ± 11.90	2.80 ± 12.23	−3.28 ± 9.24	0.045
Dietary fiber (g)	−2.21 ± 7.15	1.85 ± 9.41	2.76 ± 16.39	0.241
Micronutrients				
Zinc (mg)	−1.08 ± 4.87	1.23 ± 6.68	0.08 ± 4.29	0.276
Copper (mg)	0.07 ± 1.07	−0.05 ± 0.88	0.15 ± 1.30	0.934
Selenium (mg)	−0.01 ± 0.03	−0.01 ± 0.05	−0.00 ± 0.02	0.256
Vitamin A (RE)	−315.35 ± 2729.74	−756.51 ± 2881.97	−1197.35 ± 2591.95	0.855
Vitamin E (mg)	−4.97 ± 8.46	2.26 ± 26.14	−6.90 ± 10.51	0.080
Vitamin C (mg)	−20.59 ± 94.96	−14.44 ± 77.79	−3.48 ± 89.28	0.761

Values are expressed as mean ± standard deviation. Between-group comparisons were assessed by the Kruskal–Wallis test.

It has been shown that plant polyphenols can be investigated for the treatment of MetS (Cherniack, 2011; Akaberi and Hosseinzadeh, 2016). Rahmani *et al.* (2016) indicated that curcumin can provoke reductions in body mass index and serum levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides in patients with nonalcoholic fatty liver disease. In spite of the evidence reported by Nelson *et al.* (2017) as 'pan assay interference compounds', there are several evidences showing the molecular mechanisms of the antioxidant effects of curcumin (Ruby *et al.*, 1995; Motterlini *et al.*, 2000; Panahi *et al.*, 2015, 2017). The antioxidant role of curcumin has been marked by some of its biological activities such as inhibition of lipid peroxidation and scavenging of superoxide and hydroxyl radical (Ruby *et al.*, 1995). Motterlini *et al.* (2000) suggested that curcumin is a strong stimulator of heme oxygenase 1 in vascular endothelial cells, and the augmentation of the activity of heme oxygenase is a main part of curcumin-mediated cytoprotection against oxidative stress. Samuhasaneeto *et al.* (2009) indicated that curcumin could recover liver tissues in the primary phase of liver injury that is induced by ethanol through reduction of oxidative stress and inhibition of nuclear factor κB activation.

The results of the current study showed that there were significant increases in PAB levels in curcumin and phospholipidated curcumin groups compared with the placebo group ($p < 0.001$). Panahi *et al.* (2015) reported that short-term supplementation with a curcuminoid–piperine combination can improve serum superoxide dismutase activity and malondialdehyde level compared to the placebo in subjects with MetS. However, in a latter trial, the curcumin capsules contained piperine. Prasad *et al.* (2014) showed that piperine can decrease the conjugation of curcumin and its rapid urinary elimination. Panahi *et al.* (2017) have reported the antioxidant effects of curcumin in patients with type II diabetes mellitus. Their results showed that curcumin, co-supplemented with piperine, can decrease serum malondialdehyde and increase total antioxidant capacity and superoxide dismutase activities.

In the huge literature on curcumin, potential therapeutic effects have been referred to curcumin pro-

oxidant activity. Bhaumik *et al.* (1999) have shown that curcumin increases the ROS production and induces apoptosis in the AK-5 histiocytoma cells. In other words, curcumin may exert pro-oxidant activity in some conditions based on the underlying pathology being investigated and the dose administered. The ability of curcumin in the production of ROS (especially hydroxyl radical) in the existence of Cu^{++} ion can cause DNA cleavage, and thus, curcumin shows the pro-oxidant effects (Ahsan *et al*., 1999). Besides, curcumin at low concentrations (< 10 μM) can counteract glutathione (GSH) reduction and at a higher concentration can reduce GSH levels slowly. The addition of curcumin in the red blood cell model caused a concentration-dependent reduction of hemolysis, although curcumin in various concentration levels (for example, 23.2 ± 2.5 and 43 ± 5 μM) did not inhibit the release of intracellular K^+ in the course of hemolysis. With regard to the effects noted earlier, curcumin showed both antioxidant and pro-oxidant activities in a concentration-dependent manner (Banerjee *et al*., 2008). Moreover, Scapagnini *et al*. (2006) have reported that curcumin has a hormetic response. It means a biphasic dose response with low-dose stimulation or beneficial effect and a high-dose inhibitory or toxic effect. In the current study, it can be proposed that the doses of the simple and modified curcumin were respectively less and higher than the optimal dose at which curcumin can exert beneficial effects in these patients.

It can be suggested that future studies be applied with various doses of curcumin (higher and lower than 1 g/day) to examine the effects of curcumin on oxidative stress levels in patients with MetS.

Study limitations

The effects of different doses of curcumin were not assessed in the current study. Moreover, we did not examine the impact of absorption-enhancing adjuvants on the efficacy of curcumin in this trial.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical approval

This research was approved by the Mashhad University of Medical Sciences Ethics Committee.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

The authors confirm no conflict of interest.

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