Clin Nutr Res. 2020 Jan;9(1):63-72
https://doi.org/10.7762/cnr.2020.9.1.63
pISSN 2287-3732·eISSN 2287-3740

cnr
CLINICAL NUTRITION RESEARCH

Original Article

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A Comparative Study of the Effect of Flaxseed Oil and Sunflower Oil on the Coagulation Score, Selected Oxidative and Inflammatory Parameters in Metabolic Syndrome Patients

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OPEN ACCESS

Received: Nov 26, 2019
Revised: Jan 19, 2020
Accepted: Jan 21, 2020

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ABSTRACT

Metabolic syndrome (MetS) is a chronic disease with inflammatory and hypercoagulable states. The current study aimed to compare the effects of flaxseed oil and sunflower oil consumption on the coagulation score and selected oxidative and inflammatory parameters in patients with MetS. In this randomized controlled clinical trial, 60 patients with MetS were allocated into 2 groups. One group received 25 mL/day flaxseed oil and the other group received 25 mL/day sunflower oil for 7 weeks. Maintenance diet including 15% protein, 55% carbohydrate, and 30% fat from daily total energy intake was designed for each participant. Serum levels of total antioxidant capacity (TAC) and interleukin 6 (IL-6), as well as coagulation score were measured before and after the intervention. Three 24-hour food records were taken during the study. Fifty-two of participants (27 in sunflower oil and 25 in flaxseed oil groups) completed the study. The baseline characteristics and dietary intakes were similar between patients. After 7 weeks, no significant difference was observed between the 2 groups regarding the serum TAC level and coagulation score ($p > 0.05$). However, serum IL-6 levels significantly decreased in the flaxseed oil group compared to the sunflower oil group ($p = 0.017$). No side effect was observed during the study due to the use of sunflower and flaxseed oils. We observed that consumption of flaxseed oil improved serum IL-6 levels but had no effect on oxidative stress and coagulation score in patients with MetS. Further studies are needed to confirm the veracity of our results.

Trial Registration: Iranian Registry of Clinical Trials Identifier: IRCT2015012020737N1

Keywords: Flaxseed oil; Sunflower oil; Inflammation; Metabolic syndrome

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Conflict of Interest
The authors declare that they have no competing interests.

INTRODUCTION

Metabolic syndrome (MetS) is a chronic disease with inflammatory and hypercoagulable states [1]. This chronic inflammatory condition is called metaflammation or para inflammation, having increased levels of inflammatory cytokines, including interleukin-6 (IL-6) [2,3]. MetS patients are also vulnerable to oxidative stress due to excessive production of reactive oxygen species (ROS) and a weak antioxidant defense system. Oxidative stress is associated with insulin resistance and chronic inflammation. Nowadays, MetS is one of the most important public health issues with increasing prevalence rates [4,5]. Considering the association between the components and complications of MetS such as inflammation, excessive ROS, and endothelial and fibrinolysis dysfunction [6,7], recent studies have proposed to add some important items such as subclinical inflammatory factors to MetS components because of their potential roles in cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) pathogenesis [8].

Studies have shown that functional foods have beneficial effects on MetS status and other health issues. In fact, one or more food items in a regular diet can change metabolic features or cell signaling pathways [9,10]. Currently, flaxseed is one of the most attractive functional foods. Flaxseed oil is a major source of alpha-linolenic acid (ALA) (50%–60% of whole fatty acids composition), which has higher bioavailability in comparison to its milled or whole seed [11-13]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA possess anti-inflammatory and anti-platelet aggregation properties, while arachidonic acid (AA(, the end product of linoleic acid (LA) metabolism, has the opposite effects [10]. Other useful components of flaxseed oil are phenolic acid and phenolic compounds (*p*-coumarin acid and pherolic acid) [12]. It also contains vitamin E in form of γ-tocopherol and thus protects cellular membrane lipids from oxidation [13].

According to the results of some clinical studies, omega-3 fatty acids and ALA had a potential role against inflammatory mediators [5,13,14]. Indeed, flaxseed might be able to reduce the risk of CVD due to its antioxidant, anti-platelet adhesion, and other bioactive properties [3,14,15]. Considering the conflicting results [14,15], this study aims to compare the effects of flaxseed oil as a good source of ALA to those of sunflower oil as a common vegetable oil in the family food basket on the total antioxidant capacity (TAC), IL-6, and coagulation score.

MATERIALS AND METHODS

Study design

In this randomized controlled clinical trial, 60 participants were randomly assigned to the control (n = 30, receiving 25 mL/day sunflower oil) or the intervention group (n = 30, receiving 25 mL/day flaxseed oil) using the block method. Sample size was based on the previous study in this field and based on the formula of mean difference between the 2 groups with $\alpha = 0.05$ and 80% power and mean difference equal to 0.48 and standard deviation of 0.6. The sample size was determined at least 25. Considering a dropout rate of 20%, the number of samples increased to 30 in each group.

After a 3-week washout period, the participants were re-examined in the 2 groups. In order to increase accuracy, a measuring spoon was given to each participant. According

https://doi.org/10.7762/cnr.2020.9.1.63

to weight and estimated energy requirement equation, individualized diets were designed such a way to contain 55% carbohydrate, 30% fat, and 15% protein. The participants were asked not to change their physical activity levels and to report any changes in their diets or medications and any adverse effects following the consumption of oil throughout the study. The compliance of the participants with the study procedure was monitored via phone and interviews, twice a month. The study followed the Declaration of Helsinki guidelines and was approved by the local Ethics Committee of Shiraz University of Medical Sciences (SUMS) (IR.SUMS.REC.1394.108). It was also registered in the Iranian Registry of Clinical Trials (No. IRCT2015012020737N1).

Study population

The participants were 30–60 years old and were diagnosed with MetS. According to the National Cholesterol Education Program's Adult Treatment Panel IV report criteria (NCEP ATP IV), MetS was diagnosed by the medical doctor in healthy heart Shiraz home based on the presence of three or more of the following criteria: waist circumference ≥ 102 cm or 40 inches for males and ≥ 88 cm or 35 inches for females, fasting blood sugar (FBS) ≥ 110 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for males and < 50 mg/dL for females, fasting triglyceride (TG) level ≥ 150 mg/dL, and systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg. The patients were recruited from a screening program in healthy heart Institute in Shiraz from April to July 2017. Written informed consent was obtained from each participant before the study. The exclusion criteria of the study were suffering from any chronic diseases such as cancer, autoimmune or inflammatory diseases, and kidney and liver problems, taking lipid, blood pressure, or glucose-lowering medications, consuming dietary supplements containing omega-3 fatty acid, using aspirin, propranolol, and non-steroidal anti-inflammatory drugs or any form of steroids, participating in other studies, and having a history of hospitalization or surgery, pregnancy, and lactation. The participants who reported any adverse effects or started taking any of the aforementioned medications were also excluded from the study.

Dietary intakes and blood sampling

All participants filled out 3-day food records (2 weekdays and 1 weekend) at the beginning and after the study. At the beginning and at the end of the study, 2 mL venous blood samples were taken after a 12-hour overnight fasting. Blood clot tubes were centrifuged at 2,500 rpm at 4°C for 10 minutes. Serum TAC was measured using ELISA kit (ZellBio GMBH, Ulm, Germany). IL-6 level was also assessed using ELIZA kit (IBL International GMBH, Hamburg, Germany).

In order to measure the coagulation score, blood samples were obtained from the patients via venipuncture. The blood was decalcified (by collecting it into a tube with oxalate or citrate ions) to prevent the clotting process from starting before the test. Then, blood cells were separated from the liquid part of the blood (plasma) by centrifugation. The prothrombin time (PT) test was performed by adding the plasma to some sources of tissue factor, such as protein or thromboplastin from homogenized brain tissue that converts prothrombin to thrombin. The mixture was then kept in a warm water bath at 37°C for 1 or 2 minutes. Afterwards, calcium chloride (excess quantities of ionized calcium) was added to the mixture in order to counteract the sodium citrate and allow clotting to start. The PT test was determined by timing from the addition of calcium chloride until the plasma clotted.

In order to carry out partial thromboplastin time (PTT) test, decalcified blood was used to prevent clotting before the test. At the beginning, the plasma was separated via centrifugation.

https://doi.org/10.7762/cnr.2020.9.1.63

After that, ionized calcium and activating substances were added to the plasma to start the intrinsic pathway of the coagulation cascade. These substances included kaolin (hydrated aluminum silicate) and cephalin. Kaolin served to activate the contact-dependent factor XII, and cephalin substituted for platelet phospholipids. The PTT refers to the time it takes for a blood clot to form, measured in seconds. Normally, the sample clots in 35 seconds.

Data analysis

The data were analyzed using the SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of the variables was verified by Shapiro-Wilks test. Student's t-test and paired t-test were used to assess between-group and within-group changes, respectively. The $p < 0.05$ was considered to be statically significant.

RESULTS

The flow chart of participants through the trial is presented in **Figure 1**. Eighty-five patients with MetS were primarily assessed against the inclusion and exclusion criteria. Sixty participants met the criteria and were randomly assigned into the flaxseed oil or sunflower oil group. Five participants were excluded from the flaxseed oil group during follow-up phase due to an unwillingness to continue the study. In addition, 3 participants were excluded from the sunflower oil group during follow-up phase due to travel and personal problems. Therefore, 52 subjects completed the trial and included to final analysis. No side effects were reported in participants during the intervention.

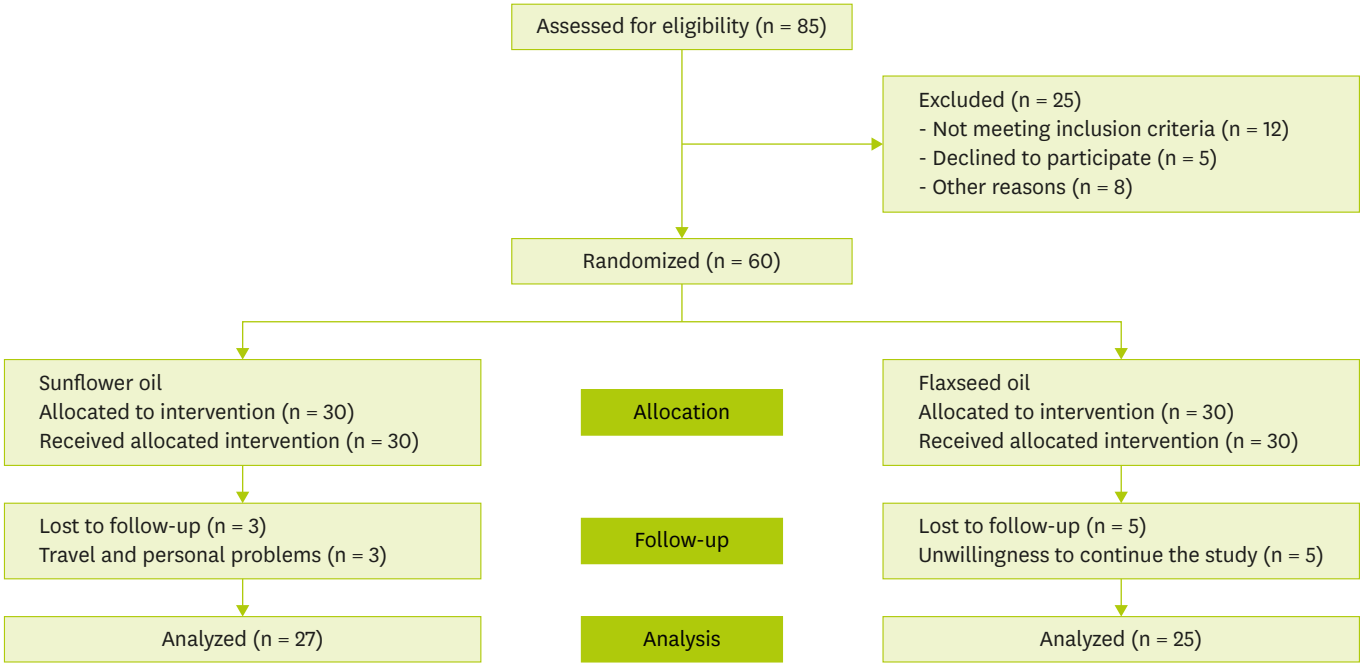

Figure 1. Flow diagram of the enrolled participants.

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Table 1. Flaxseed oil and sunflower oil fatty acids specifications

Fatty acids	Sunflower oil	Flaxseed oil
C16	7.8	7.1
C18	4.9	8.3
C20	0.4	0
C22	0.9	0
C18:1	27.6	27.5
C18:2	58.0	16.1
C18:3	0	41.0
C20:1	0.4	0
SFA	14.0	15.4
MUFA	28.0	27.5
PUFA	58.0	57.1

All values represent the percentage of total fatty acids.
SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

Oils specifications have been presented in **Table 1.** Accordingly, the amounts of saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) were equal in flaxseed oil and sunflower, but the percentages and kinds of PUFAs were different.

Demographics

According to **Table 2**, no significant differences were observed between the flaxseed oil and sunflower oil groups regarding demographic and biochemical characteristics at the baseline. Sex and age distributions were also similar in the 2 groups.

Dietary intake

Based on the 24-hour recall assessment, no statistically significant difference was seen between the 2 groups in terms of dietary intakes of energy, fat and omega-3 fatty acids (**Table 3**).

Table 2. The participants' baseline characteristics

Factor	Group			
	Total (n = 52)	Sunflower oil (n = 27)	Flaxseed oil (n = 25)	p value*
Age (yr)	46.57 ± 5.44	46.11 ± 4.76	47.03 ± 6.11	0.546
Sex (M/F)	27/25	14/12	13/13	0.786
Weight (kg)	80.24 ± 10.46	81.20 ± 11.31	79.28 ± 9.68	0.514
IL-6 (pg/mL)	9.30 ± 1.03	9.22 ± 0.92	9.37 ± 1.15	0.621
TAC (pg/mL)	0.23 ± 0.03	0.24 ± 0.03	0.23 ± 0.03	0.440
PT (sec)	13.85 ± 3.01	13.44 ± 0.95	14.27 ± 4.16	0.328
PTT (sec)	37.62 ± 7.61	38.58 ± 8.75	36.65 ± 6.31	0.368
INR	1.08 ± 0.24	1.08 ± 0.15	1.09 ± 0.31	0.867

Data have been presented as mean ± standard deviation.
IL-6, interleukin 6; TAC, total antioxidant capacity; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.
*The p value was obtained from Independent samples t-test.

Table 3. The participants' dietary intakes at the baseline and during the intervention

Dietary intakes	Baseline			During the intervention		
	Sunflower oil (n = 27)	Flaxseed oil (n = 25)	p value*	Sunflower oil (n = 27)	Flaxseed oil (n = 25)	p value*
Energy (kcal/day)	2,445.79 ± 143.22	2,387.80 ± 162.40	0.178	2,453.63 ± 90.62	2,400.31 ± 116.12	0.071
Fat (% of energy)	25.00 ± 1.51	24.91 ± 1.99	0.856	27.74 ± 2.05	26.99 ± 2.13	0.199
SFA (% of total energy)	12.52 ± 1.19	12.77 ± 1.09	0.446	7.00 ± 0.76	7.37 ± 0.83	0.109
PUFA (% of total energy)	3.80 ± 0.48	3.92 ± 0.41	0.324	15.98 ± 0.94	16.29 ± 0.99	0.256
Omega-3 fatty acids (% of total energy)	1.34 ± 0.11	1.38 ± 0.24	0.444	0.80 ± 0.12	0.85 ± 1.05	< 0.001

Data have been presented as mean ± standard deviation.
SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid.
*Paired t-test (within groups before and after the intervention).

https://doi.org/10.7762/cnr.2020.9.1.63

Table 4. Comparison of changes in TAC, IL-6, PT, PTT, and INR between and within the 2 groups

Factor	Group						p value†
	Sunflower oil (n = 27)			Flaxseed oil (n = 25)			
	Before	After	p value	Before	After	p value*	
Weight (kg)	81.20 ± 11.31	80.41 ± 11.18	0.001	79.28 ± 9.68	78.26 ± 9.55	0.002	0.460
IL-6 (pg/mL)	9.22 ± 0.92	8.48 ± 1.06	0.006	9.37 ± 1.15	7.90 ± 0.52	< 0.001	0.017
TAC (pg/mL)	0.24 ± 0.03	0.26 ± 0.05	0.013	0.23 ± 0.03	0.27 ± 0.03	< 0.001	0.339
PT (sec)	13.44 ± 0.95	13.29 ± 1.05	0.622	14.27 ± 4.16	13.77 ± 3.99	0.138	0.552
PTT (sec)	38.58 ± 8.75	37.69 ± 2.13	0.120	36.65 ± 6.31	36.10 ± 3.59	0.210	0.840
INR	1.08 ± 0.15	1.05 ± 0.18	0.595	1.09 ± 0.31	1.00 ± 0.00	0.163	0.174

All values represent mean ± standard deviation.
IL-6, interleukin 6; TAC, total antioxidant capacity; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.
*The p value was obtained from paired t-test; †p value was obtained from analysis of variance.

Findings recorded in the 2 groups of participants before and after intervention

The results depicted in **Table 4** illustrated a reduction in serum IL-6 level in comparison to the beginning of the study. Changes in IL-6 level were also significant within and between the 2 study groups ($p = 0.017$). Nonetheless, no significant differences were found in the two groups concerning the TAC and coagulation scores compared to the baseline ($p > 0.05$).

DISCUSSION

The study results revealed that flaxseed oil had favorable effects on reducing the inflammatory status, including serum IL-6 concentration, in MetS patients. The adjusted diet for the participants altered the n-6: n-3 ratio. n-6 and n-3 compete for the main enzymes in the fatty acid metabolism pathway, namely lipoxygenase and cyclooxygenase. Consumption of the two fatty acids leads to a decline in the production of prostaglandin E2 and leukotriene B4. It has been proposed that the reduction of these two eicosanoids could decrease the production of inflammatory markers, such as IL-6 [16].

Su et al. [17] and Nelson et al. [18] reported that consumption of 5% of total energy from (ALA) had no significant effects on reduction of serum IL-6 level in healthy abdominally obese adults. Indeed, receiving 3 g/day ALA caused no significant changes in IL-6 levels among patients with type 2 diabetes mellitus. In another study, the low and high doses of flaxseed oil were unable to change IL-6 and some other inflammatory parameters in MetS patients [19]. In the present study, the patients were required to consume approximately 10 g/day ALA. However, inflammatory status is different in various diseases. For instance, CVD has an elevated level of inflammatory markers. On the other hand, MetS is a proinflammatory status and has different conditions in comparison to abdominal obesity. These discrepancies may result from the baseline levels of inflammatory markers as well as habitual diets, which are the main influential factors. Consequently, replacement of various fatty acids in the diet may be accompanied with different outcomes, indicating the importance of a habitual diet. On the other hand, it seems that replacement of n-3 with n-6 fatty acids was not effective in healthy individuals or those with low levels of inflammatory markers [20]. In this regard, observational studies have shown conflicting results [21,22]. Rallidis et al. [16] reported that ALA from flaxseed oil (15 mL/day) reduced C-reactive protein (CRP), serum amyloid A (SAA), and IL-6 in dyslipidemic patients. In another trial, taking 8.1 g/day ALA decreased IL-6 and other inflammatory markers, such as CRP, SAA, and soluble vascular cell adhesion molecule type 1 (sVCAM-1) in dyslipidemic men [20]. In that study, the participants' dietary pattern was high in saturated fatty acids. Thus, some

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other factors, such as dietary background, total fat, or other sources of n-3 received during the study, might have interfered with their results.

The current study results indicated no changes in the TAC among the participants who received flaxseed oil. In the research performed by Mirfatahi et al. [23] on hemodialysis patients, consumption of 6 g/day flaxseed oil had no significant effects on oxidative stress factors, such as soluble intercellular adhesion molecule type 1, sVCAM-1, sEselectin, and malondialdehyde. However, a significant decline was detected in high-sensitive CRP in the flaxseed oil group [23]. In another study, Rahmani et al. [24] reported that 1,000 mg omega-3 fatty acids (400 mg α-linolenic acid plus 400 IU vitamin E) improved oxidized low-density lipoprotein and lipoprotein gene expression among women with polycystic ovary syndrome [24]. In that study, adding vitamin E to omega-3 fatty acids improved oxidative status. PUFAs containing more than three double bonds can produce hydroperoxy epidioxides as the primary oxidation products are easily oxidized in our tissues or cell membrane because of the high degree of unsaturation [25]. Other antioxidants, such as vitamin E or C, are required to protect PUFAs or help their activity.

In another experimental study on rats with non-alcoholic fatty liver disease, flaxseed oil and lipoic acid increased superoxide dismutase, catalase, and glutathione peroxidase activities as well as glutathione levels [26]. It seems that enriched flaxseed oil with an antioxidant agent has a protective effect and increases the antioxidant defense.

It is worth mentioning that 2 or more antioxidant factors were evaluated in the above-mentioned studies. On the other hand, one of the strong points of the current study was the measurement of TAC, which indicates power and change in all antioxidant systems in the body.

The present study results revealed no significant differences between the two groups regarding PT or PTT at the end of the study. Evidence has shown that n-3 fatty acid improved endothelial function and platelet aggregation markers in patients with coronary heart disease as well as in healthy cigarette smokers [27]. It seems that inflammatory status affects endothelial dysfunction in patients with MetS, and eventually increases the coagulation factors. However, details and mechanisms of the antithrombotic effects of ALA are unclear. Therefore, further studies on the issue are warranted. ALA can inhibit thrombosis formation, tissue expression, and platelet activation. Although the coagulation mechanism is well known in some diseases, it is unknown in MetS. For example, obesity is a moderate risk factor for venous thromboembolic events, but limited evidence is available for MetS [28,29]. Since MetS and CVD are closely related, in addition to the traditional MetS identification factors, efforts to identify the common causes of MetS and CVD are worthwhile. Many factors contribute to blood coagulation or thrombosis, some of which are affected by inflammatory factors or vascular atherosclerosis. Thus, comprehensive studies are needed to measure all relevant factors.

Although the positive effects of flaxseed on health have been reported, a particular concern about flaxseed in some populations including pregnant women and men in their reproductive ages should be considered. Especially in chronic use, this possible adverse effect due to hormonal action of the lignans must not be neglected [30].

This study has some limitations that should be addressed. The main limitation of the present study is the lack of an appropriate placebo for the flaxseed oil. In addition, other known

https://doi.org/10.7762/cnr.2020.9.1.63

inflammatory and oxidative stress markers were not measured. Finally, relatively short intervention period and small sample size are considered as other limitations of the study.

CONCLUSIONS

Dietary intake of flaxseed oil as the main source of dietary fat could improve the inflammatory status among MetS patients. However, no significant changes were observed in serum levels of TAC and coagulation score. With regard to the baseline level of inflammation in MetS that leads to CVD and T2DM and the importance of dietary fat in these patients, flaxseed oil might be helpful. However, further studies are needed to confirm the veracity of our results.

ACKNOWLEDGEMENTS

The present article was a part of the M.Sc. thesis written by Atefeh Akrami at Shiraz University of Medical Sciences (code: 93-01-87-8898). The authors would like to thank all the personnel of Shiraz Healthy Heart Institute for their cooperation. They are also grateful for Ms. A. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript.

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