# Effect of crocin, a carotenoid from saffron, on plasma cholesteryl ester transfer protein and lipid profile in subjects with metabolic syndrome: A double blind randomized clinical trial

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**Original Article**

## Abstract

**BACKGROUND:** Metabolic syndrome is defined by insulin resistance and a clustering of other cardiovascular risk factors. Crocin is a carotenoid derived from the stigmas of the saffron flower and had previously been shown to affect lipid profile. However, the mechanism for this function is not well understood. The present trial aimed to investigate the possible effect of crocin on plasma levels of cholesteryl ester transfer protein and lipid profile in individuals with metabolic syndrome.

**METHODS:** This was a randomized, double-blind, placebo-controlled, clinical trial consisting of an 8-week treatment with crocin, or placebo tablets between April and June 2014, in the Nutrition Clinic of Ghaem Teaching Hospital, Mashhad, Iran. Participants were randomly assigned to take a 30 mg/day crocin (n = 22) in the intervention group or placebo (n = 22) in the control group. Anthropometric, hematological and biochemical parameters were measured and recorded during pre and post-treatment periods.

**RESULTS:** Whilst plasma cholesteryl ester transfer protein was increased in the group taking the crocin tablet by 27.81% during the trial period (P = 0.013), the difference between the crocin and placebo groups was not significant (P = 0.116). Moreover, the percent changes in cholesterol (P = 0.702), triglyceride (P = 0.080), low-density lipoprotein (LDL) (P = 0.986), high-density lipoprotein (HDL) (P = 0.687) and fasting blood glucose (P = 0.614) did not differ significantly between intervention and control groups.

**CONCLUSION:** Although crocin supplements increased the serum cholesteryl ester transfer protein in patients with metabolic syndrome, this change was not significant between treatment and placebo groups.

**Keywords:** Cholesteryl Ester Transfer Protein, Crocin, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, Metabolic Syndrome, Saffron

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## Introduction

Cholesteryl ester transfer protein (CETP) is present in serum and enables transfer of cholesteryl esters from high-density lipoprotein (HDL) to triglyceride-rich lipoprotein, leading to a lowering of plasma HDL cholesterol (HDL-C) concentrations.[1,2] HDL metabolism and remodeling is related to the metabolism of triglyceride-rich lipoprotein and is determined by CETP and phospholipid transfer protein (PLTP). Plasma concentrations of CETP are associated with fat

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mass and a reduction in fat mass can lead to a decrease in serum CETP level reciprocally.[3]

Saffron (Crocus sativus *L*), is a bulbous perennial plant that contains more than 300 volatile and non-volatile components, including safranal, crocin, picrocrocin and some other carotenoids.[4] Saffron appears to be effective in several human health problems, as demonstrated in clinical trials.[5] The potential pharmacological effects of saffron are due to the presence of crocetin (mono and diglycosyl esters of polyene dicarboxylic acid) and crocin (digentiobiosyl ester of crocetin) carotenoids.[6] Crocin has been shown to have hypolipaemic,[7,8] antitumor,[9,10] antiulcer[11] and antioxidant[12,13] effects. It also has the ability to alter learning behavior[8] and cardio-protective properties.[14,15]

Metabolic syndrome is defined by a clustering of cardiovascular risk factors and is associated with a state of chronic low-grade inflammation. Endothelial dysfunction, insulin resistance, hyperuricemia, high blood pressure, cardiovascular diseases, obesity and type 2 diabetes are associated with metabolic syndrome and may be responsible for some of the poor outcomes associated with this condition.[16-18]

Since abnormal levels of low-density lipoprotein cholesterol (LDL-C), HDL-C, triglyceride (TG) as well as changes in plasma CETP are important features of metabolic syndrome[19] and few studies have investigated the relationships between crocin administration and the above factors, this study was conducted to assess the effect of crocin on changes in serum CETP and lipid profile.

## Materials and Methods

A double-blind, placebo-controlled study was conducted using a parallel design over a period of eight weeks between April and June 2014, in the Nutrition Clinic of Ghaem Teaching Hospital, Mashhad, Iran. Forty-four patients with metabolic syndrome (MetS), aged from 18 to 70 years, were recruited for this study. MetS was defined according to 3 of the following criteria proposed by the National Cholesterol Education Program (Adult Treatment Panel III) report (ATPIII): high waist circumference (> 102 in men and > 88 in women), impaired glucose tolerance and insulin resistance (fasting blood glucose or FBG > 100), dyslipidaemia with raised serum triglycerides (TG > 150), and low serum HDL-C (HDL < 40 in men and HDL < 50 in women), and a high blood pressure (> 130/85 mmHg).[20] The sample size was determined based on 27.6% changes in HDL level after crocin administration, according to the results reported by Nikbakht-Jam et al.[21] considering the type one (α) error of 0.050 and power of 0.900, using Stata Statistical Software, Release 11.0 (Stata Corporation, College Station, TX, USA).

Subjects were allocated into one of two groups, an active intervention group (10 men, 12 women) and a control group (8 men, 14 women) (Figure 1).

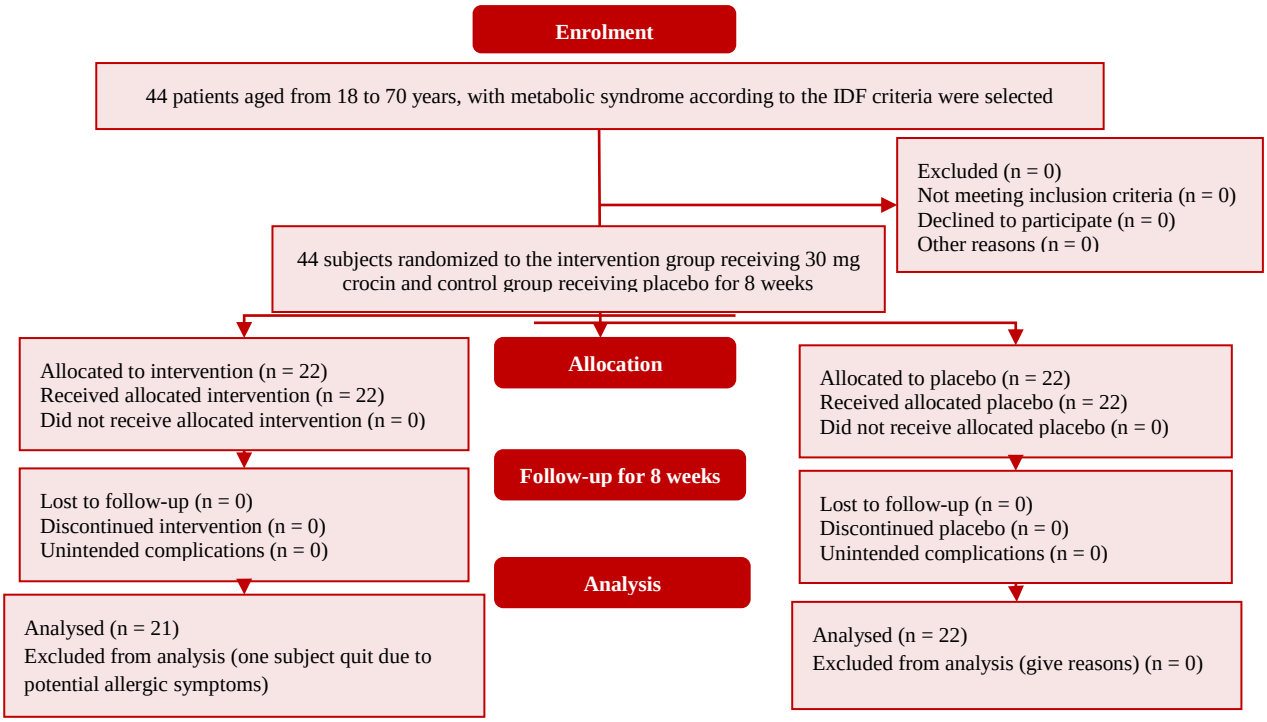


**Figure 1.** Flowchart of the participants in the randomized clinical trial
IDF: International Diabetes Federation

The allocation was carried out randomly by an experienced researcher using random number tables of patients referred to the clinic. The intervention group received 30 mg crocin tablets twice a day based on the results of the previous studies,[21,22] and the control group received a placebo for 8 weeks by a researcher who was blinded to the group. Subjects who were pregnant, lactating, or had systemic diseases with or without relevant treatments (e.g. immunodeficiency syndrome, rheumatoid arthritis, gout, asthma, insulin treatment in the diabetic patients) were excluded from the study.

The study was a part of a research project, approved by the Ethics Committee of the Mashhad University of Medical Sciences, Iran (No. IRCT2013080514279N1).

After obtaining informed consent, standard anthropometric data including height, weight, waist circumference and hip circumference were measured and initial biochemical tests were performed. Standing height was measured using a wall-mounted stadiometer (the subjects were shoeless and wore light clothing). Maximum hip circumference and minimum waist circumference (between below the chest and above the navel) were measured respectively as hip and waist circumference, using a tape measure to the nearest 0.1 cm. Body weight (kg), body fat (%) and body mass index (BMI) were measured using Tanita BC-418 bioelectrical impedance analysis device (Tanita Corp., Tokyo, Japan).

According to American Heart Association (AHA) guidelines, similar dietary advice was provided to all participants. Compliance with the research protocol was reviewed by a research technician who contacted the subjects every two weeks.

Plant material Crocus sativus *L.* stigma was provided by Novin Saffron Co. (Mashhad, Iran). The method of extraction has been described previously.[23] Crocin tablets were manufactured according to the method described by Nikbakht-Jam et al.[21] and contained 30 ± 0.8 mg per tablet. The placebo tablet matched the crocin tablet in size and shape and contained starch and permitted colouring. An industrial pharmacy specialist supervised quality control tests including hardness, weight variation, disintegration time, drug content and dissolution tests.

Fasting blood samples (20 ml serum) were taken from volunteers before and after the intervention for measurements of fasting blood glucose level, triglyceride, total cholesterol, HDL and LDL. Samples were transferred to the laboratory of Nutritional Science and Technology Group, Mashhad, Iran, for routine tests. The samples were taken prior to starting the trial and at the end of the 8th week. All biochemical measurements were carried out using an AutoAnalyzer BT3000 (BioTechnica, Italy).

Plasma CETP concentration was measured by enzymatic methods using commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cusabio, China) on a ELISA STAT Fax instrument (Awareness Technology, Inc., USA). The assay was performed as follow: after preparation of reagents, samples and standards, 0.1 ml standard or sample was added to each well, incubated at 37 °C for 2 hours and liquid of each well was removed. 0.1 ml Biotin antibody was added and the plates were incubated at 37 °C for 1 hour. After aspiration and washing for 3 times, 0.1 ml horseradish peroxidase-conjugated avidin was added and incubated at 37 °C for 1 hour. 0.09 ml 3,3',5,5'-tetramethylbenzidine (TMB) substrate was added to each well and incubated at 37 °C for 20 minutes. Finally, 0.05 ml of stop solution was added to stop the enzymatic reaction and optic density absorbance at 450 nm in a microplate reader was read.

Data are shown as mean ± standard deviation (SD) and median (interquartile range) respectively, for normally and non-normally distributed variables. The normality distribution of continuous data was assessed by Kolmogorov-Smirnov test. CETP and other factors measured during the study were compared before and after the intervention using paired t-test (for normally distributed data) and Wilcoxon test (for non-normally distributed data). The percent changes between intervention and control groups were compared using Student's independent t-test (for normally distributed data) or Mann-Whitney test (for non-normally distributed variables). Categorical data were compared using chi-square test. P less than 0.050 was considered statistically significant. All data analyses were performed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA).

## Results

At baseline, there were no significant differences between the groups regarding age (P = 0.297), body mass index (P = 0.136), waist circumference (P = 0.500), hip circumference (P = 0.433), the prevalence of diabetes mellitus (P = 0.909), hypertension (P = 0.909) and cardiovascular disease (P = 0.527) (Table 1).

**Table 1.** Baseline characteristics of intervention and placebo groups

| Baseline factors | | Intervention group (n = 22) | Placebo group (n = 22) | P |
|---|---|---|---|---|
| Gender | Women | 12 ± 54.50 | 14 ± 63.60 | 0.540* |
| | Men | 10 ± 45.50 | 8 ± 36.40 | |
| Age (year) | Women | 44.50 (24.75-51.50) | 46.00 (32.25- 51.50) | 0.297† |
| | Men | 33.10 (29.85-35.42) | 34.90 (31.80-37.92) | 0.408† |
| Body fat | | 38.70 (27.77- 41.60) | 39.20 (29.97-43.20) | 0.751† |
| TG (mg/dl) | | 151.00 (111.50-204.25) | 151.00 (117.50-224.50) | 0.618† |
| Fasting serum values | | | | |
| LDL (mg/dl) | | 163.50 (120.25-204.25) | 122.00 (110.25-165.50) | 0.069† |
| HDL (mg/dl) | | 37.00 (31.75-46.00) | 39.00 (31.00-44.50) | 0.896† |
| FBG (mg/dl) | | 92.50 (84.50-105.25) | 95.50 (89.00-123.75) | 0.295‡ |
| CETP (µg/ml) | | 0.32 (0.26-0.43.00) | 0.34 (0.30-0.37) | 0.916† |
| WC (cm) | | 109.91 ± 8.94 | 111.91 ± 10.50 | 0.500‡ |
| HC (cm) | | 114.73 ± 8.55 | 116.84 ± 9.14 | 0.433‡ |
| Cholesterol | | 232.18 ± 66.52 | 209.19 ± 38.41 | 0.175‡ |
| Diabetics§ | | 5 (31.3) | 5 (29.4) | 0.909* |
| Hypertensive‖ | | 5 (31.3) | 5 (29.4) | 0.909* |
| Cardiovascular disease¶ | | 2 (13.3) | 1 (7.1) | 0.527* |

Categorical data are presented as number (%) and continuous data as mean ± standard deviation (SD) in the case of normal distribution or median (Interquartile range) in the case of non-normal distribution; * Chi-square test; † Mann-Whitney test; ‡ paired t-test; § Diabetes was diagnosed by a medical history and taking diabetic drugs or high blood glucose (FBG ≥ 126); ‖ Hypertension disease was diagnosed by a medical history and taking blood pressure drugs; ¶ Cardiovascular disease was diagnosed by the medical history and use of heart disease medications

WC: Waist circumferences; HC: Hip circumferences; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBG: Fasting blood sugar; CETP: Cholesteryl ester transfer protein

As illustrated in table 2, the median (interquartile range) of the percent change of serum CETP after intervention among crocin and placebo groups were 12.23 (0-31.49) and zero (-19.42- 27.12), respectively. In the intervention group, the average increase of CETP was 27.81%, while in the placebo group the average increase was just 2.83%. The difference between CETP before and after the intervention was statistically significant (P = 0.013), while no difference was observed during this period of time in the placebo group (P = 0.881). However, these changes in crocin and placebo groups were not statistically different (P = 0.116).

Among patients in the crocin group, the average changes in serum cholesterol, TG, LDL, HDL and FBG after eight weeks of treatment were 0.14% (P = 0.390), 27.48% (P = 0.355), -5.49% (P = 0.058), 31.84% (P = 0.004) and 7.97% (P = 0.495) compared to the baseline values. The corresponding outcomes for placebo group were -3.02% (P = 0.398), -7.27% (P = 0.079), -5.76% (P = 0.281), 36.50% (P < 0.001) and 3.20% (P = 0.681), respectively. We did not observe any significant difference between the intervention and placebo groups regarding the above average changes in cholesterol (P = 0.702), TG (P = 0.080), LDL (P = 0.986), HDL (P = 0.687) and FBG (P = 0.614) (Table 3).

We also investigated the crocin effect on CETP changes based on the TG levels. We did not observe any significant CETP changes between intervention and placebo groups either in hypertriglyceridemic (> 200 mg/dl) (P = 0.530) or in normotriglyceridemic (< 200 mg/dl) (P = 0.230) subjects.

**Table 2.** Plasma cholesteryl ester transfer protein mass before and after the intervention

| Interventionor placebo | | Median (IQ range) (µg/dl) | Percent change median (IQ range) | P for change from baseline | Difference between the changes in the two groups |
|---|---|---|---|---|---|
| Intervention | Before | 0.32 (0.26-0.43) | 12.23 (0-31.49) | 0.013* | 0.116† |
| | After | 0.37 (0.32-0.62) | | | |
| Placebo | Before | 0.34 (0.30-0.37) | 0 (-19.42-27.12) | 0.881* | |
| | After | 0.32 (0.26-0.45) | | | |

Data are presented as Median (Interquartile range); * Wilcoxon test; † Mann-Whitney test

IQ: Interquartile

**Table 3.** Lipid profile and fasting blood glucose before and after intervention between intervention and placebo groups

| Variables | Intervention group | | P | Placebo group | | P | P between two groups |
|---|---|---|---|---|---|---|---|
| | Before | After | | Before | After | | |
| Cholesterol | 232.18 ± 66.52 | 220.09 ± 55.60 | 0.390* | 209.19 ± 38.41 | 199.95 ± 50.10 | 0.398* | 0.702* |
| TG | 151.00 (111.50-204.25) | 160.50 (102.00-227.25) | 0.355† | 151.00 (117.50-224.50) | 144.00 (111.00-206.00) | 0.079† | 0.080† |
| LDL | 163.50 (120.25-204.25) | 121.00 (102.00-170.75) | 0.058* | 122.00 (110.25-160.50) | 115.00 (72.25-161.25) | 0.281* | 0.986* |
| HDL | 37.00 (31.75-46.00) | 50.00 (40.50-56.25) | 0.004* | 39.00 (31.00-44.50) | 51.50 (43.50-62.50) | < 0.001* | 0.687* |
| FBG | 92.50 (84.50-105.25) | 88.50 (79.25-105.25) | 0.495† | 95.50 (89.00-123.75) | 100.50 (90.50-120.50) | 0.681† | 0.614† |

Data are presented as mean ± standard deviation (SD) in the case of normal distribution or median (Interquartile range) in the case of non-normal distribution; * Paired or Student's independent t-test; † Wilcoxon or Mann-Whitney tests

TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBG: Fasting blood sugar

## Discussion

Metabolic syndrome is a complex of cardiovascular risk factors such as high lipid profiles, low HDL, high FBG, hypertension and abdominal obesity.[20,24] Identification and management of metabolic syndrome is very important for controlling the risk of subsequent disorders.[25] CETP is a protein playing an important role in the modulation of plasma lipids and lipoproteins.[26] Therefore, it can contribute to developing metabolic syndrome and atherosclerotic disease.[19,27]

Elevation of HDL-C via inhibiting CETP appears to be an attractive strategy for reducing the risk of cardiovascular events among high-risk patients. Four CETP inhibitors including torcetrapib,[28] dalcetrapib,[29] anacetrapib[30] and evacetrapib[17] have been assessed in clinical trials, but no benefits have been demonstrated in terms of clinical outcomes.[31] Therefore, there is a growing interest in using traditional medicine as an alternative for the effective prevention of cardiovascular risk factors.

Results of the current study showed that crocin supplements were associated with a significant increase in the serum CETP concentration, although no significant change was observed after receiving placebo. To the best of our knowledge, this study was carried out as the first clinical trial of administrating crocin tablets among patients with metabolic syndrome for evaluating CETP changes. Therefore, it is not possible to make any comparisons with other similar studies. As a known mechanism, crocin can affect the lipid profile through a high selectivity for pancreatic lipase activity.[32] Previous studies have also suggested that a Taq1B polymorphism of CETP gene may be associated with the development of metabolic syndrome.[26]

Although crocin treatment was associated with a reduction in cholesterol, LDL and FBG levels and increase in TG and HDL concentrations in the intervention group, only the changes in HDL was statistically significant. These results are in contrast with those observed in some previous studies. Sheng et al. showed that treatment with crocin (25 to 100 mg/kg per day) significantly reduced TG, total cholesterol, LDL-C and very low-density lipoprotein cholesterol (VLDL-C) in rats as a result of inhibiting pancreatic lipase and malabsorption of fat and cholesterol.[32] Such discordance between the results might be due to different study subjects (human in this trial) and low sample size of this study. Desired clinical results will be achieved when a CETP inhibitor affect both HDL-C and LDL-C concurrently.[31] In the current study, HDL-C increase was significant in both intervention and placebo groups during the study period, possibly due to the effects of dietary change. However, it did not differ between these groups, and therefore does not suggest a beneficial application of crocin for patients with metabolic syndrome.

The observed effect of crocin on lipid profile and FBG were similar to the findings of another previous study.[21] It was suggested in some studies that CETP mass is the rate-limiting factor in changing lipid profile of hypertriglyceridemic patients (> 400 mg/dl),[33] whereas subjects in our trial had lower TG levels, indicating undesired results. However, comparing the effect of crocin on CETP level between patients with different TG levels (upper and lower than 200 mg/dl) did not show any significant differences.

Sandhofer et al. reported that women have higher plasma CETP levels than men because of higher subcutaneous adipose tissue.[34] In the current study, the frequency of both gender, as well as other factors, was the same in the intervention and placebo groups due to the random allocation design of the study. This group matching suggests that the observed findings of the crocin effect are independent of the above potential confounding factors.

One of the limitations of our study was the *ex* vivo quantification of CETP levels which gives a measure of the amount of CETP in serum, while the potential function of crocin by inhibiting CETP activity is in vivo. The low sample size of the participants was another limitation of the study which can lead to the low power of the analysis.

## Conclusion

In conclusion, a significant increase in the CETP and HDL levels following treatment with crocin among patients with metabolic syndrome was observed. However, these changes were not significantly different from those observed in the placebo group. Further studies with longer follow-up periods, larger sample size and different doses of crocin are suggested to investigate the exact effect of crocin on CETP and lipid profile among different groups of patients.

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## Conflict of Interests

Authors have no conflict of interests.

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