Review

Naringin reduces body weight, plasma lipids and increases adiponectin levels in patients with dyslipidemia

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Abstract: Naringin is a citrus-flavonoid which has been shown to have positive metabolic and anti-inflammatory effects. For this reason, we believe it would be interesting to study the effects of Naringin administration on body weight, BMI, lipid profile and adiponectin levels in patients with dyslipidemia, especially considering that dyslipidemias along with obesity and subsequent cardiometabolic complications are some of the most important public health issues plaguing our society today. A double-blind, randomized clinical trial was conducted in a group of 28 adult patients previously diagnosed with dyslipidemia who attended the Institute of Experimental and Clinical Therapeutics. Patients were divided into two groups; the first group (n = 14) received 450 mg of naringin every 24 hours, in the mornings, while the second group (n = 14) was given a homologated placebo over the course of a 90-day period. Significant differences were observed in naringin group compared to the placebo group in terms of decreased BMI (30.6 ± 3.19 vs 33.3 ± 3.23 kg/m^2; p = 0.03), total cholesterol (182 ± 20.2 vs 245 ± 24.1 mg/dl; p < 0.01), LDL cholesterol (100 ± 17.5 vs 125 ± 38.3 mg/dl; p = 0.03) and an increase in adiponectin levels (0.82 ± 0.25 vs 0.59 ± 0.19 μg/ml; p = 0.01). Our results support the use of Naringin as a potential therapeutic agent which could play an important role in the management of metabolic disorders.

Keywords: Naringin, phytopharmaceuticals, dyslipidemia, obesity

Introduction

In recent years, the prevalence of chronic non-transmissible diseases has increased dramatically on a global scale [1]. This includes the likes of cardiovascular diseases, type 2 diabetes mellitus (DM2), and cerebrovascular diseases, which are currently the three leading causes of mortality in Mexico [2, 3]. Obesity and dyslipidemias are some of the most important factors which contribute to the development of these chronic diseases, due to the metabolic and inflammatory alterations which are inherent to these conditions [4]. According to data from the most recent National Health and Nutrition Survey (ENSANUT) 2016, approximately 72.5% of the Mexican adult population is overweight or obese, and 28% of this group suffers from hypercholesterolemia. This is highly concerning, considering that dyslipidemias are one of the most common risk factors for cardiovascular disease, DM2, metabolic syndrome, and atherosclerosis among this group of individuals [4].

Conditions such as obesity and DM2, which are associated with insulin resistance and the development of cardiovascular diseases, have also been linked to decreased plasma adiponectin levels [4]. Adiponectin is an adipocytokine secreted by adipocytes that regulate the body's metabolism by stimulating fatty acid oxidation, reducing plasma triglycerides and improving glucose metabolism by increasing insulin sensitivity. For this reason, any drug which could increase the concentration of adiponectin or its effects could potentially be used as a therapeutic agent for the treatment of cardiometabolic disease [5].

On the other hand, there is a group of chemical substances which are secondary metabolites produced in plants, characterized by the presence of two or more phenol

groups (closed ring-shaped chemical structure) called polyphenols; these molecules possess antioxidant effects, which reduces cellular oxidative damage, among other biological and pharmacological effects [6, 7].

These polyphenols are classified according to the variety of compounds joined to the phenol group, one of the most common in our diet are flavonoids (60% of polyphenols); characterized by two or more aromatic rings bound together by a 3-carbon bridge forming an oxygenated heterocycle, some of the most studied are catechins like epigallocatechin gallates present in green tea, carvacrol, resveratrol, curcumin, among others; flavonoids have been attributed with mechanisms of action that help to prevent the membrane lipids oxidation, lipoxygenase inhibition, oxidative stress reduction, inhibition of oxidation of LDL cholesterol. They also reduce the viability of adipocytes and the proliferation of preadipocytes, suppress adipocyte differentiation and accumulation of triglycerides, stimulate lipolysis and fatty acids oxidation, and reduce inflammation [6–9].

Naringin is a citrus flavonoid that is currently used in the pharmaceutical and food industries, it's found in a greater proportion in the grapefruit pericarp, however, due to its potential inhibitory mechanism on the intestinal absorption of other drugs, its consumption is not recommended especially while taking any additional medication [10]. Studies in cell culture and animal models have shown that naringenin, which is the active metabolite of naringin, has antioxidant, anti-diabetic, anti-obesity, lipid-lowering, anti-atherogenic and anti-inflammatory properties, but the effects of this molecule in humans have not yet been completely reported [11–17].

Therefore, further studies are required to determine the full potential of this promising substance and its effects on body weight, plasma lipid profile, and adiponectin levels in patients with dyslipidemias. May even, naringin could be considered as an alternative therapy that could be given to patients suffering from dyslipidemia with statin hypersensitivity.

Materials and methods

Study design

A double blind, randomized, clinical trial was carried out in a group of 28 participants, both men and women, between the ages of 30 and 60 years who attended the Institute of Experimental and Clinical Therapeutics (INTEC) in the University of Guadalajara.

Subjects

All participants were carefully screened, required to have been previously diagnosed with class 1 obesity (Body mass index (BMI) 30–34.9 kg/m^2), and dyslipidemia (total cholesterol from 200–400 mg/dl), however, participants who suffered from additional lipid profile alterations were not excluded from this study. All participants were required to sign an informed consent format prior to the initiation of the trial.

The exclusion criteria were: any type of pharmacological treatment for obesity or dyslipidemia over the course of the three months leading up to the study, familial hypercholesterolemia, having additional comorbidities as well other chronic degenerative diseases; thyroid gland disorders, renal disorders, and liver disorders, pregnant or lactating female patients, consuming food supplements, multivitamin/mineral products, weight loss drugs, antidiabetic drugs, contraceptives or any other type of medications, or who were found to abuse alcohol, drugs or tobacco.

Groups and intervention

Two groups were formed, with the study group (n = 14) receiving a 450 mg capsule of naringin, (98% purity by HPLC, obtain from Xiaina Biological, Xián, China) every 24 hours, in the mornings, for 90 days, while the control group (n = 14) received a homologated placebo (calcined magnesia obtain from Almacen de drogas S.A. de C.V., Guadalajara Jalisco, Mexico) every 24 hours, in the morning, for 90 days.

Ethical considerations

The study protocol was approved by the Bioethics Committee of the University of Guadalajara with registry number DF/CB054/13.

All study-related tasks were conducted in accordance with current good clinical practice (GCP) guidelines, the Declaration of Helsinki, and the general healthcare law in the field of research in Mexico.

Data collection

A complete clinical history was collected for each participant and blood samples were obtained on two occasions, first to establish the basal values at the initial visit and again after 90 days at the end of the intervention for the final values. Bodyweight and other anthropometric parameters were measured using a "Tanita monitor BF-350" via electric bio-impedance and a "Seca" anthropometric tape. The lipid profile, as well as the renal and hepatic safety profiles, were evaluated by means of spectrophotometry using the ERBA analyzer Mannheim XI 100 and adiponectin levels were measured by sandwich ELISA assay.

Statistical analysis

The collected data were analyzed using the statistical software SPSS version 22 considering $p \leq 0.05$ as significant. All values are expressed in mean ± standard deviation, and a reliability of 95% and a power of 80% were established. A descriptive analysis was carried out to assess the

distribution and characteristics of the patients; the Shapiro Wilks test was used to determine the distribution of the variables in the sample and Levene for equality of variance [18], the results of the test in some variables and the number of patients conditioned the statistical analysis of the results to be performed with "non-parametric" tests. The U Mann Whitney test was used to identify the difference for unrelated samples (naringin vs placebo) of baseline values, and the change in values post-intervention (obtained from the difference of the basal vs final values, i.e., the deltas "δ"). The Wilcoxon test was used to determine the intra-group differences (basal vs final of each group) [18]. This study was conducted using two parallel groups.

Results

100% of the 28 patients successfully concluded the study, with an adherence to treatment greater than 90%; the basal values of both groups are shown in Table 1. No significant differences were observed between both groups in terms of age, weight, BMI (Body mass index), waist circumference, hip circumference, total cholesterol, HDL cholesterol (high-density lipoprotein), LDL cholesterol (low-density lipoprotein), triglycerides, and adiponectin levels. Body fat percentage was slightly different between groups, this being higher in the study group. Therefore, both groups were considered to be comparable.

Table 2 shows the results of the intra-group comparison (baseline vs. final) of placebo and naringin groups. Significant negative differences can be observed when comparing the basal and final values within the placebo group, as can be seen in Table 2, which shows increases in total cholesterol, and triglycerides; with decreased adiponectin levels. There also appears to be an unexpected difference in body fat percentage between baseline and final values. No additional statistically or clinically significant differences could be found among the other variables.

On the other hand, intra-group differences between baseline and final values within the naringin group showed decreases in weight, BMI, waist circumference, hip circumference, body fat percentage, total cholesterol, LDL cholesterol, and triglycerides. These results also indicate a slight increase in both HDL cholesterol and adiponectin levels; however, these changes were not statistically significant (Table 2).

Significant differences can be observed when comparing both groups (Figure 1), i.e., the comparison of the deltas "δ" [18]. The results of this study showed that weight, BMI, total cholesterol, LDL cholesterol, and triglycerides were statistically significantly lower in the naringin group than in the placebo group, while adiponectin was slightly increased. Serum creatinine and hepatic enzymes, such as ALT (alanine aminotransferase) and AST (aspartate aminotransferase), were slightly elevated in the naringin group, however, these values were not clinically or statistically significant when compared to baseline values or to the placebo group (Table 3).

Discussion

Nutraceuticals are foods or food extracts that are pharmacologically active and have medicinal value. These products

Table 1. Comparison of the baseline values of both groups

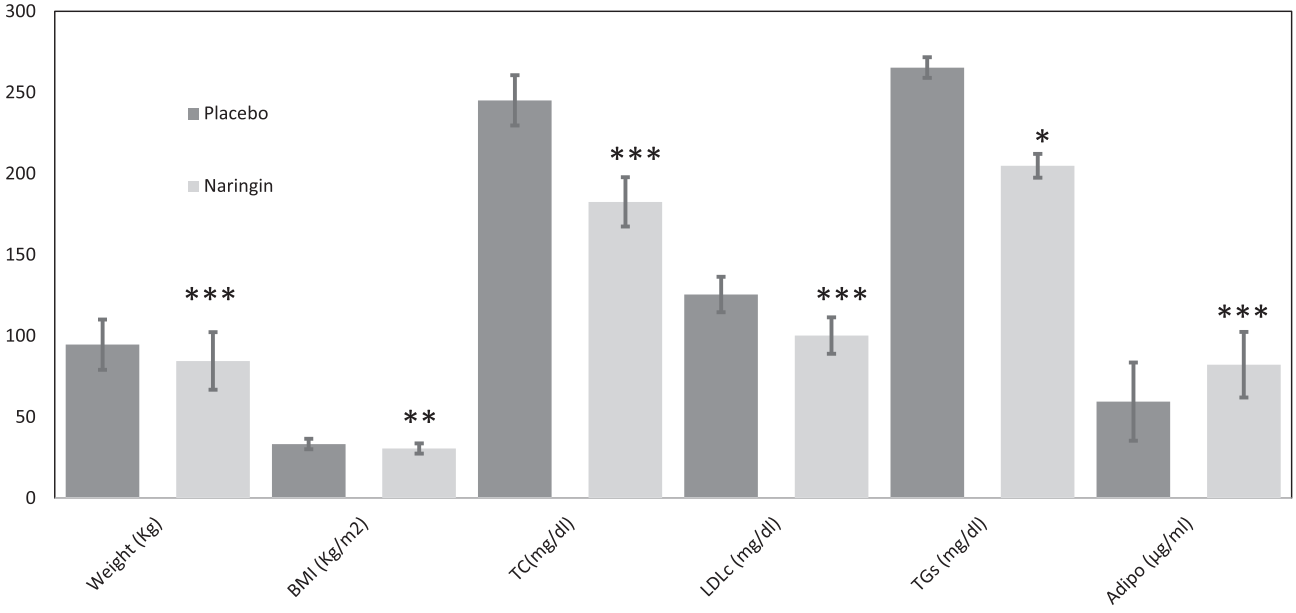
	Placebo	Naringin	
	Mean ± SD	Mean ± SD	*p*-value
Gender	9 M/5F	8 M/6F	
Age in years	50.1 ± 7.83	50.1 ± 5.48	0.98
Weight (kg)	94.5 ± 14.4	89.6 ± 18	0.43
BMI (kg/m^2)	33.5 ± 2.94	33 ± 2.89	0.64
Waist circumference (cm)	108 ± 14.1	102 ± 13.6	0.26
Hip circumference (cm)	108 ± 9.95	109 ± 9.57	0.65
Body fat (%)	36.2 ± 4.55	39.7 ± 4.10	0.04*
Total cholesterol (mg/dl)	222 ± 14.3	218 ± 12.7	0.42
Cholesterol HDL (mg/dl)	40.7 ± 4.85	43.4 ± 8.09	0.31
Cholesterol LDL (mg/dl)	117 ± 28.2	135 ± 18.3	0.07
Triglycerides (mg/dl)	231 ± 70.9	217 ± 82.2	0.62
Adiponectin (μg/ml)	0.77 ± 0.18	0.72 ± 0.18	0.41

Comparison of the baseline values between placebo and naringin groups. No statistically significant differences were observed, except in body fat % values. The values are presented in mean and SD (standard deviation). *$p < 0.05$,
M: male; F: female; Kg: kilograms; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; m^2: meters squared; cm: centimeters; mg: milligrams; dl: deciliters; μg: micrograms.

Table 2. Comparison of the results intragroup in the placebo and naringin groups

	Placebo				Naringin			
	Basal	Final			Basal	Final		
Measures	Mean ± SD	Mean ± SD	"δ"	*p*-value	Mean ± SD	Mean ± SD	"δ"	*p*-value
Weight (kg)	94.5 ± 14.4	94.6 ± 15.4	0.06	0.97	89.6 ± 18	84.5 ± 17.8	−5.1	<0.001***
BMI (kg/m^2)	33.5 ± 2.94	33.3 ± 3.23	−0.2	0.89	33 ± 2.89	30.6 ± 3.19	−2.42	<0.001***
Waist C (cm)	108 ± 14.1	106 ± 15.5	−2.17	0.06	102 ± 13.6	98.7 ± 15.2	−3.78	<0.001***
Hip C (cm)	108 ± 9.95	107 ± 10.9	−1.07	0.08	110 ± 9.57	106 ± 11.2	−3.21	0.007**
Body fat (%)	36.2 ± 4.55	32.7 ± 6.32	−3.5	0.003**	39.7 ± 4.10	33.8 ± 7.35	−5.93	0.001**
Total cholesterol (mg/dl)	222 ± 14.3	245 ± 24.1	23	0.002**	217 ± 12.7	182 ± 20.2	−35.4	<0.001***
Cholesterol HDL (mg/dl)	40.7 ± 4.85	40 ± 5.68	−0.71	0.64	43.4 ± 8.09	45.1 ± 10	1.71	0.53
Cholesterol LDL (mg/dl)	117 ± 28.2	125 ± 38.3	7.75	0.73	135 ± 18.3	100 ± 17.5	−34.9	<0.001***
Triglycerides (mg/dl)	232 ± 70.9	265 ± 106	33.5	0.035*	217 ± 82.2	204 ± 78.3	−12.3	0.41
Adiponectin (μg/ml)	0.77 ± 0.18	0.56 ± 0.19	−0.15	0.002**	0.72 ± 0.18	0.82 ± 0.25	0.09	0.09

The comparison between the baseline values and the values obtained after the use of placebo or naringin for 90 days are shown. Values are presented in mean and SD (standard deviation). "δ" were obtain from the difference of the basal vs final values. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The Wilcoxon test for intra-group comparison was used.
BMI: body mass index; C: circumference; HDL: high-density lipoprotein; LDL: low-density lipoprotein.



Comparison between the results after the 90-day intake of placebo against naringin. There are observed statistically significant anti-obesogenic and lipid-lowering effects.The values are presented in mean and SD, standard deviation.
*$p<0.05$, **$p\leq0.01$, ***$p<0.001$. "p" results were obtained from the comparison of deltas "δ"; obtained from the difference of the basal vs final values. Mann-Withney U test was used. The adiponectin values were multiplied by 100 to achieve representativeness in the graph.
BMI: body mass index; TC: total cholesterol; c: cholesterol; TGs: triglycerides; Adipo: adiponectin.

Figure 1. Comparison of final values of naringin against placebo groups.

are commonly used as part of alternative treatments, and may even promote greater adherence to treatment for certain pathologies. Due to their many benefits, the popularity of nutraceuticals has increased among the general public and healthcare providers with the increasing availability of nutraceutical supplements [19]. Currently, certain nutraceuticals are considered as scientifically viable supplements that can be used for the treatment of certain diseases, including chronic metabolic diseases like dyslipidemias [20, 21]. Flavonoids, such as naringin, are one of the many different types of nutraceuticals which have been used in the treatment of dyslipidemia, and they could even be applied in circumstances where patients cannot tolerate therapy with statins [22, 23].

Table 3. Treatment biosafety comparison

Groups	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)
Placebo (Mean ± SD)			
Basal	20.6 ± 8.3	22.4 ± 9	0.81 ± 0.16
Final	35.4 ± 19.9	27.6 ± 5.8	0.93 ± 0.2
Naringin (Mean ± SD)			
Basal	22.3 ± 8.8	24.1 ± 4.2	0.71 ± 0.13
Final	26.9 ± 10.1	26.4 ± 9.9	0.76 ± 0.12

Results of the liver and kidney Biosafety before (basal) and after (final) the intervention of naringin or placebo, no clinical or statistically significant changes were observed in any of the groups. $p \geq 0.05$. ALT: alanine aminotransferase; AST: aspartate aminotransferase; SD: standard deviation.

Table 2 and Figure 1, show the main results obtained within our study. Table 2 elucidates the intra-group differences between the basal and final values for the control group, which expectedly does not show many changes save for those which are to be expected based upon the natural evolution of the disease, such as a 10% increase in total cholesterol, 15% increase in triglycerides and a 23% decrease in adiponectin levels. An anomalous decrease in body fat percentage by approximately 4% was also observed, however, no changes were seen in body weight or BMI. On the other hand, the same Table 2 shows the intra-group differences between the baseline and final values within the naringin group, where we can observe statistically significant decreases in body weight, BMI, waist circumference, and body fat percentage (6%). Both clinically and statistically significant decreases can also be observed in total cholesterol (−35 mg/dl), which could mainly be attributed to a reduction in LDL cholesterol.

The significant statistical differences are only in the values of weight, BMI, total cholesterol, LDL cholesterol, triglycerides, and adiponectin levels when we compare these results with those of the placebo group, as shown in Figure 1.

A study by UJ Jung, in 2003 [14], conducted with 30 patients with hypercholesterolemia who were treated with a 400 mg naringin daily over the course of 8 weeks obtained results that were similar to those found in the current study. Results showed that the consumption of naringin reduced total cholesterol by 17% and LDL cholesterol by 14%. Likewise, our study found that total cholesterol was reduced by 16%, while LDL cholesterol was reduced by 26% (From a baseline average of 135 mg/dl to 100 mg/dl by final measurements). Our observations showed greater reductions in lipid profiles than those reported by Jung [14], however, this could have been a result of the longer duration of our study [24].

The results obtained are clinically significant given that 85% of patients achieved a goal of < 200 mg/dl of total cholesterol and 57% of patients achieved LDL cholesterol values of < 100 mg/dl [25, 26]. These results are very promising even when compared to traditional statin therapy. Sponseller, for example, conducted a study in 2014 [27], comparing the use of pitavastatin 4 mg vs pravastatin 40 mg. Both statins are recommended for the treatment of moderate dyslipidemia [25, 28]. The results of this comparative study demonstrated that a 3 months' course of treatment with pitavastatin reduced LDL cholesterol by 38% and total cholesterol by 25%, while pravastatin reduced LDL cholesterol by 26% and total cholesterol by 18%. The results obtained with the use of pravastatin in the above-mentioned trial are similar to those obtained with the use of naringin in the current study. Although, we must also take into account that the Sponseller's study was conducted in patients with total cholesterol and LDL cholesterol values which were greater than those in our study. These results obtained by statins are not in any way isolated, and are highly reproducible, as can be seen in a study conducted by Saito in 2003 where similar values were obtained [29]. These results could easily be obtained with the use of other statins, as we can clearly see in an analysis conducted by Meor Anuar Shuhaili in 2017 [30].

Naringin's mechanism of action for lowering lipids seems to be similar to that of statins, which act by reducing the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) and ACAT (acetyl-coenzyme A acetyltransferase) [15].

Table 2 and Figure 1 show the beneficial effects which naringin administration may have upon body weight, BMI and adiponectin levels. These values, however, are only statistically significant when compared to the control group; nevertheless, the potential application of naringin for weight management and even for the treatment of obesity is clear. A clinically significant reduction in body weight of approximately 5 kg was observed in the naringin group, which is important especially considering the lack of dietary control and the absence of a similar decrease in the control group. The Intra-group comparison between the basal and final values within the naringin group also demonstrated significant decreases in BMI by 3 kg/m^2, waist circumference by 3.8 cm, hip circumference by 3.2 cm and body fat percentage by 5.9% as well as an increase in adiponectin by 1.8 μg, which could be potentially be associated to the decreased body weight and increased HDL cholesterol, given their close relationship [31].

The mechanism of action for the anti-obesity effects of naringin, according to the review conducted by Alam MA [15], is based upon the reduction of adipose tissue mass and the inhibition of preadipocyte proliferation. Naringenin, which is the active metabolite of naringin, suppresses the proliferation of preadipocytes without having harmful effects in subsequent adipogenesis. On the other hand, naringenin also increases the oxidation of fatty acids in

hepatocytes by increasing peroxisomal β-oxidation and also increases the activity of acetyltransferases (ACAT, also known as thiolase), acyl-coenzyme A oxidase, carnitine O-octanoyl transferase (COT), carnitine acyltransferase medium chain/long chain and 3-ketoacyl-coenzyme A [15, 32].

Hepatic transaminase and creatinine levels were measured in order to insure hepatic and renal biosafety, respectively. The results of Table 3 demonstrate that no clinically or statistically significant changes were observed, thus we can infer that naringin is a safe treatment. Additionally, no adverse effects were observed during this study in either group.

While this study does show promising results, it should be taken into account that all results were obtained from a small group of participants which were selected based upon specific inclusion criteria. Additionally, only 450 mg of naringin was administered to these participants given the lack of information available in the literature relating to minimum and maximum effective doses for this substance. We would also like to emphasize that no additional studies could be located which investigated the effects of monotherapy treatment with naringin upon anthropometric measurements and adiponectin levels in humans. Furthermore, the results obtained in our study did, in fact, reaffirm the results found in other studies, and could potentially provide a new perspective from which further studies could be conducted.

In conclusion, the consumption of naringin improves the lipid profile in patients with dyslipidemia, with statistically significant decreases in total cholesterol and LDL cholesterol. In addition, naringin has a positive effect on obesity by decreasing body weight, BMI, and improving the metabolic profile of the patient by contributing to the increase of serum adiponectin levels. Our results support the use of naringin as a therapeutic agent which may play an important role in the treatment of metabolic disorders.

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History
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