

Therapeutic Effects of Green Tea on Nonalcoholic Fatty Liver Disease in 10-16-Year-Old Children

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ABSTRACT

Introduction: Nonalcoholic Fatty Liver Disease (NAFLD) is characterised by fat accumulation in the liver. Treatment of NAFLD in children is an important issue but the options are limited. Green tea has antioxidant and anti-hyperlipidemic effects but studies; on the effect of green tea in children are limited.

Aim: To investigate effect of green tea on NAFLD in children.

Materials and Methods: In this study, 52 children aged 10-16 years with NAFLD were divided into two groups of 26 each: Intervention and control. For both groups, modification of diet and intensification of physical activity were prescribed for three months. Intervention group was also treated with green tea tablets. Sonography and measurements of liver enzymes {Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)}, lipid profile and Body Mass Index (BMI) were conducted

before and after the intervention. The data were analysed by the Statistical Package for the Social Sciences (SPSS) version 19.0 using ANCOVA.

Results: After treatment with green tea, fatty liver grade decreased significantly in the intervention group compared to control group ($p < 0.0001$). In addition, this treatment caused significant decrease in ALT, AST, and triglyceride levels and significant increase in High-Density Lipoprotein (HDL) level ($p < 0.05$), but Low-Density Lipoprotein (LDL) level did not decrease significantly in the intervention group compared to control.

Conclusion: Oral prescription of green tea was effective in improving fatty liver grade, decreasing hepatic fat accumulation and improving liver function, weight loss and reducing ALT and AST without any side effects. These effects can be due to green tea compounds such as polyphenols especially catechin and antioxidant and anti-hyperlipidemic effects.

Keywords: Alanine aminotransferase, Aspartate aminotransferase, Green tea extract, Nonalcoholic steatohepatitis

INTRODUCTION

NAFLD is characterised by hepatic fat accumulation despite low amounts of alcohol intake, presenting with hepatomegaly signs [1]. NAFLD is a metabolic disorder frequently diagnosed in western and eastern countries, resulting in increased liver and cardiovascular disease-related morbidity and mortality [2]. The prevalence of NAFLD is 34% in adults [3]. Most NAFLD patients are 40-60 years-old but children aged over 10 years are also likely to develop NAFLD [4].

NAFLD is now considered an independent condition as with obesity, hypertension and diabetes. It is widely acknowledged that NAFLD has close association with central obesity. However, 20-40% of NAFLD patients are not obese. It has been widely accepted that hyperlipidaemia leads to NAFLD [1].

The cause and treatment for NAFLD have not yet been definitely determined [1]. Early diagnosis of this disease is essential and its treatment can prevent progression to cirrhosis [5,6]. Lifestyle interventions such as exercise and weight loss are the only widely accepted treatments for this disease but they are difficult to adhere to for most NAFLD patients [5].

Camellia sinensis (Green tea) is a medicinal plant that originated from China and South East Asia thousands of years ago and is one of the most widely known beverages across the world [7].

In green tea drinkers, a significant reduction has been reported in the risk of developing hepatic diseases such as hepatocellular carcinoma, liver cirrhosis, liver steatosis, chronic liver disease and hepatitis [8]. *C. sinensis* is one of the richest sources of flavonoids with different health benefits [9].

Green Tea Polyphenol (GrTPs) have different health benefits [9]. GrTPs have antimutagenic, antioxidant, antidiabetic, antibacterial and anti-inflammatory properties [10]. GrTPs prevents hyperlipidaemia in the

liver and causes increase in energy consumption, oxidation of fat and decrease in the body fat percentage [11]. In animals on high-fat diets that received *C. sinensis* and GrTPs, lower Triglyceride (TG) and cholesterol levels and higher faecal fat levels compared to controls were observed [12]. *C. sinensis* therefore has potential to control the weight of obese people. In vitro, *C. sinensis* extract is involved in the process of lipid emulsification, inhibition of fatty acids activity and synthesis as well as decrease in the hepatic fat accumulation [5,13].

The main polyphenolic compounds of *C. sinensis* are catechins, such as Epigallocatechingallate (EGCG), epigallocatechin, epicatechingallate, and epicatechin, which have been reported to have beneficial effects on human health [13]. Increased serum levels of liver enzymes indicate liver injury and ALT is the most important marker of liver injury [14]. The increased liver enzyme levels can be observed alongside simple steatosis in over 50% of the patients, and are observed in approximately 80% of patients with advanced NAFLD [15].

To treat NAFLD patients, it is necessary to use plant-based drugs that cause comparatively fewer side-effects and are available and inexpensive as well as effective in improving liver enzymes, hepatic lipids, and liver morphology with regard to unsatisfactory effects of weight loss and exercise protocols as well as inefficiency, long-term effects and serious side-effects of certain chemical drugs [5,16,17]. Recent studies have highlighted the necessity of conducting further studies for confirming the effects of flavonoids, *C. sinensis* and its extract on liver injury [1,18].

Although a number of studies have been conducted in different countries, most of them have been conducted on mice [5,12,19,20], and few clinical trials have investigated this issue [21]. This study aimed to investigate the effect of *C. sinensis* on NAFLD, fatty liver

grade, TG and cholesterol levels, the body weight and liver enzymes in children aged 10-16 years.

MATERIALS AND METHODS

This Quasi-experimental study (single-blind clinical trial) was done in a university endocrine clinic in Shahrekord, southwest of Iran from November 2014 to October 2015. The study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (code: IR.SKUMS.REC.1394.57). The present study population consist of 10-16 years old children. The sample size of this study was estimated 26 people in each group according to a formula of sample size calculation (Equation 1) and taking its parameters into account:

Equation 1:

$$n = \frac{(z_{1-\beta} + z_{1-\alpha})^2 (s_1^2 + s_2^2)}{d^2}$$

Children with body mass index (BMI) $\geq 85^{\text{th}}$ percentile or hypertriglyceridaemia (TG >150 mg/dL and/or cholesterol >200 mg/dL) [22] and apparently healthy were examined by a paediatric endocrinologist and gastroenterologist. A detailed history and physical examination was done for all patients. Diagnosis was confirmed by ultrasound and laboratory evidence of fatty liver. The authors selected children with fatty liver on sonography and increased AST and ALT levels after exclusion of other causes. Grading of the fatty liver was conducted according to the protocol described by Saverymuttu SH et al., [23]. All the imaging was done by the same radiologist who was unaware of intervention.

The participants were selected by convenience sampling and were divided into two groups after they provided informed consent to participate in the study and were ensured that the data would be kept private. The present authors used minimisation for randomisation. The data on demographics (age, sex, BMI), the results of ultrasound, ALT, AST, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and TG, as well as weight before and after the intervention and any side-effects were recorded in a checklist.

Exclusion criteria were: taking ethanol and hepatotoxic drugs and suffering from cirrhosis of the liver, peptic ulcer, hyperthyroidism, severe anxiety, and severe liver, heart, and renal failure, and systemic diseases.

For both groups, modification of diet and intensification of physical activity were prescribed for three months. Meanwhile, intervention group was treated with green tea 500 mg tablet (Green teadin, Dineh Iran Company.), prepared from pulverised *C. sinensis* leaf and containing 50 mg total standardised polyphenol, three times per day. The participants were examined monthly for drug side-effects and were followed up for adherence to the drug use. At completion of the 3-month intervention, height, weight, liver enzymes and lipid profile were measured again; ultrasound was conducted again by the sonographer who conducted the baseline sonography, and the data were recorded.

STATISTICAL ANALYSIS

Data analysis was conducted by ANCOVA using SPSS version 19.0. The p-value <0.05 : were considered significant.

Groups	Difference after intervention (Mean \pm SD)						
	AST U/L	ALT U/L	LDL mg/dL	HDL mg/dL	Triglyceride mg/dL	Weight Kg	BMI (kg/m ²)
Control	25.03 \pm 1.50	2.34 \pm 2.79	2.19 \pm 4.57	-1.64 \pm 1.35	10.07 \pm 8.97	1.53 \pm 0.42	0.06 \pm 0.18
Intervention	-4.5 \pm 1.34	-13.07 \pm 3.18	-8.19 \pm 7.96	2.26 \pm 0.25	-40.76 \pm 25.36	-0.63 \pm 0.52	-1.18 \pm 0.26
p-value	<0.0001	0.006	0.6	<0.01	0.034	0.006	0.006

[Table/Fig-2]: Comparison of mean difference in studied variables before and after intervention in green tea group and control group. p <0.05 : Significant

RESULTS

A total of 52 patients with NAFLD participated in this study. Thirteen girls and thirteen boys were participated in each of the two groups. The age range of the participants was 10-16 years with mean age of 12.53 \pm 1.99 years and 11.84 \pm 1.53 years in intervention group and control group, respectively. There was no significant difference in age between the two groups (p=0.16). The mean weight of intervention group was 63.76 \pm 16.25 kg and that of control group was 57.38 \pm 12.74 kg; and the mean height of intervention group was 148.84 \pm 8.15 cm and that of control group was 150.255 \pm 49.11 cm. There was no significant difference in weight and height between the two groups (p=0.9 and 0.62, respectively).

In the control group, before intervention, 22 children had Grade 1 fatty liver and four children had Grade 2 fatty liver. After intervention, 21 children had Grade 1 fatty liver and five children had Grade 2 fatty liver. In the intervention group, before intervention, 19 children had Grade 1 fatty liver and seven children had Grade 2 fatty liver. After intervention, 10 children had grade 1 fatty liver and no child had Grade 2 fatty liver. In 16 children, fatty liver did not change and their ultrasound results were normal. Changes in fatty liver grade were significant in intervention group and non-significant in control group [Table/Fig-1].

Groups		Intervention diet and exercise+green tea	Control diet and exercise
Grade of fatty liver		Number (%)	Number (%)
Before intervention	Grade II	7 (27%)	4 (15.4%)
	Grade I	19 (73%)	22 (84.6%)
After intervention	Grade II	0 (0%)	5 (19.2%)
	Grade I	10 (38.5%)	21 (80.8%)
	Grade 0	16 (61.5%)	0 (0%)
p-value		<0.0001	0.59

[Table/Fig-1]: Comparison of fatty liver grade before and after intervention in green tea group and control group. p <0.05 : Significant

The levels of TG, HDL, LDL, ALT, AST, weight and BMI were recorded before and after intervention in both groups and mean changes in these variables were estimated. Except for the changes in LDL, the changes in other variables were significant in both groups (p <0.05) [Table/Fig-2].

DISCUSSION

In this study, the effect of *C. sinensis* tablets on NAFLD in 52 children aged 10-16 years with NAFLD was investigated. As NAFLD is seen in children over 10 years of age so, this age group was selected [4]. Intervention and control groups were not significantly different in terms of age, sex, weight, and BMI. Because fatty liver grade and lipid profile are associated with these variables, their confounding effects on results were neutralised and therefore the results are more likely to be attributed to the effect of *C. sinensis* in reducing lipidaemia, weight and BMI as well as improving fatty liver. Because antioxidant and anti-inflammatory properties of certain medicinal plants have already been confirmed and the effects of such plants in preventing steatohepatitis in the cases on high-fat diet are promising [20], The authors were encouraged to investigate the effect of *C. sinensis* consumption on NAFLD. In this study using *C. sinensis* tablet could improve fatty liver grade, while in control group, fatty liver did not

improve. *C. sinensis* effect on the liver may be attributed to its antioxidant effect. *C. sinensis* did not cause significant decrease in LDL levels. Moreover, the changes in serum TG levels displayed significant effect of *C. sinensis* in decreasing TG levels compared to the effects of either diet or exercise. In addition to antioxidant effects, *C. sinensis* has also anti-hyperlipidemic effects that are possibly due to inhibitory effect of catechin in *C. sinensis* on phospholipase A2 that leads to decreased absorption of lipids [6]. *C. sinensis* has also been reported to have anti-apoptotic, nutrient-reducing, and inflammatory response-modulating effects [24]. Animal studies have shown that consumption of tea and catechin decreases triacylglycerol and serum total cholesterol concentration, prevents fat accumulation in the liver and body and stimulates thermogenesis [21]. In addition, drinking 690 mg catechin-containing beverage for 12 weeks caused significant decrease in the body and subcutaneous fat in Japanese healthy men [25]. In the current study, the changes in serum HDL levels confirmed the significant effect of *C. sinensis* in increasing HDL levels compared to control group, representing its contribution to weight loss even in the short term. In a study using different doses, daily diet +1.3 mg/g EGCG led to weight loss in DSS-treated BALB/c mice [19]. However, indefinite results regarding the anti-obesity effects of *C. sinensis* have also been reported [15]. A study showed significant weight loss, decrease in BMI and waist circumference as well as similar decreases in the plasma levels of total cholesterol and LDL after 12 weeks' treatment with high dose of EGCG in women aged 20-60 years. The anti-obesity mechanism might be, to a certain extent, related to inhibition of ghrelin secretion, which resulted in increased adiponectin [26].

In many studies, decrease in LDL has occurred after treatment with *C. sinensis* [27-30]. Decreased absorption of cholesterol and liver cholesterol concentration leads to increase in expression and activity of LDL receptors and this increased activity in the liver-specific cells cause cholesterol uptake from the blood flow [28]. In the present study, such decrease was also seen but it was not significant. This inconsistency in the findings can be due to differences in patients and duration of *C. sinensis* treatment and dose as well as the route of administration.

A study indicated that 24-week treatment with *C. sinensis* in overweight Japanese children, compared to those followed up on exercise and diet, caused significant decrease in LDL [27]. These children, however, were not NAFLD patients. In this regard, the study of Basu A et al., demonstrated significant decrease in weight and BMI, decrease in LDL and total cholesterol and increase in HDL after eight-week treatment with *C. sinensis* in obese men and women [30], which is consistent with the present findings regarding weight loss and HDL improvement. Consistent with the current study, Suliburska J et al., reported that supplementation with *C. sinensis* led to decreased total levels of cholesterol, LDL and triglyceride and increased levels of HDL and cholesterol in obese people [31]. Another study showed that taking *C. sinensis* caused significant decrease in LDL and remarkable increase in HDL [29]. In addition, eight-week treatment with *C. sinensis* extract did not cause any significant change in total cholesterol and TG, but resulted in increase in HDL concentration, decrease in adipose and improvement of lipolytic pathways [32]. In a study on diabetic people, one-month consumption of *C. sinensis* did not lead to significant change in total cholesterol, TGs, HDL, and LDL [33]. GrTPs can decrease the risk of certain complications such as cirrhosis, non-alcoholic steatohepatitis, and hepatic cellular carcinoma [5].

In the present study, the levels of ALT and AST decreased after *C. sinensis* treatment as compared to control group. This medicinal plant has potential to prevent steatosis and therefore injuries due to oxidative stress, i.e., steatohepatitis. A study with mice reported that consumption of *C. sinensis* extract alongside exercise decreased plasma ALT level by 92% [34]. Significant decrease was observed in AST and ALP levels in rats orally administered with 10% aqueous

C. sinensis extract compared to rats treated with 20% *C. sinensis* extract while the level of ALT in group fed with 20% of *C. sinensis* extract decreased significantly [35]. A study on diabetic people reported that only ALT increased significantly after *C. sinensis* consumption compared to controls. Other liver enzymes and the lipid factors did not change significantly [33]. Besides that, Hasanein AM et al., reported the most prominent decrease in the mean levels of AST, ALT and ALP was observed in the group on high-fat diet and treated daily with aqueous *C. sinensis* extract [36]. In the study of Pezeshki A et al., *C. sinensis* extract (500 mg tablet/day) caused significant decrease in ALT and AST compared to placebo in 20 to 50 years-old patients with NAFLD [37], which is consistent with the present results on children aged 10-16 years. The present authors used *C. sinensis* tablet in the current study, but studies with animals have demonstrated that parenteral administration of *C. sinensis* is better than taking it orally [29].

The present study showed that *C. sinensis* compounds exerted protective effects against liver diseases in children and caused decrease in AST and ALT levels and hepatic fat accumulation, improvement of liver function and weight loss. The contribution of phenolic compounds and catechin in *C. sinensis* to these observations should be taken into account. However, such effects are more prominent when treatment is accompanied by exercise and appropriate diets. Although authors did not observe any side-effects, lack of prescribing polyphenolic compounds in high doses for children should be seriously considered because long-term use of *C. sinensis* extract in the mice on high-cholesterol diet has led to adverse effects and induced liver injury [9]. Overall, inconsistency in results can be due to differences in duration of *C. sinensis* treatment, dose, the type and compounds of the tablet or extract used, people's habitual drinking of *C. sinensis* in some regions and the form of administration (tablet, syrup, bag, brewed, etc.).

LIMITATION

Limitations of the current study was small sample size and short follow-up duration. It is recommended to design future study on larger sample and longer follow-up.

CONCLUSION

With regard to the positive effects of *C. sinensis* in decreasing weight, BMI and hepatic fat accumulation as well as improving liver function, decreasing liver enzymes ALT and AST and improving blood lipid profile in children aged 10-16 years in this study, prescription of this medicinal plant, in 500 mg dose, is recommended particularly for preventing development of liver diseases in children especially NAFLD. These effects can be due to certain compounds such as polyphenols especially catechin in *C. sinensis* and its antioxidant and anti-hyperlipidemic effects.

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