

Research Article

Potential additive effects of garcinia cambogia on atorvastatin treated hyperlipidemic patients: randomized crossover clinical study

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ABSTRACT

Background: Dyslipidemia is a major risk factor linking in the direction of the progression of ischemic heart diseases, which is measured to be the chief principal reason of international morbidity and mortality. Numerous lessons seeming for substitute treatments include attempted herbal medicine for reducing the expansion of ischemic heart and vascular diseases. Along with herbs with hypolipidemic actions were garlic, garcinia cambogia, gum guggul and others plants. Garcinia cambogia is an herbal agent found in different fruit plants inhibit lipid synthesis via its active materials hydroxycitric acid that inhibit cytoplasmic adenosine triphosphate-dependent citrate lyase, which responsible for hepatic lipogenesis in dose dependent manner. Thus, the objective of this experimental research was for elucidation the potential combined effects of atorvastatin and garcinia cambogia resting on lipid profile in hyperlipidemic patients.

Methods: A total of 25 hyperlipidemic patients enrolled in this clinical trial under scientific approval committee and spoken consent taken from all patients. Five patients were withdrawn from this study due to incompliance so, only 20 patients (12 males + 8 females) continue this clinical trial. All patients not took any medications through 2 weeks and all non-diabetic or hypertensive with age ranged 45-65 years. The patients divided into two groups: Group A: 10 patients (4 females + 6 males) take atorvastatin 40/day. Group B: 10 patients (6 males + 4 females) take atorvastatin 40/day + garcinia cambogia 500/day. The duration of treatment was 8 weeks, and baseline lipid profile measurements were done and regarded as control.

Results: The atorvastatin effects during 8 weeks treatment at dose of 40 mg/day produced significant effects on all lipid profile $p < 0.05$, mainly on serum cholesterol and low-density lipoprotein (LDL) levels and less significant effects on atherogenic index (AI), triglyceride and very LDL (VLDL). While garcinia cambogia produced significant reductions in serum lipid and improve other lipid parameters, garcinia cambogia 500 mg/day significantly improve serum cholesterol, VLDL, and LDL $p < 0.05$ but produced insignificant effect on high-density lipoprotein and AI $p > 0.05$. The combined effects of garcinia cambogia 500 mg/day and atorvastatin 40 mg/day showed significant effects on all lipid profiles and AI $p < 0.05$.

Conclusion: This study scrutinizes the value of garcinia cambogia in treatment of hyperlipidemia alone or in combination with atorvastatin. It produced significant additive effect with atorvastatin and hence atorvastatin doses can be reduced and substituted with garcinia cambogia for reduction serious atorvastatin associated adverse effects.

Keywords: Hyperlipidemia, Atorvastatin, Garcinia cambogia

INTRODUCTION

Dyslipidemia is a major risk factor linking in the direction of the progression of ischemic heart diseases which is

measured to be the chief principal reason of international morbidity and mortality.¹ Crossover revisions had been showed a encouraging association among the frequency of ischemic heart diseases and hyperlipidemia. Therefore;

a lowest effectual treatment intended for decreasing lipid profile might so be of substantial attention.² Numerous lessons seeming for substitute treatments include attempted herbal medicine for reducing the expansion of ischemic heart and vascular diseases. Along with herbs with hypolipidemic actions were garlic, garcinia cambogia, gum guggul and others plants. Thus many different articles boast and recommended long-standing utilization of garlic improve dyslipidemia and reducing the risk of hyperlipidemia associated cardiovascular complications and development of atherosclerosis also; long-term management with garlic enhance cardiac antioxidant actions and participate for optimal cardiac protections, garlic also guards vasculature beds via seizing bad and harmful cholesterol within a fewer detrimental variety, plus through overcrowding unwanted alteration within vascular endothelium.³

Guggulipid be a herbal agent that lessen the hazard of hyperlipidemia associated vascular and cardiac damage, via elevating level of high-density lipoprotein (HDL) through its active component (gugulsteron).⁴ Concerning the capsaicinoid of capsain, which produced significant effects on lowering and improving dyslipidemia in animal model study via amelioration of *de novo* cholesterol synthesis.⁵ Garcinia cambogia is a herbal agent found in different fruit plants inhibit lipid synthesis via its active materials hydroxycitric acid (HCA) that inhibit cytoplasmic adenosine triphosphate (ATP)-dependent citrate lyase which responsible for hepatic lipogenesis in dose dependent manner.⁶ It has been shown with the intention of the provider through herbal flavonoid augments the efficiency of rodents from dyslipidemia. Flavonoids from Garcinia Cambogia successfully improved hyperlipidemia in animal model studies through protection from lipid peroxidation and prevention of tissue damages.⁷

Atorvastatin is potent long acting inhibitor of hydroxymethyl glutaryl coenzyme A (HMG-COA) reductase inhibitor, is efficient hypolipidemic agent so reducing cardiovascular complications, mortality and morbidity, nevertheless, valuable belongings of atorvastatin appear to produce immediate effects regardless of cholesterol level.^{8,9} Numerous previous studies have been established a quick enhancement in cardiac function by atorvastatin, but independent exclusively on rapid cholesterol lessening. Consequently, atorvastatin might have pleotropic effects like antioxidant and antiinflammatory further than hypolipidemic effect.¹⁰ Atorvastatin is inducing more potent reduction in plasma lipid than other statin. it cause irreversible inhibition of (HMG-COA) enzyme so decreasing serum cholesterol, low-density lipoprotein (LDL), very LDL (VLDL) and less effect on triglyceride (TG), all these diminish risk of atherogenesis.¹¹⁻¹³

Garlic synergize atorvastatin effects via pharmacokinetic profile, while coconut agent produced pharmacodynamic synergism with atorvastatin in lowering plasma cholesterol and augmentation of HDL level, so both can be combined for experimental treatment of hyperlipidemia in.¹⁴ Furthermore, coconut oil be able to for that reason be worn

beside atorvastatin in the direction of presenting substitute management against dyslipidemia.¹⁵

Thus, the objective of this experimental research was for elucidation the potential combined effects of atorvastatin and garcinia cambogia resting on lipid profile in hyperlipidemic patients.

METHODS

This study conducted in Department of Pharmacology, College of Medicine, Almustansiriyah University in cooperation with Central Health Laboratory, Ministry of Health, Iraq-Baghdad from January to March of 2014. Twenty-five hyperlipidemic patients enrolled in this clinical trial under scientific Approval Committee, and spoken consent was taken from all patients. Five patients were withdrawn from this study because of incompliance so, only 20 patients (12 males + 8 females) continue this clinical trial. All patients not took any medications through 2 weeks and all non-diabetic or hypertensive with age ranged 45-65 years.

The patients divided into two groups:

Group A: 10 patients (four females + six males) take atorvastatin 40/day.

Group B: 10 patients (six males + four females) take atorvastatin 40/day+garcinia cambogia 500/day.

The duration of treatment was 8 weeks, and baseline lipid profile measurements were done and regarded as control.

Materials

1. Lipid profile kit (manufacturer part no: 2700 wkp) Linear Chemical, Spain
2. Atorvastatin 40 mg (Lipitor, India) and garcinia cambogia (Mepaco Slim, India).

All patients serum lipid measured at morning after overnight fasting (12 h) and considered as control then informing the patient for taken the medications for 4 weeks at night and after the duration of treatment, 10 ml of blood taken for lipid profile assessment then centrifuged at 2500 round/min to obtain serum, which was stored in anticipation of used. Enzymatic colorimetric method was used as following:¹⁶

Total serum cholesterol: 0.5 ml serum + 1 ml cholesterol reagent → 5 min centrifugation → wait 5 min → read at 500 wvl.

Total serum TG: 0.5 ml serum + 1 ml TG reagent → 5 min centrifugation → wait 5 min → read at 500 wvl.

HDL: 0.5 ml serum + 0.05 HDL reagent → wait 10 min → 5 min centrifugation → take 0.05 ml supernant → wait 5 min → read at 500 nn.

VLDL: $VLDL = TG/5$

LDL: $LDL = TG - (HDL + VLDL)$

Atherogenic index (AI): $AI = (TC - HDL) / HDL$ ¹⁷

Data analysis

The entire data of this study are accessible as mean ± standard deviation using *t*-test (unpaired) and a significant difference was regarded when $p < 0.05$.

The characteristic of the study was showed in Table 1.

RESULTS

The atorvastatin effects during 8 weeks of treatment at dose of 40 mg/day produced significant effects on all lipid profile $p < 0.05$, mainly on serum cholesterol and LDL levels and less significant effects on AI, TG and VLDL (Table 2).

While garcinia cambogia produced significant reductions in serum lipid and improve other lipid parameters, garcinia cambogia 500 mg/day significantly improve serum cholesterol, VLDL, and LDL $p < 0.05$, but produced insignificant effect on HDL and AI $p > 0.05$ (Table 3).

The combined effects of garcinia cambogia 500 mg/day and atorvastatin 40 mg/day showed significant effects on all lipid profiles and AI $p < 0.05$ (Table 4). Regarding the AI which reflect the potential effect of hyperlipidemia, garcinia reduced the AI from 5.5 ± 0.91 to 4.63 ± 0.341 , so it produced insignificant effect ($p > 0.064564896$), but atorvastatin fashioned significant reduction from 5.5 ± 0.91

to 2.72 ± 0.42 ($p < 0.001147061$), while the dual combined effects of garcinia cambogia and atorvastatin produced more significant effects than atorvastatin alone they were reduced AI from 5.5 ± 0.91 to 1.59 ± 0.90 ($p < 0.000001$) (Figures 1 and 2).

DISCUSSION

Hyperlipidemia or hyperlipidemia might be overturn able in numerous conditions throughout regular feeding and habitual exercise. Hyperlipidemia was defined as exaggerated or elevations in the ranks of serum lipid mainly total cholesterol and TG.¹⁸ Even though it asymptomatic but significantly elevate the risk of cardiac and vascular disorders like angina pectoris, myocardial infarction, and peripheral vascular

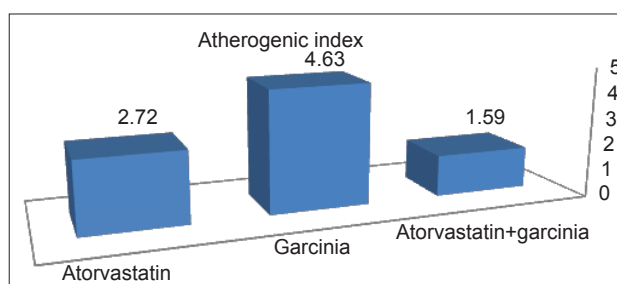


Figure 1: Effects of garcinia cambogia and/or atorvastatin on atherogenic index.

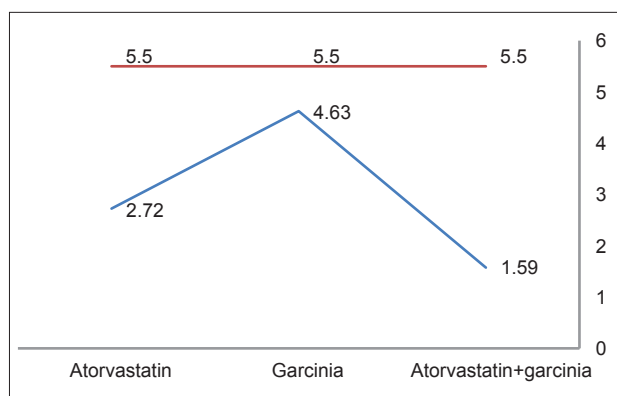


Figure 2: Reduction in atherogenic index from baseline values after treatments with atorvastatin, garcinia cambogia or both.

Table 1: The characteristic of study.

Patients	
Age	45-65 years
Gender	8 Females 12 Males
Drugs	Atorvastatin Garcinia cambogia
Duration of study	8 weeks
Lipid profile measurement	Enzymatic colorimetric method

Table 2: Effect of atorvastatin on plasma lipid profile in hyperlipidemic patients during 8 weeks of treatment.

Lipid profile	Control (mean±SD)	Atorvastatin (mean±SD)	<i>p</i> value
Cholesterol (mg/dl)	277.45±3.43	213.21±1.45	0.000496*
TG (mg/dl)	396.65±5.63	341.00±3.23	0.005771553*
VLDL (mg/dl)	79.33±1.126	68.2±0.64	0.002872813*
LDL (mg/dl)	165.26±0.344	87.78±1.73	4.11E-05*
HDL (mg/dl)	42.86±1.97	57.23±2.54	0.000221587*
AI	5.5±0.91	2.72±0.42	0.001147061*

*Significant effect. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TG: Triglyceride, AI: Atherogenic index, SD: Standard deviation

Table 3: Consequence of garcinia cambogia on lipid profile during 8 weeks of treatment 500 mg/day.

Lipid profile	Control (mean±SD)	Garcinia cambogia (mean±SD)	p value
Cholesterol (mg/dl)	277.45±3.43	244.54±1.65	3.87E-05*
TG (mg/dl)	396.65±5.63	311.19±1.87	7.45E-05*
VLDL (mg/dl)	79.33±1.126	62.23±0.37	0.000373*
LDL (mg/dl)	165.26±0.344	138.91±0.05	0.000484*
HDL (mg/dl)	42.86±1.97	43.4±1.23	0.064475
AI	5.5±0.91	4.63±0.341	0.064564896

*Significant effect. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TG: Triglyceride, AI: Atherogenic index, SD: Standard deviation

Table 4: Combined effects of atorvastatin and garcinia cambogia on lipid profile in hyperlipidemic patients within 8 weeks of treatment.

Lipid profile	Control (mean±SD)	Atorvastatin+garcinia cambogia (mean±SD)	p value
Cholesterol (mg/dl)	277.45±3.43	199.12±2.67	4.06E-05*
TG (mg/dl)	396.65±5.63	277.32±1.85	8E-05*
VLDL (mg/dl)	79.33±1.126	55.46±0.37	0.000267*
LDL (mg/dl)	165.26±0.344	66.99±0.9	4.15E-09*
HDL (mg/dl)	42.86±1.97	76.67±1.40	0.000283*
AI	5.5±0.91	1.59±0.90	0.000001*

*Significant effect. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TG: Triglyceride, AI: Atherogenic index, SD: Standard deviation

disease. Since of these hazards, management is frequently suggested intended for hyperlipidemia patients.

In clinical management of hyperlipidemia atorvastatin and other statins group mainly indicated for dyslipidemia chiefly involving cholesterol rising but; atorvastatin successfully reduce blood LDL though, atorvastatin alone ineffective for optimal LDL level as recommended via the current guiding principle National Cholesterol Education Program.¹⁹ Moreover; concentrated atorvastatin treatment elevate the risks of rhabdomyolysis and hepatotoxicity which *per se* leading to atorvastatin discontinuation mainly at higher doses, thus alternative herbal therapy may be used alone or in combinations with atorvastatin for reducing these sever adverse effects.²⁰ Hence; garlic and lasuna definitely might be an encouraging treatment with statin for hyperlipidemia, also these herbal medications may decrease the dose of atorvastatin and so minimizing the adverse effects and improving the hypolipidemic effect.²¹

Therefore; the present study showed significant hypolipidemic effect of garcinia cambogia alone or in combination with atorvastatin through 8 weeks period of treatment. In this study garcinia, cambogia produced significant reductions in serum lipid and improve other lipid parameters like VLDL, and LDL $p < 0.05$.

The active constituents of garcinia cambogia are HCA, garcinol and gluten.²² HCA is potent inhibitors of extra mitochondrial citrate lyase, pancreatic alpha-amylase and

intestinal glucosidase so causing inhibition of lipogenesis and gluconeogenesis via reduction in fatty acid biosynthesis and diminish the intestinal carbohydrate absorptions.²³

The effect of HCA on lipid profile was investigated in hyperlipidemic animal model, HCA diminish and reduced homogeneously the hepatic and peripheral lipid biosynthesis in isolated hepatic cells (*in vitro* study) but *in vivo* study HCA studies showed significant reduction in cholesterol, TG and fatty acid hepatic biosynthesis but these reduction were fat meal dependent, thus; HCA improve lipid profile both *in vitro* and *in vivo* studies.²⁴

Moreover; HCA upregulated the abdominal fat enzyme such as aldolase B, lipocalin and prostaglandin D synthetase which regulate the abdominal fat metabolism.²⁵ In addition; HCA augment fat oxidation, via acute or chronic administration of garcinia cambogia, but it significantly inhibit carbohydrate oxidation, so HCA increase urinary lipid metabolites excretion, which indicated exaggerated peripheral fat metabolism²⁶ also; abdominal fat oxidation via HCA lead to increase in urine malondialdehyde which suggested to be upshot of body fat β -oxidation.²⁶ Furthermore; HCA down-regulated of fat related genes like lipogenic transcribing factor which is extremely articulated in peripheral fat accumulation and fatty acid synthesis.²⁷

Garcinol from garcinia cambogia have a potent antioxidant effect thus decreasing the LDL oxidation and so decrease

the deleterious effect of LDL on vascular endothelium, also it inhibit protein and lipid oxidation so inhibit the oxidative stress of hyperlipidemia.²⁸

Gluten is another active constituent of *garcinia cambogia* contributing in prevention of oxidized LDL (oxiLDL) via antioxidant activity, thus it modify the percentage of oxiLDL/LDL ratio.²⁹

Atorvastatin is an artificial or synthetic hypolipidemic agent via reversible competitive inhibition of HMG-COA reductase leading to inhibition of hepatic cholesterol synthesis consequential in exhaustion of cholesterol, this inhibition was come with upregulation of liver LDL receptors which encourages uptake of blood LDL, also it increase HDL and decrease levels of TG and VLDL.^{30,31}

Atorvastatin produced pleiotropic effects independent on serum cholesterol these are (antioxidant, anti-inflammatory and antiatherogenic), the antioxidant possessions of atorvastatin might be due to atorvastatin hydroxyl active metabolites which improve endogenous antioxidants such as glutathione, and all these lead to amelioration of vascular endothelial functions.³²

Dual effects of atorvastatin plus *garcinia cambogia* demonstrated potent improvement in all lipid profile more than atorvastatin or *garcinia cambogia* alone, consequently; improved serum LDL rank which could be establish as valuable in hyperlipidemia and limitations of vascular complications.

Feeding on saturated fatty acid up-regulate the HMG-COA due to accessibility of acetyl-COA so increase cholesterol synthesis and down-regulation in LDL receptors also this effect leading to increasing in cholesteryl ester transfer protein causing decrease serum HDL plus elevation in TG level.³³

ATP-citrate lyase which is a major enzyme supplying cytosolic acetyl-COA involved in the activation of (HMG-COA) reductase enzyme for denovo cholesterol biosynthesis and lipogenesis but under fasting state liver acetyl-COA come from acetoacetate bypassing citrate lyase enzyme, therefore; HCA from *garcinia cambogia* partially inhibitor of (HMG-COA) so reduce cholesterogenesis.³⁴ Consequently; *garcinia cambogia* may produce a synergistic effect with atorvastatin during feeding condition and additive effect during fasting condition on serum cholesterol and other lipid profiles.

Moreover; *garcinia cambogia* inhibit adipose tissue phospholipids so indirectly reduced the VLDL level and reduce the substrates for hepatic cholesterogenesis.³⁵

Regarding the AI that is a significant interpreter of atherosclerosis, and should be <5 and higher AI associated with cardiovascular complications. Furthermore; AI is mandatory when level of HDL appear normal also; AI observed to be a diagnostic option for treatment efficiency and cardiovascular threat.³⁶

AI is a sign of latent atherogenic impending, because non-HDL regarded as parallel to Apo-B of lipoprotein in evaluating bad oxiLDL load.³⁷

CONCLUSION

This study scrutinizes the value of *garcinia cambogia* in treatment of hyperlipidemia alone or in combination with atorvastatin. It produced significant additive effect with atorvastatin, so atorvastatine doses can be reduced and substituted with *garcinia cambogia* for reduction serious atorvastatin associated adverse effects.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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