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ORIGINAL ARTICLE

Comparative Evaluation of Prophylactic and Therapeutic Hypolipidemic Potential of *Crataegus Oxyacantha* (Hawthorn) Fruit with Atorvastatin in Murine Model of Dyslipidemia

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ABSTRACT

Background: Dyslipidemia or hyperlipidemia is a consequential condition resulting from derangement in lipid profile. Standard treatment such as Atorvastatin though beneficial, causes many serious adverse effects thus an alternative like *Crataegus oxyacantha* (Hawthorn) with hypolipidemic potential was investigated.
Aims: To evaluate prophylactic and therapeutic hypolipidemic potential of *crataegus oxyacantha* (hawthorn) fruit in comparison with atorvastatin in murine model of dyslipidemia through assessing physiological parameter i.e., weight and serum biochemical parameters i.e., lipid profile: TC, TGs, VLDL, LDL and HDL.
Study design: This experimental study was carried out in research laboratory of Akhtar Saeed Medical and Dental College and National Health Research Centre (NHRC), Lahore
Methods: A murine study of 60 days was conducted on 64 male albino Wistar rats (Age ± 6 weeks) divided into 8 groups with 8 rats each weighing 180-200 grams. Group 1 (healthy control) received normal diet and 2 ml of normal saline for 60 days. Group 2 (disease control) received HFD and 2 ml of normal saline for 30 days while 3-5 (prophylactic groups) were given HFD along with ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination in doses of 40 mg/kg OD, 80 mg/kg OD and 20+40 mg/kg OD orally respectively for the same period. 6-8 (therapeutic groups) received ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination respectively after induction of dyslipidemia from 30th till 60th day in the same doses as mentioned above. Each rat was weighed and fasting samples for biochemical parameters were drawn by cardiac puncture in all groups at baseline and repeated at 30th day in all groups while also at 60th day in therapeutic groups as well as healthy control group. The results were analyzed using one way ANOVA for Mean±SD, post hoc Tukey's test for group comparison in the Graph-Pad Prism (V.5) software. A p-value ≤ 0.05 was considered as statistically significant.
Study period: This study was conducted from September, 2020-November, 2020.
Results: Our murine study concludes that *Crataegus oxyacantha* (40 mg/kg OD orally) when administered prophylactically and therapeutically shows a noteworthy hypolipidemic potential when compared with Atorvastatin (80mg/kg OD orally). Better results were obtained in prophylactic doses as well as in low dose combination with Atorvastatin (20 mg/kg + 40 mg/kg respectively).
Conclusion: Results suggest that *Crataegus oxyacantha* can be used as alternative in treating hyperlipidemias.
Keywords: *Crataegus oxyacantha,* Atorvastatin, Hyperlipidemia.

INTRODUCTION

Dyslipidemia / Hyperlipidemia is one of the most common insidious disorders resulting in significant increase in morbidity and mortality around the world. Underlying the disease is derangement in one or more blood lipid levels i.e. TC (<200), TGs (<150), VLDL (<30), LDL (<130) and HDL (>60) mg/dl which results from usually high caloric intake, sedentary lifestyle or genetic predisposition.[1] The pathogenesis of hyperlipidemia involves deficiency of lipoprotein lipase activity or the absence of apoprotein CII31 which leads to the defective lipid metabolism.[2] The oxidative stress results in vascular lining injury thus enhancing atherosclerotic plaque formation. This results in ischemic CVDs such as angina, myocardial infarction and stroke.[3] Many metabolic diseases e.g., diabetes mellitus are associated with hyperlipidemia.[4] Non-alcoholic fatty liver disease (NAFLD) is a major hepatic pathology caused by hypertriglyceridemia, a subset of hyperlipidemia[5].

It is imperative that dyslipidemia be prevented before being treated by dietary and lifestyle modifications e.g., low calorie, high fiber diet and exercise.[6] The medical treatment includes statins, fibrates, bile acid binding resins and niacin. They are considered to be effective in prevention and treatment of CVDs especially statins (HMG Co-A Reductase Inhibitors) which are the mainstay of dyslipidemia treatment.[7] Atorvastatin is being given worldwide due to its hypolipidemic effects[8,9]. It is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase, which is a rate determining enzyme in cholesterol biosynthesis by mevalonate pathway. Statins also increase hepatic LDL receptors expression thus lowering LDL-C levels.[10] Atorvastatin acts primarily in liver. Decreased hepatic cholesterol levels lead to increase hepatic uptake of cholesterol thus reducing cholesterol levels in plasma[11].

Although prophylactic use of statins (even starting at a young age) in cases of familial hyperlipidemia has also been established but mild adverse effects like myalgia often result in poor compliance thus leaving the root cause dyslipidemia and its subsequent problems untreated.[12] Amongst all the adverse effects known, severe musculoskeletal pain due to statins is the worst culprit for poor compliance and therefore compounds the multiple ailments stemming from uncontrolled dyslipidemia as well. In past years statins have been discontinued due to increased number of deaths associated with renal or multi organ failure caused by statin induced myopathy (rhabdomyolysis)[13,14]. Other adverse effects include hepatotoxicity and renal damage[13].

As this is a serious issue and cannot be ignored, other treatment options should be considered for dyslipidemia. Many plant extracts alone or in combinations have been utilized in dyslipidemia treatment. *Crataegus oxyacantha* (Hawthorn), owing to its antioxidant properties due to presence of Flavonoids, is considered to have hypolipidemic potential[15,16] .

This research was designed to investigate the prophylactic as well as therapeutic hypolipidemic effects of *Crataegus oxyacantha* fruit as an alternative for treating hyperlipidemia in comparison to atorvastatin.

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MATERIALS & METHODS

This 2-month study was approved by Ethical Review Board and was conducted on 64 male albino Wistar rats weighing 180-200 grams divided into 8 groups (n=8). Group 1 (healthy control) received normal diet for 60 days while group 2 (disease control) received HFD for 30 days and after the development of dyslipidemic model, was sacrificed. Prophylactic groups (3-5) were given HFD along with ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination in doses of 40mg/kg OD, 80 mg/kg OD and 20+40 mg/kg OD orally respectively for the first month. Therapeutic groups (6-8) received HFD during the entire 2-month period and within this time frame, from the end of the first month (after induction of dyslipidemia), ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination were administered respectively in the same doses as mentioned above till the end of the study. Baseline, first month and second month weight was measured and fasting serum samples for lipid profile including TC, TG, HDL-C, VLDL-C and LDL-C were drawn through cardiac puncture. As mentioned earlier, animals from disease control and prophylactic groups were sacrificed at the end of first month while the remaining groups including healthy control group were sacrificed at the end of the second month. *Crataegus oxyacantha* was purchased from Masood pharmaceuticals and Atorvastatin from Clinix pharmacy. The tests were conducted using biochemical kit method on chemistry analyzer.

Statistical Analysis: The results were analyzed using one way ANOVA for Mean±SD, post hoc Tukey's test for group comparison in the Graph-Pad Prism (V.5) software. A p-value ≤ 0.05 was considered as statistically significant.

RESULTS

Group 1 = Healthy control (sacrificed at day 60 of study), Group 2 = Disease control (sacrificed at day 30 of study). Group 3 = *Crataegus oxyacantha* 40 mg/kg/day, Group 4 = Atorvastatin 80 mg/kg/day and Group 5 = Combination (*Crataegus oxyacantha* 20 mg/kg/day + Atorvastatin 40 mg/kg/day) along with high fat diet (to evaluate prophylactic effects– sacrificed at day 30 of study). Group 6 = *Crataegus oxyacantha* 40 mg/kg/day, Group 7 = Atorvastatin 80 mg/kg/day, Group 8 = Combination (*Crataegus oxyacantha* 20 mg/kg/day+Atorvastatin 40mg/kg/day) after inducing hyperlipidemia (to evaluate therapeutic effects – sacrificed at day 60 of study).

at the end of study i.e., Day 30 for G-2,3,4,5 and 60 for G-1,6,7,8

Table 1: Mean ± SD of Lipid Profile (in mg/dl) at the End of Study.

Parameters (mg/dl)	Group 1 (n=8) Mean ± SD	Group 2 (n=8) Mean ± SD	Group 3 (n=8) Mean ± SD	Group 4 (n=8) Mean ± SD	Group 5 (n=8) Mean ± SD	Group 6 (n=8) Mean ± SD	Group 7 (n=8) Mean ± SD	Group 8 (n=8) Mean ± SD
Triglycerides	76.25 ± 4.528	104.1 ± 4.454	79.00 ± 2.619	78.00 ± 4.536	79.00 ± 5.318	82.50 ± 4.504	77.00 ± 5.757	81.00 ± 4.140
Total Cholesterol	83.50 ± 8.384	152.9 ± 10.27	91.63 ± 7.800	80.75 ± 12.75	87.75 ± 7.005	132.4 ± 7.909	125.6 ± 7.009	126.6 ± 7.909
HDL – C	52.63 ± 5.208	30.38 ± 4.307	46.63 ± 4.627	52.00 ± 4.811	49.13 ± 3.980	48.00 ± 4.276	49.75 ± 6.628	45.75 ± 5.312
VLDL – C	15.25 ± 0.8864	21.00 ± 0.9258	15.75 ± 0.7071	15.50 ± 1.069	15.88 ± 0.9910	16.50 ± 0.9258	15.38 ± 1.061	16.13 ± 0.8345
LDL – C	16.38 ± 7.891	101.5 ± 8.619	25.50 ± 13.70	15.25 ± 11.23	22.75 ± 10.10	68.13 ± 12.68	60.50 ± 10.35	64.75 ± 6.563

Figure 1: Triglycerides at the end of study – P value < 0.0001 shows statistically significant result indicated by *** in comparison to disease control group represented by ###

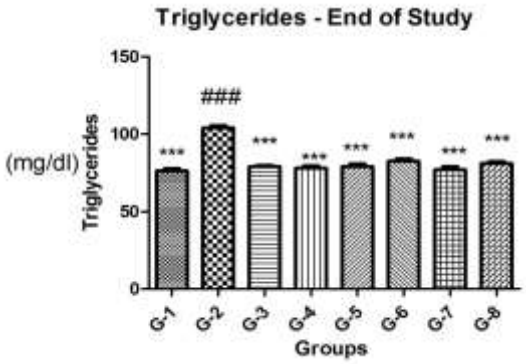


Figure 2: Total Cholesterol at the end of study – P value < 0.0001 shows statistically significant result indicated by *** in comparison to disease control group represented by ###. represented by ###. represented by ###.

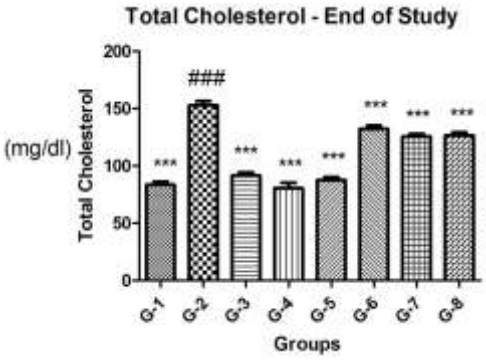


Figure 3: HDL – C at the end of study – P value < 0.0001 shows statistically significant result indicated by *** in comparison to disease control group represented by ###.

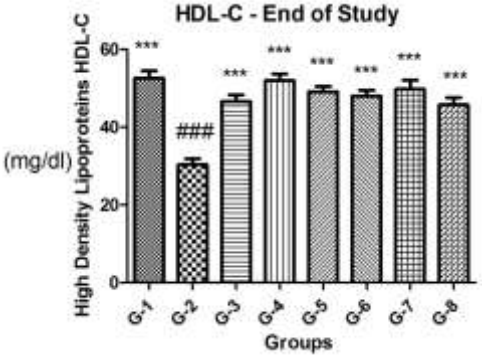


Figure 4: VLDL – C at the end of study – P value < 0.0001 shows statistically significant result indicated by *** in comparison to disease control group represented by ###.

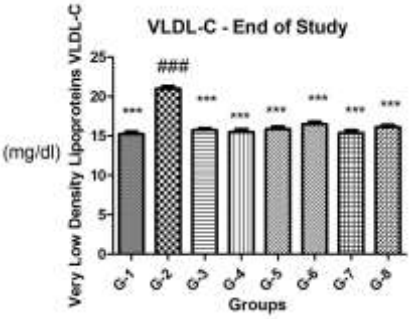
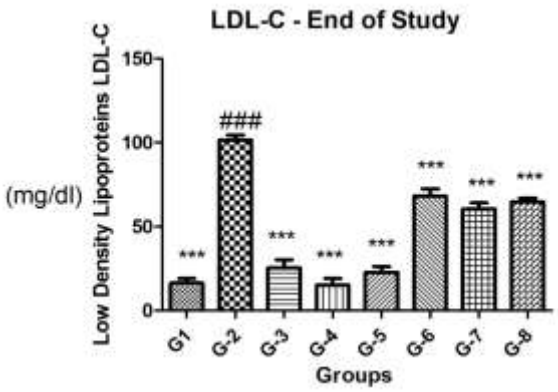


Figure 5: LDL – C at the end of study – P value < 0.0001 shows statistically significant result indicated by *** in comparison to disease control group



DISCUSSION

Hyperlipidemia affects many individuals worldwide[17]. The derangements in TC, TGs, HDL, VLDL and LDL levels are the underlying causes. Many animal studies conducted on hyperlipidemia reinforce that high fat diet, obesity, tobacco intake and other factors such as family history exhibit a very major part in the development of hyperlipidemia[1]. Standard treatment such as statins including Atorvastatin cause many serious skeleto-muscular and hepato-renal adverse effects[13,18], therefore an alternative like *Crataegus oxyacantha* (Hawthorn) with hypolipidemic potential [19] should be investigated. Keeping in mind these factors, the current study was carried out to evaluate the changes in weight and lipid profile of prophylactic and therapeutic groups.

A 2-month study was conducted on 64 male albino Wistar rats weighing 180-200 grams divided into 8 groups (n=8). Group 1 (healthy control) received normal diet for 60 days while group 2 (disease control) received HFD for 30 days and after the development of dyslipidemic model, was sacrificed. Prophylactic groups (3-5) were given HFD along with ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination in doses of 40 mg/kg OD, 80 mg/kg OD and 20+40 mg/kg OD orally respectively for the first month and were sacrificedthereafter. Therapeutic groups (6-8) received HFD during the entire 2-month period and within this time frame, from the end of the first month (after induction of dyslipidemia), ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination were administered respectively in the same doses as mentioned above till the end of the study. Baseline, first month and second month weight was measured and fasting serum samples for lipid profile including TC, TG, HDL-C, VLDL-C and LDL-C were drawn through cardiac puncture. As mentioned earlier, animals from disease control and prophylactic groups were sacrificed at the end of first month while the remaining groups including healthy control group were sacrificed at the end of the second month. The results were analyzed using one way ANOVA for Mean ± SD, post hoc Tukey's test for group comparison in the Graph-Pad Prism (V.5) software. A p-value ≤ 0.05 was considered as statistically significant.

At day 0, there was no statistically significant difference between any groups i.e., all the groups had more or less similar weight (in grams) and lipid profile (in mg/dl) before the start of study.

After one month, there was a slight change in weight and lipid profile of healthy control group (G-1) even on normal rat diet. This increased weight could have been due to physiological increased size due to age. In the HFD induced disease control group (G-2), a significant increase of 38%, 46%, 94%, 50%, 1000% in weight, TG, TC, VLDL, LDL respectively and 47% decrease in HDL levels with P value < 0.0001 were observed vs their baseline. At the same time, the disease control group (G-2) which had been maintained on HFD, showed a very highly significant increase 24%, 41%, 95%, 40%, 742% in weight, TG, TC, VLDL, LDL and 43% decrease in HDL levels with P value <0.0001 vs the healthy control group (G-1).

During the same duration, after one month (Day 30), prophylactic groups (that received HFD along with ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination in doses of 40 mg/kg OD (G-3), 80 mg/kg OD (G-4) and 20+40 mg/kg OD (G-5) showed non-significant difference in weight and lipid levels compared to that of healthy control group (G-1). However, versus G-2, significant difference with P value < 0.0001 was observed as the weight gain and lipid derangement in G-4,5 and 6 was still significantly less than that of G-2 i.e., weight: 16-19-16%, TG: 24-25-24%, TC: 40-47-123%, VLDL: 24-29-24%, LDL: 75-84-86% less and HDL: 20-70-60% more than that of G-2.

This proved that the addition of ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination was able to counteract the anticipated weight gain and lipid derangement with HFD. The prophylactic effect of *Crataegus oxyacantha* on lipid and weight has also been proposed by other studies[20,21]. It has been used as monotherapy or in combination with low dose statin or other antihyperlipidemic regimens.[22] Our study is supported by this data. Thus, looking at the above stated data, results of prophylactic therapy with *Crataegus oxyacantha,* Atorvastatin alone and their low dose combination were found to be better.

In comparison at the end of first month, therapeutic groups (that received HFD without any treatment till this point i.e., one month) G-6, G-7 and G-8 showed a significant increase in weight and lipid profile except HDL vs G-1 (healthy control group receiving normal diet) ranging from 24-27-29 % increase in weight as well as in TG: 36-50-39 %, TC: 87-95-94 %, VLDL: 33-47-40 %, LDL: 700-733-733 % and decrease in HDL levels: 43-43-41 % respectively with P value < 0.0001. Understandably there was no statistically significant difference between the therapeutic and disease control groups which had both received only HFD till this point of the study. This proves the development of hyperlipidemic model in G-2, G-6, G-7 and G-8. Disease control group G-2 was also sacrificed at this stage of study.

Between the 30th to 60th day, till the **end of second month** (**study completion**), healthy control group G-1 had a slight physiological change in weight and lipid profile levels only because of increase in size and age even on normal diet. Also, in comparison to their baseline, healthy control group showed the same trend. Within the therapeutic groups, G-6, G-7 and G8 who received HFD along with ethanolic extract of *Crataegus oxyacantha* fruit, atorvastatin and their combination in the same doses of 40 mg/kg OD (G-6), 80 mg/kg OD (G-7) and 20+40 mg/kg OD (G-8), showed highly significant decline in weight and improvement in lipid profile due to medication i.e., weight: 5-7-8%, TG: 18-29-21%, TC: 10-18-16%, VLDL: 15-32-24%, LDL: 29-39-35 % decrease and HDL: 60-61-48 % increase respectively with P value < 0.0001 from previous month. However, with their own baseline at the start of study, their weight and lipid profile had still not normalized.

As referred by[23] the expected trend in weight gain and derangement in lipid levels on HFD alone would have continued unabated. Bearing this in mind, even an earlier sacrifice of our disease control group G-2 at the end of the first month was sufficient and essential to match in time with the 1-month treatment period for prophylactic and therapeutic groups. Despite administration of HFD in both groups, when G-2 data was compared with that of therapeutic groups, G-6, G-7 and G-8, a significant decline in weight and improvement in lipid levels was observed i.e., weight: 14-14-15 %, TG: 20-26-22%, TC: 14-18-17%, VLDL: 24-29-24%, LDL: 32-40-36% decrease and 60-63-50% increase in HDL levels with P value < 0.0001.

At the end of the study, the therapeutic groups (G-6, 7 and 8) were relatively less effective in controlling weight gain and

recovering normal lipid levels in comparison to the healthy control G-1 and prophylactic groups G-3, 4, 5 (in which hyperlipidemia was not developed in the first place because of early administration of therapy). They showed a significant increase in weight and lipid profile except HDL levels i.e., 13-12-14% increase in weight as well as TG: 8-3-7%, TC: 57-50-51 %, VLDL: 7-0-7%, LDL: 319-275-300% increase and HDL: 9-6-17% decrease with P value < 0.0001.

These results point towards the importance of initiating drug treatment prophylactically which would help in maintaining the weight and normal lipid range especially in people with familial hyperlipidemia. In our study, this effect can be observed especially in group 4 and 7 which were given Atorvastatin alone prophylactically and therapeutically respectively in 80 mg/kg/day OD. These groups showed maximum hypolipidemic potential as the weight and lipid profile i.e., TG, TC, HDL – C, VLDL – C and LDL – C levels were similar to those of healthy control group (G-1). Low dose combination groups i.e. G-5 and G-8, that received *Crataegus oxyacantha* 20mg/kg/day + Atorvastatin 40mg/kg/day also showed decrease in weight and improvement in lipid profile but to lesser extent as compared to G-4 and G-7.

Thus, our study provided a detailed insight into comparative prophylactic and therapeutic hypolipidemic and weight lowering effects of *Crataegus oxyacantha* vs Atorvastatin. However, our results are in accordance with the few researches available where *Crataegus oxyacantha* has been used as monotherapy or in combination with low dose statin or other antihyperlipidemic regimens.[22] The positive role of *Crataegus oxyacantha* in reducing dyslipidemia and weight with more prophylactic benefit than therapeutic may be due to Oligomeric Procyanidins (OPCs) and flavonoids which have a multipronged antioxidant activity counteracting oxidative stress[19-.]

CONCLUSION

Our murine study concludes that *Crataegus oxyacantha* (40 mg/kg OD orally) when administered prophylactically and therapeutically shows a considerable hypolipidemic potential and weight loss when compared with Atorvastatin (80mg/kg OD orally). Better results were obtained in prophylactic doses as well as in low dose combination with Atorvastatin (20 mg/kg + 40 mg/kg respectively) thus *Crataegus oxyacantha* can be used as an alternative in treating hyperlipidemia.

Conflict of interest: Nil

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