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# A preclinical study to evaluate hypolipidemic effects of aerial parts of *Carica papaya* plant

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**Abstract**

Deranged serum lipids also known as Dyslipidemia is the major cause of Cardio-Vascular Diseases. Correction of the dyslipidemic state greatly prevents the future cardio-vascular events. Conventional anti-hyperlipidemic drugs are associated with numerous adverse effects and are costly. Globally people prefer plant based remedies to treat their unhealthy conditions. And among the plant based remedies people prefer those natural products which are commonly available in homes and are consumed daily. Papaya is a well-known nutritious plant famous for its health promoting benefits. Different parts of papaya are consumed for different purposes. Papaya fruit aids digestion, prevents and treats constipation, papaya seeds are used as spice in cooking, papaya unripe fruit is used as meat tenderizer, papaya leaves are used in fever states. Considering these application, this study is designed to evaluate the hypolipidemic effects of different aerial parts of papaya i.e. ripe fruit, seeds, unripe fruit and leaves after acute and chronic dosing. The results of this study revealed strong hypolipidemic potential of papaya ripe fruit and papaya leaves as they significant ($P<0.05$) decreased serum triglycerides (16.2 & 53.9 mg/dL respectively) and VLDL (10.6 and 9.7 mg/dL respectively) in comparison to control group.

**Keywords:** Dyslipidemia, Papaya parts, Hypolipidemic effects, Lipid Profile

**Full length article** **Corresponding Author*, e-mail: osama_hum@hotmail.com

## 1. Introduction

Human beings have been utilizing plant and plant based products since their existence in treating numerous unhealthy conditions [1]. These botanical preparations are generally considered pure, safe, economical and healthy since they belong to natural origin [2]. It has been estimated that almost 75 to 80% of world's population uses natural preparations as a treatment in their disease states [3]. Today 50% of the medicines that are used clinically are of natural origin [4]. In nature, majority of the herbs possess notable pharmacological

potential [5]. Irrespective of remarkable scientific and medical advancement, still a massive investigation on natural products is going on to explore new therapeutic options [6]. *Carica papaya* Linn. belongs to the family of Caricaceae. It is a herbaceous plant widely grow at tropical areas of the world. This plant possesses unique nutraceutical potential and health promoting benefits. Papaya plant has drawn the attention of many researchers and scientists. Numerous part of this tropical plant such as fruits, leaves, roots, peel, seeds have different distinctive medicinal importance. Papaya fruit has been consumed traditionally in preparing jams, jellies, pickles etc. Papaya seeds have anti-tumor action whereas Papaya leaves facilitate bowel movements [7]. Some common pharmacological uses of papaya are shown in figure 1. Conventional anti-hyperlipidemic drugs have different mechanisms through which they control serum lipids. A brief mechanism of these conventional anti-hyperlipidemic drugs is shown in figure 2. Currently there is a need to discover newer anti-hyperlipidemic agents with good efficacy and lesser side effect profile because conventional anti-hyperlipidemic drugs have problematic adverse effects including rhabdomyolysis. Some common adverse effects of these conventional drugs are shown in figure 3. The rising popularity and utilization of natural remedies all over the globe has also carried many clinical challenges. The OTC like nature of these natural remedies and their easy availability greatly facilitate the population upon its consumption in different unhealthy states along with conventional drugs and supplements which not only raise chances of adverse effects but herb-drug and herb-supplement interactions too [8]. Due to high consumption of different parts of papaya plant for different therapeutic purposes, this study is planned to observe and investigate the effect of short-term and long-term dosing of different edible (ripe and unripe fruit) and non-edible (seeds and leaves) parts of papaya on serum lipid profile in rabbits.

## 2. Materials and Methods

### *Research Animals*

Albino rabbits of both genders were selected for this study. 40 rabbits weighing between 2.3 to 2.6 kg were separated out from the breeding area of animal house of Pharmacology Department of University of Karachi. The study animals had full free access of food and water and were kept under 12 hours light and 12 hours dark cycle with controlled temperature (24 ± 3ºC) and humidity (63%). The guidelines declared by NRC (National Research Council) were strictly followed for animal care and handling [9]. Proper animal ethical approval was taken before initiating the study from ASRB (Advanced Study and Research Board) (ETHICAL APPROVAL: [BASR/No./02145/Pharm]).

### *Identification of plant*

All the study parts of papaya i.e. fruit (ripe & unripe), leaves and seeds were identified by Herbalist/Pharmacognocist Prof. Dr. Iqbal Azhar (Professor & Chairman Department of Pharmacognosy & Ex-Dean, Faculty of Pharmacy & Pharmaceutical Sciences).

### *Extract Preparation*

Aqueous extract of study parts were prepared according to the method mentioned in Table 1.

### *Grouping of study animals and their dosing protocol*

5 groups of 10 animals were set for biochemical testing. Group I was control whereas the rest of the groups i.e. group II, III, IV and V were the treatment groups. Animal groups and their dosing is represented in Table "2"

The dosing was continued for 2 months (60 days) and all dosing was by oral route. The blood was withdrawn on day 61st for estimation of serum Lipids [12],[13],[14],[15],[16].

Estimation of Serum Lipids. For estimation of serum lipids, blood samples were taken in gel tubes. After blood withdrawal, these tubes were centrifuged for 600 to 900 seconds at 3000 RPM to get the pure plasma which was then analyzed using Semi-Automatic Chemistry Analyzer (Human-Germany, Model# 16700) for the estimation of serum Cholesterol, triglycerides, HDL, LDL and VLDL. For estimation of these tests, standard kits were used which were purchased from the Human company.

### *Statistical Analysis*

The data collected was expressed as Mean ± Std. Dev and analyzed using SPSS version-20. ANOVA (one-way) followed by post-hoc Tukey's test is used for evaluation of statistical significance. All P-values of less than 0.05 were considered significant. However P-values $p<0.05$*#!$^, $p<0.01$ **##!!$$^^, $p<0.001$ ***###!!!$$$^^^ represent level of significance i.e. significant, very significant and highly significant difference in comparison to control, PFE, PSE, PUFE and day 11th of dosing respectively.

## 3. Results & Discussion

Table 3, 4, 5, 6 and 7 demonstrate the acute and chronic effects of different parts of papaya tree on serum Cholesterol, triglycerides, HDL, LDL and VLDL respectively. As represented in Table 3, in comparison to control group, acute and chronic dosing of both PFE and PUFE showed no effect on serum cholesterol whereas the other two parts i.e. PSE and PLE lowered the serum cholesterol levels significantly. No significant difference was found between the acute and chronic dosing days of each group except of PSE group in which chronic dosing decreased the serum cholesterol more efficiently than acute dosing. Among all the treatment groups PSE showed highest tendency to lower the serum cholesterol levels. As represented in Table 4, acute as well as chronic dosing of all parts i.e. PFE, PSE, PUFE and PLE markedly decreased serum triglyceride levels in comparison to control group. Among all the dosing groups, PFE showed highest tendency to decrease serum triglyceride levels both after acute and chronic dosing. As represented in Table 5, acute as well as chronic dosing of all parts i.e. PFE, PUFE, and PLE markedly raised serum HDL levels in comparison to control group except acute and chronic dosing of RSE and chronic dosing of PUFE which showed no changes in HDL. Among all the treatment groups, PLE showed highest tendency to raise serum HDL levels both after acute and chronic dosing.

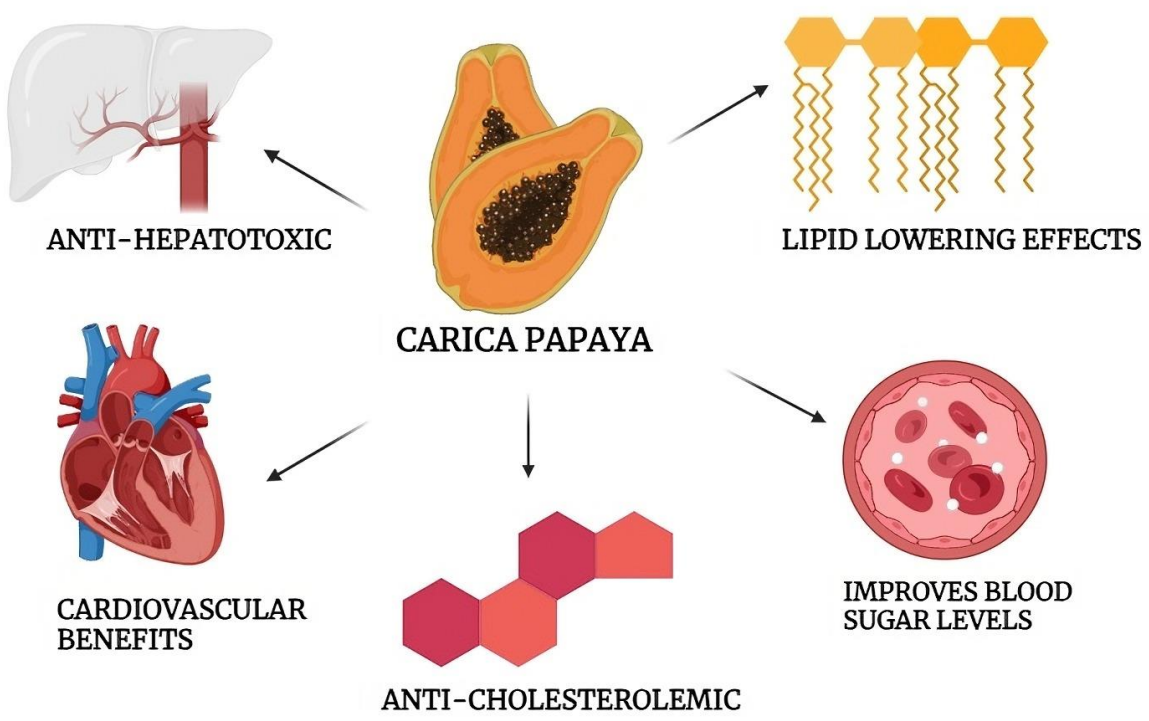


**Figure 1:** Medicinal uses of *Carica papaya*

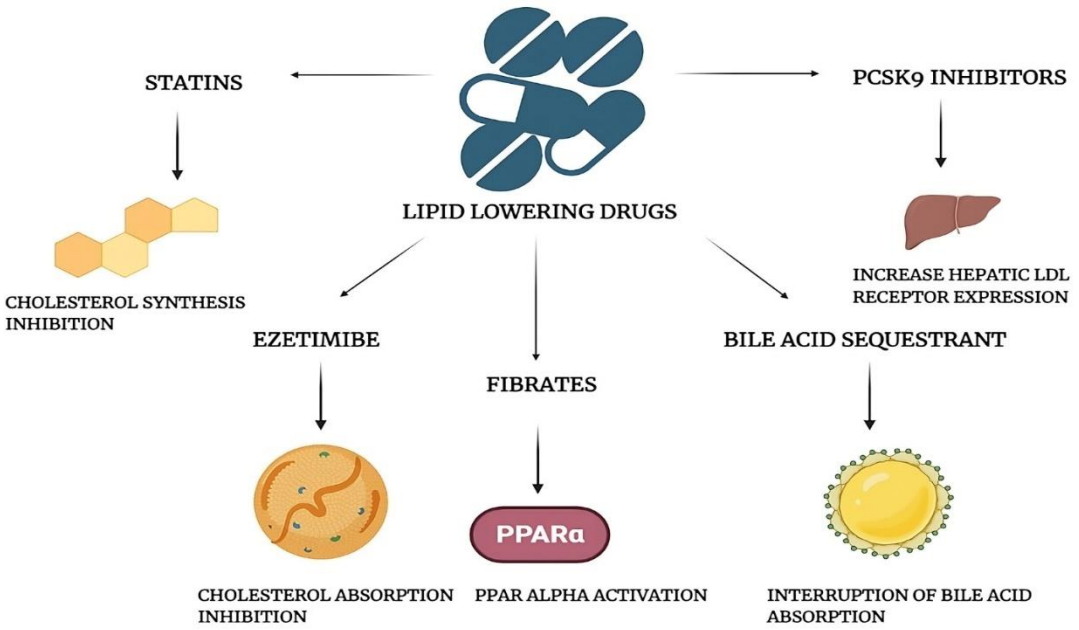


**Figure 2:** Mechanism of Action of Conventional Anti-hyperlipidemic drugs

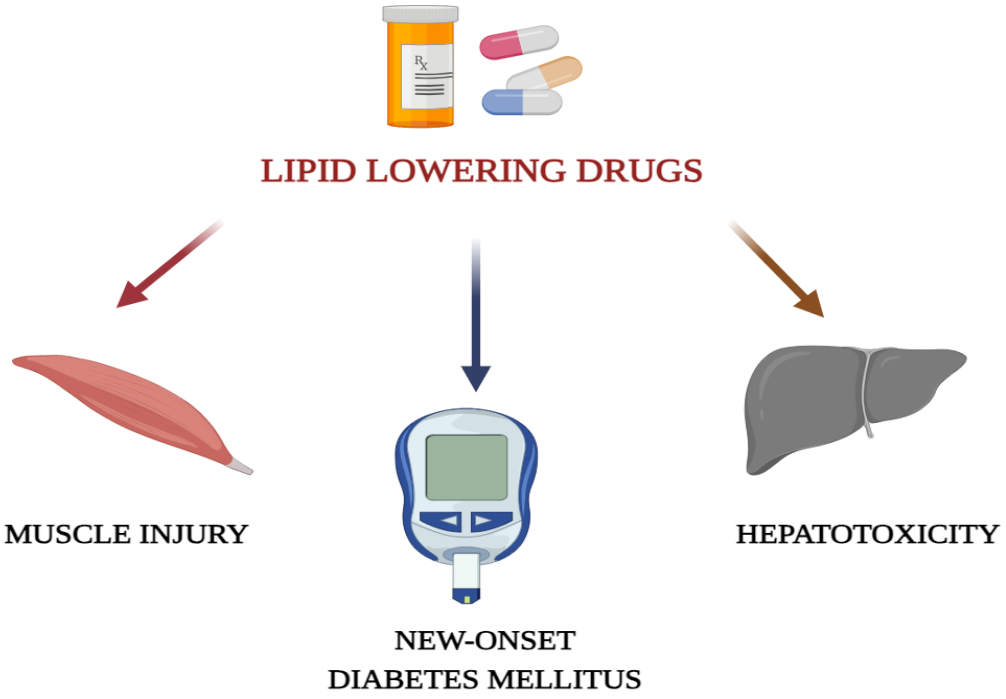


**Figure 3:** *Adverse effects of conventional anti-hyperlipidemic drugs*

**Table 1:** *Method of preparing plant extracts*

| S.NO | STUDY PART | PROCEDURE |
|---|---|---|
| 1. | Papaya Fruit Extract (PFE) | Ripe papaya fruit was obtained from the Karachi local market. The fruit was washed with tap water and peel was removed. All seeds were removed. PFE was prepared in 100mg/ml concentration for which 6 grams of ripe fruit was homogenized and blended with 60 millilitres of purified water using local mixer & grinder. The extract prepared was then stored in a glass bottle and denoted by "PFE" [10]. |
| 2. | Papaya Seed Extract (PSE) | Ripe papaya fruit was obtained from the Karachi local market. The fruit was washed with tap water and peel was removed. Seeds were separated and washed with purified water and were dried at room temperature. The seeds were then manually crushed using domestic mortar & pestle. This mixture (6 gram) was then added to the grinder along with the purified water (60ml) for the purpose of blending and grinding to produce 100mg/ml concentration of PSE. The extract prepared was stored into a glass bottle and denoted by "PSE" [10]. |
| 3. | Unripe Fruit Extract (PUFE) | Unripe papaya fruit was obtained from the Karachi local market. The fruit was washed with tap water and peel was removed. All seeds were removed. PUFE was prepared in 100mg/ml concentration for which 6 grams of unripe fruit was homogenized and blended with 60 millilitres of purified water using local mixer & grinder. The extract prepared was then stored in a glass bottle and denoted by "PUFE" [10]. |
| 4. | Papaya Leaf Extract (PLE) | Fresh mature leaves of papaya of size (8 to 9 inch) were plucked from papaya tree. Leaves were washed with tap water thoroughly and air dried. These air-dried leaves (60gm) were added to the local mixer/grinder along with purified water (60ml) where they were properly grinded and blended. PLE prepared was of 1000mg/ml concentration, which was stored in a glass bottle and denoted by "PLE" [11]. |

**Table 2:** *Animal Grouping and Dosing Protocol*

| GROUP | DOSING MATERIAL | DOSE |
|---|---|---|
| **Group I** | Distilled water | 2ml daily |
| **Group II** | PFE | 250mg per kg daily |
| **Group III** | PSE | 200mg per kg daily |
| **Group IV** | PUFE | 250mg per kg daily |
| **Group V** | PLE | 800mg per kg daily |

**Table 3:** Effect of acute and chronic dosing of different parts of *Carica papaya* Linn. on cholesterol

| GROUPS | Cholesterol (mg/dL) | |
|---|---|---|
| | **Acute dosing (MEAN±S.D)** | **Chronic dosing (MEAN±S.D)** |
| Control | 35±1.92 | 35.5±1.83 |
| RFJ (ripe fruit juice) | 31.3±6.29 | 30.4±6.11 |
| RSE (ripe seed extract) | 28.9±6.04$^{**}$ | 17.4±1.71$^{***,\wedge\wedge\wedge}$ |
| URFJ (unripe fruit juice) | 37.5±3.75$^{!!}$ | 34.3±3.59$^{!!!}$ |
| PLE (papaya leaf extract) | 26.4±2.79$^{**, \#, \$\$\$}$ | 29.9±3.54$^{!!!}$ |

**Table 4:** Effect of acute and chronic dosing of different parts of *Carica papaya* Linn. on triglycerides

| GROUPS | Triglycerides (mg/dL) | |
|---|---|---|
| | **Acute dosing (MEAN±S.D)** | **Chronic dosing (MEAN±S.D)** |
| Control | 83.5±11.46 | 84±11.46 |
| RFJ (ripe fruit juice) | 12.6±4.14$^{***}$ | 16.2±5.13$^{***}$ |
| RSE (ripe seed extract) | 24.9±9$^{***, \#\#}$ | 30.9±5.54$^{***}$ |
| URFJ (unripe fruit juice) | 61.5±7.29$^{***, \#\#\#, !!!}$ | 82.9±6.60$^{\#\#\#, !!!, \wedge\wedge\wedge}$ |
| PLE (papaya leaf extract) | 51.4±6.93$^{***, \#\#\#, !!!, \$}$ | 53.9±8.09$^{***,\#\#\#,!!!,\$\$\$}$ |

**Table 5:** Effect of acute and chronic dosing of different parts of *Carica papaya* Linn. on HDL

| GROUPS | HDL (mg/dL) | |
|---|---|---|
| | **Acute dosing (MEAN±S.D)** | **Chronic dosing (MEAN±S.D)** |
| Control | 5.8±2.53 | 5.5±2.53 |
| RFJ (ripe fruit juice) | 14.9±2.37*** | 10.1±3.63*,^^ |
| RSE (ripe seed extract) | 7.35±2.75## | 8.2±2.53 |
| URFJ (unripe fruit juice) | 16.2±4.51***, !!! | 6±1.56#,^^^ |
| PLE (papaya leaf extract) | 20.2±6.01***, #, !!! | 15.6±3.20***, ##, !!!, $$$ |

**Table 6:** Effect of acute and chronic dosing of different parts of *Carica papaya* Linn. on LDL

| GROUPS | LDL (mg/dL) | |
|---|---|---|
| | **Acute dosing (MEAN±S.D)** | **Chronic dosing (MEAN±S.D)** |
| Control | 10.6±2.32 | 11.1±2.32 |
| RFJ (ripe fruit juice) | 14.3±8.09 | 10±3.36 |
| RSE (ripe seed extract) | 14.95±9.31 | 12.5±2.63 |
| URFJ (unripe fruit juice) | 16.8±3.29* | 15.3±2.54**, ### |
| PLE (papaya leaf extract) | 12.1±3.1$ | 11.6±2.06$ |

**Table 7:** Effect of acute and chronic dosing of different parts of *Carica papaya* Linn. on VLDL

| GROUPS | VLDL (mg/dL) | |
|---|---|---|
| | **Acute dosing (MEAN±S.D)** | **Chronic dosing (MEAN±S.D)** |
| Control | 24±9.15 | 24.5±9.15 |
| RFJ (ripe fruit juice) | 2.6±1.26*** | 10.6±2.36***,^^^ |
| RSE (ripe seed extract) | 4.4±2.36*** | 11.3±2.21***,^^ |
| URFJ (unripe fruit juice) | 12.1±1.79***, ###, !! | 15.5±2.01***,^^ |
| PLE (papaya leaf extract) | 9.8±1.68***, ##, ! | 9.7±1.63***, $ |

As represented in Table 6, acute as well as chronic dosing of all parts i.e. PFE, PSE and PLE showed no significant effect on serum LDL levels in comparison to control group except PUFE which slightly raise LDL both after acute and chronic dosing. As represented in Table 7, acute as well as chronic dosing of all parts i.e. PFE, PSE, PUFE and PLE markedly decreased serum VLDL levels in comparison to control group. Among all the dosing groups, PFE after acute dosing and PLE after chronic dosing showed highest tendency to decrease VLDL levels. Dyslipidemia is one of the major causes of atherosclerosis and various cardio-vascular diseases [17],[18],[19],[20]. Conventional allopathic anti-hyperlipidemic drugs are not only associated with vast adverse effect profile but are also costly [21][22][23]. In nature, there are several plants with anti-hyperlipidemic activity. Few examples are Allium sativum, Alpinia galangal, Catharanthus roseus L., Cassia fistula, *Glyccyrrhiza glabra*, *Moringa oleifera*, *Pipper longum*, *Terminalia chebula*, *Withania somnifera*, *Zingiber Officinale* etc. [24][25]. Globally several plants and plant derived preparations are used therapeutically in treating different unhealthy conditions [26][27][28][29]. Different parts of papaya are used for different purposes like papaya fruit is commonly consumed in Asian region for the relief of constipation, unripe fruit is commonly used as meat tenderizer, seeds are used as spice/condiment, leaves in different infectious fever states [30]. Due to its frequent utilization this study is designed to investigate the short term and long-term effects of papaya fruit, seeds, unripe fruit and leaves on serum lipid profile. As per the findings of our study, among all the study parts, PFE (papaya fruit extract) and PLE (papaya leaf extract) showed the most positive effects on serum lipid profile both after acute and chronic dosing. Both these parts have strong tendency to decrease serum cholesterol, triglycerides, LDL and VLDL and possess tremendous potential to improve serum HDL levels. PSE (papaya seed extract) showed positive effects on serum cholesterol, triglycerides and VLDL i.e. has tendency to decrease these bad lipid levels but has no (negative) effects on serum HDL and LDL. Overall PSE has no negative effect on serum lipid profile. Among all the study parts PUFE was the only part with least positive hypo-lipidemic effects. It only decrease VLDL and had no effect on rest of the lipids.

Anti-hyperlipidemic effects of papaya fruit has been reported by a study in which it has been demonstrated that papaya fruit contains phyto-chemicals which possess tendency to alter the enzymes such as pancreatic lipases and cholesterol estrases which in turn responsible for lipid lowering effects [31]. Anti-hyperlipidemic activity of papaya leaves have also been reported in 2018 in which the scientists concluded that papaya leaves have the tendency to inhibit HmG-CoA-reductase enzyme [32]. In another study it has been revealed that papaya leaves not only possess hypo-lipidemic effects but also have the potential to decrease atherogenic index [33]. Anti-hyperlipidemic effects of papaya seeds were reported in a study which proposed that these lipid lowering effects are due to unique composition including flavonoids, tannins, saponins, cardiac glycosides etc. [34].

## 4. Conclusions

The findings of this study have led to the conclusion that papaya fruit and leaves are highly beneficial to be consumed daily due to their lipid lowering potential. However future studies are necessary to confirm these finding by evaluating these effects in hyperlipidemic animals and after comparison with the standard conventional anti-hyperlipidemic drugs.

## Conflict of Interest

There is no conflict of interest.

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