# Assesment of Anti-hyperlipidemic and Anti-oxidant activity of polyherbal formulation (BA019)

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**Abstract :** Hyperlipidemia is a disorder of elevated levels of plasma concentrations of the various lipid and lipoprotein fractions, which is the key risk factor for cardiovascular disorders (CVD). Since synthetic drugs have been shown to have several side effects, clinical importance of the herbal drugs in treatment of hyperlipidemia has received considerable attention in recent years. Psidum guajava, carica papaya and cinnamomum verum are traditionally used as antihyperlipidemic drugs as per ayurvedic literature .Hence the present study was undertaken to investigate the antihyperlipidemic effect of a polyherbal formulation, prepared using the above three medicinal plants against Triton X-100 and Fructose diet induced hyperlipidemia in rats. ethanolic extract of the polyherbal formulation at 200 and 400 mg/kg dose inhibited the elevation of serum cholesterol and triglyceride levels and increase high density lipoprotein levels in hyperlipidemic rats. The extract also shows antioxidant activity. Thus the ethanolic extract of polyherbal formulation at the dose of 400mg/kg; p.o. showed good antihyperlipidemic activity in Triton X-100 and fructose diet induced hyperlipidemic rats. The above results propose that this Polyherbal formulation may be a potential source for the development of the new antihyperlipidemic drug.

**KEY WORDS** - Antihyperlipidemic activity, Polyherbal formulation, Triton X-100 and fructose diet.

## I. INTRODUCTION

Hyperlipidemia is a disorder of lipid metabolism manifested by elevation of plasma concentrations of the various lipid and lipoprotein fractions, which is the key risk factor for cardiovascular disorders (CVD)[1] and has been reported as the most common cause of death in developed as well as developing nations.[2,3] The current antihyperlipidemic therapy includes principally fibrates ,statins; the former correct the altered blood lipid profile by inhibiting the biosynthesis of cholesterol and the latter acts by enhancing the clearance of triglyceride rich lipoproteins.[4] Since synthetic drugs have been shown to have side effects, clinical importance of the herbal drugs in treatment of hyperlipidemia has received considerable attention in recent years.[5] Various medicinal products of herbal origin have been reported to have antihyperlipidemic and hypocholesteremic activities.[6]

WHO defines herbal medicines as finished, labelled medicinal products that contain ingredients from aerial or underground parts of plant or other materials of plants or combinations thereof, whether crude state or other preparations. The world health organization(WHO) in 1991 estimated that there were some 11,000 species of herbal plants for medicinal use and about 500 species of them are commonly used in complementary medicine. Many other herbs and minerals formulations used in Ayurveda were later described by ancient Indian Herbalists such as Charaka and Sushrutha in 6$^{th}$ century BC describes 700 medicinal plants, 64 preparations from mineral sources and 57 preparations based on animal sources. A significant number of modern pharmaceutical drugs are derived from various medicinal plants, The derivatives from medicinal plants are non narcotic with little or no side effects.

The various indegious systems such as Siddha, Ayurveda, Unani and Allopathy use several plant species to treat different ailement. In india , the herbal remedy is so popular that the government of india has created a separate department- AYUSH- under the ministery of health& family welfare. The national medicinal plant Board was also established in 2000 by govt. Of india in order to deal with the herbal medicinal system.

Natural product research methods can often be guided by ethnopharmacological knowledge. And it can make substantial contributions to drug innovation by providing novel chemical structures and/or mechanism of action. An innovative research effort to define the advantages of traditional system of medicine with respect to their safety and efficacy could result in a better utilization of these complementary systems of medicine without toxic effects.

## 2. MATERIAL AND METHODS

Collection of Medicinal plants from various regional places of India in August and September was done. Further, the plant was identified taxonomically and authentified by botanist Dr.P.Satyanarayana Raju from Acharya Nagarjuna University Nagarjuna nagar(khaza) and authentification certificate was enclosed. Herbarium of the plant was deposited in Hindu college of pharmacy.

### 2.1Preparation of Herbal extract:[7,8]

The individual drugs were collected and shade dried at room temperature at about 37°C and powdered the whole fruit of guava , bark of cinnamomum verum and leaves of carica papaya were weighed, placed in a stoppered container with the solvent 95% v/v of etanol and allowed to stand at room temperature for seven days in a conical flask with occasional shaking and stirring. At the end of the extraction, the filtrate was filtered and concentrated in vaccum at 60°C under reduced pressure by means of a rotary evaporator. The concentrated extracts were further dried in a desiccator to yield dry powder.

### 2.2Preparation of Polyherbal formulation:

The polyherbal formulation was prepared by adding all the extracts, i.e. psidium guajava, cinnamomum verum and carica papaya in equal portions(100 gms) of each are mixed thoroughly to prepare the polyherbal formulation and stored in air tight container.

### 2.3 EXPERIMENTAL ANIMALS

Adult wistar albino rats (150-200g ) of either sex were procured from the animal house, Hindu College of Pharmacy , Guntur, Andhra Pradesh, India and used in the study. The animals were kept under standard environmental conditions of room temperature(22° ± 2° C), relative humidity (50% ± 5%) and 12 h light and dark cycle. The animals were housed in the colony cages (three rats per cage) and provided feed (commercial pellets contain a balanced ratio obtained from the Sri Venkateswara Enterprises, Bangalore) and water ad libitum.

All the animals were acclimatized to the laboratory environment 5 days prior to experiment . the animals were fasted overnight just prior to the experiment but allowed free access to drinking water . all the experiments were carried out in accordance with the guidelines of Institutional Animal Ethical Committee. The study was conducted after obtaining ethical committee clearance from the Institutional Animal Ethical Committee No: HCOP/IAEC/PR-3/2019

### 2.4 Experimental methods

#### 2.4.1 Triton X100(TR) induced hyperlipidemia:[9]

Thirty wistar rats weighing 150-200gm were randomly divided into 5 groups of 6 each. . The first group was administered with normal saline (p.o). The II, III and IV, and V group animals were injected i.p. with 10% aqueous solution of triton (100mg/kg body weight). After 72 hours of triton injection, the second group was received a daily dose of normal saline (p.o) for 7 days.the third group was given the Polyherbal formulation-BA019 (200 mg/kg; p.o), fourth group received Polyherbal formulation-BA019 (400 mg/kg; p.o) and the fifth group was administered a daily dose of standard Atorvastatin (10mg/kg; p.o.) for 7 days. Food was withdrawn 10 h prior to the blood sampling.

Group I : control

Group II : Triton control

Group III : Triton+ Polyherbal formulation-BA019 (200 mg/kg, p.o)

Group IV : Triton+ Polyherbal formulation- BA019 (400 mg/kg, p.o)

Group V : Triton+ Atorvastatin (10mg/kg, p.o)

On 8 th day , blood was collected by retero orbital sinus puncture, under mild ether anaesthesia. The collected blood samples were centrifuged for 15 mimutes at 2500rpm. Then serum samples were estimated for Total Cholesterol, Triglycerides, HDL, LDL and VLDL.

**Statistical analysis :**

Results were analyzed by one way ANOVA, followed by Dunnet's test , 'P'Value less than 0.05 were taken as significant.

#### 2.4.2 Fructose induced hyperlipidemia:[10]

Wistar rats weighing between 150-200 g were divided into five groups of six animals each. The animals of the control group had free acess to tap water while other groups were fed with food pellet and water ad libitum. 10 % fructose was used as inducing agent for hyperlipidemia. II , III, IV and V group received 10% fructose in drinking water for a period of one week along with drugs.After one week the second group was received a daily dose of normal saline (p.o) for 7 days. the III group

received Polyherbal formulation-BA019 (200 mg/kg; p.o), fourth group was received Polyherbal formulation-BA019 (400 mg/kg; p.o) and the fifth group was administered a daily dose of standard Atorvastatin (10mg/kg; p.o.) for 7 days .

Group I : control (normal saline)

Group II : Fructose control

Group III : Fructose + Polyherbal formulation-BA019 (200 mg/kg, p.o)

Group IV : Fructose + Polyherbal formulation- BA019 (400 mg/kg, p.o)

Group V : Fructose + Atorvastatin (10mg/kg, p.o)

On 8 th day , blood was collected by retero orbital sinus puncture, under mild ether anaesthesia. The collected blood samples were centrifuged for 15 mimutes at 2500rpm. Then serum samples were estimated for Total Cholesterol, Triglycerides, HDL, LDL and VLDL .

**Statistical analysis :**

Results were analyzed by one way ANOVA, followed by Dunnet's test , 'P'Value less than 0.05 were taken as significant.

### 2.5 *IN-VITRO* STUDIES

#### 2.5.1 ANTI OXIDANT ACTIVITY:

In vitro antioxidant studies Oxidation is one of the important biological processes for the production of energy in living organism. Living organisms uses oxidation for the production of energy to fuel biological processes. A variety of physiological and biochemical lesions increasingly deteriorate degenerative diseases such as aging, cancer and coronary artery disease due to free radicals Despite of anti-oxidant defence and other defence mechanism in human these systems are insufficient to prevent the damage entirely. Antioxidants are the substances that can inhibit or restrict oxidative cellular oxidizable substrates. [11]

**Nitric oxide scavenging activity**[12]

Nitric oxide was generated by sodium nitroprusside and measured by Griess reaction. Sodium nitroprusside (5 mM) in standard phosphate buffer saline solution (0.025 M, pH: 7.4) was incubated with different concentrations of ethanolic extact (50, 100, 200, 400, 800, 1000 µg/ml), Vitamin C as reference standard (50, 100, 200, 400, 800, 1000 µg/ml) and dissolved in phosphate buffer saline (0.025 M, pH: 7.4) and the tubes were incubated at 250C for 5 hr [16-19]. Control experiments is without the test compounds but equivalent amounts of buffer were conducted in an identical manner. After 5 hours, 0.5 ml of incubation solution is removed and dilution made with 0.5 ml of Griess reagent (1% sulphanilamide, 2% O-phosphoric acid and 0.1% naphthyl ethylene diamine dihydrochloride). The absorbance of the chromophore formed during diazotization of nitrite with sulphanilamide and its subsequent coupling with naphthyl ethylene diamine was read at 546 nm. All the determinations were performed in 6 replicates. Percentage inhibition of nitric oxide radical was calculated by using the formula is:

$$\% \text{ Inhibition} = \frac{\text{Absorbance of basal control} - \text{Absorbance of sample}}{\text{Absorbance of basal control}} \times 100$$

## 3.RESULTS

Preliminary phytochemical screening of the Polyherbal formulation showed the presence of various chemical constituents like flavonoids, triterpenes, sterols, tannins and Saponins (TABLE-1)

**Table-1: Preliminary phytochemical screning**

| Test | P. Guajava | Cinnamomum verum | Carica papaya |
|---|---|---|---|
| Carbohydrates | + | - | + |
| Tannins | + | + | + |
| Proteins | - | - | + |
| Glycosides | - | - | - |
| Sterols | + | + | - |
| Triterpinoids | - | + | + |
| Alkaloids | - | + | + |
| Flavonoids | + | + | + |
| Saponins | - | + | + |

Sign (+) indicates present and sign (−) indicates absent

**Table-2: Effect of Polyherbal Formulation on Total Cholesterol, Triglycerides, HDL-C levels in Triton induced Hyperlipidemic rats.**

| S.no | Groups | Total cholesterol | Triglycerides | HDL-C |
|---|---|---|---|---|
| I | Normal control | 34.8±1.5 | 173.2±1.4 | 51.1±0.1 |
| II | Hyperlipidemic control | 82.4±2.2 | 158.1±2.2 | 35.4±1.2 |
| IV | PHF(200mg/kg) | 92.5±2.1* | 66.9±1.2* | 72±0.3** |
| V | PHF(400mg/kg) | 67.1±2.3** | 58.5±1.7** | 77.8±1.4* |
| VI | Atorvastatin(10mg/kg) | 76.2±1.4** | 95.9±1.2** | 45.8±1.6** |

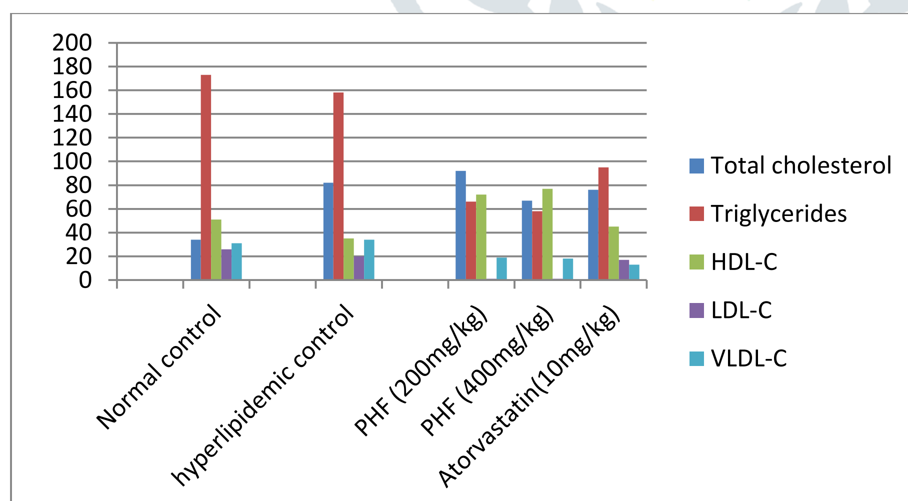
Values were mean ± SEM (n=6). Values are statistically significant at *p<0.05 and more significant at **p<0.01 Vs hyperlipidemic control using one way ANOVA followed by Dunnet's test.

**Table-3: Effect of polyherbal formulation on LDL-C, VLDL-C, and Atherogenic index in Triton induced Hyperlipidemic rats.**

| S.no | Groups | LDL-C | VLDL-C | Atherogenic index |
|---|---|---|---|---|
| I | Normal control | 26.1±2.2 | 31.6±1.2 | 0.5±0.1 |
| II | Hyperlipidemc control | 20.1±0.4 | 34.6±1.7 | 0.6±0.01 |
| IV | PHF(200mg/kg) | 1.2±0.2* | 19.1±1.5* | 0.004±0.001* |
| V | PHF(400mg/kg) | 1.0±0.1** | 18.5±0.5** | 0.1±0.01** |
| VI | Atorvastatin (10mg/kg) | 17.2±1.0** | 13.4±1.4** | 0.6±0.1** |

Values were mean ± SEM (n=6). Values are statistically significant at *p<0.05 and more significant at **p<0.01 Vs hyperlipidemic control using one way ANOVA followed by Dunnet's test.

**Graph-1: Effect of polyherbal formulation on Lipid profie levels in Triton induced Hyperlipidemic rats.**




**Graph-2: Effect of polyherbal formulation on Atherogenic index in Triton induced Hyperlipidemic rats.**

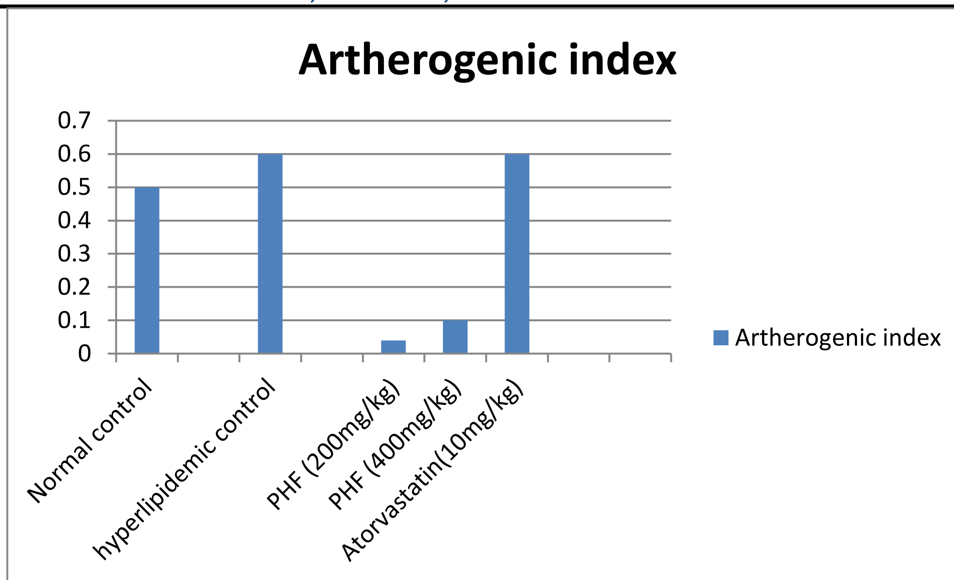



Table-4: **Effect of polyherbal formulation on Total Cholesterol, Triglycerides, HDL-C levels in Fructodse induced Hyperlipidemic rats.**

| **S.no** | **Groups** | **Total cholesterol** | **Triglycerides** | **HDL-C** |
|---|---|---|---|---|
| I | Normal control | 80.9±1.7 | 123.7±0.1 | 134.1±0.5 |
| II | Hyperlipidemic control | 155±1.5 | 147.2±1.2 | 251.2±1.4 |
| IV | PHF(200mg/kg) | 150.3±1.7* | 130.4±0.4* | 180.1±2.4** |
| V | PHF(400mg/kg) | 110.2±2.3** | 80.2±1.3** | 250.4±1.7* |
| VI | Atorvastatin (10mg/kg) | 130.1±1.2** | 75.4±2.4** | 220.1±0.5** |

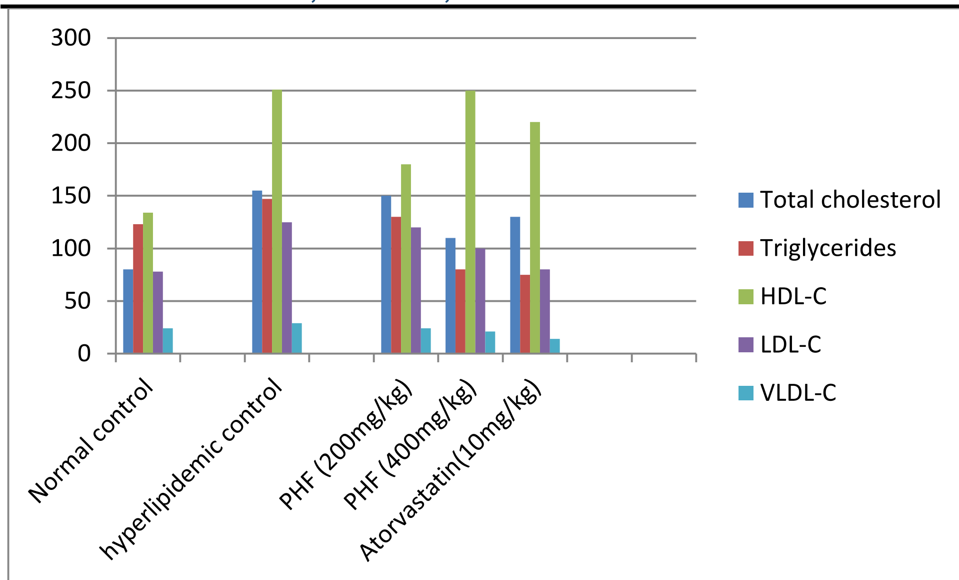
Values were mean ± SEM (n=6). Values are statistically significant at *p<0.05 and more significant at **p<0.01 Vs hyperlipidemic control using one way ANOVA followed by Dunnet's test.

**Table-5: Effect of polyherbal formulation on LDL-C, VLDL-C, and Atherogenic index in Fructose induced Hyperlipidemic rats.**

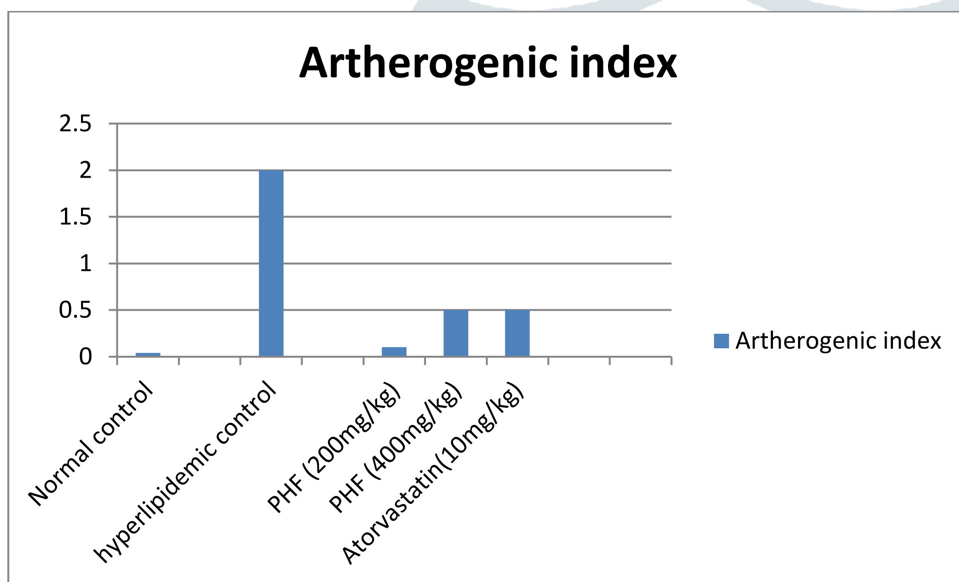
| S.no | Groups | LDL-C | VLDL-C | Atherogenic index |
|---|---|---|---|---|
| I | Normal control | 78.1±1.2 | 24.7±2.3 | 0.004±0.01 |
| II | Hyperlipidemc control | 125.4±1.0 | 29.4±0.4 | 2.0±0.4 |
| IV | PHF(200mg/kg) | 120.8±0.4* | 24±03* | 0.1±0.01** |
| V | PHF(400mg/kg) | 100.1±2.1** | 21.2±1.2* | 0.5±0.1* |
| VI | Atorvastatin (10mg/kg) | 80.3±2.3** | 14.1±0.3** | 0.5±0.2** |

Values were mean ± SEM (n=6). Values are statistically significant at *p<0.05 and more significant at **p<0.01 Vs hyperlipidemic control using one way ANOVA followed by Dunnet's test.

**Graph-3: Effect of polyherbal formulation on Lipid profile levels in Fructose induced Hyperlipidemic rats.**




**Graph-4: Effect of Polyherbal Formulation on Atherogenic index in Fructose induced Hyperlipidemic rats.**




**Antioxidant activity:**

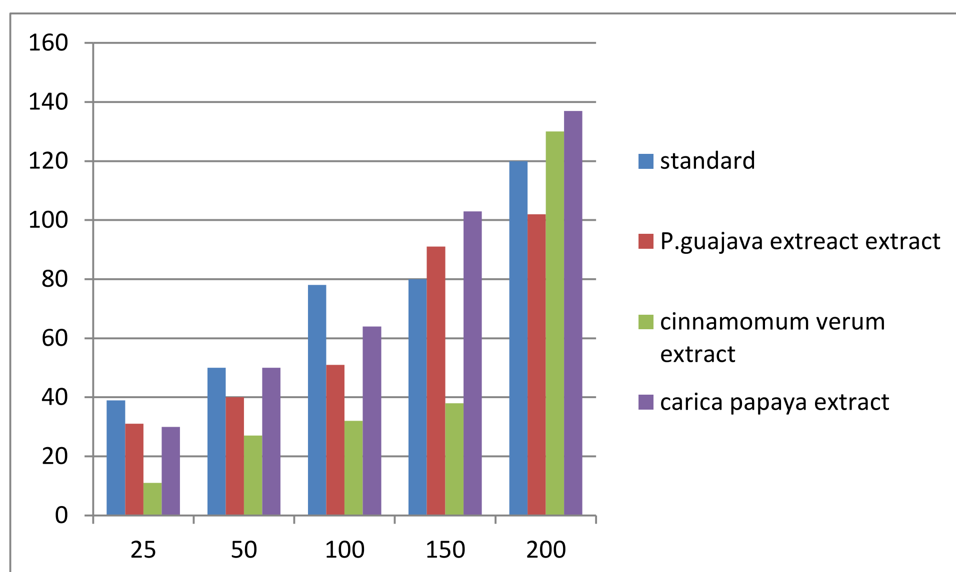
Several concentrations of the ethanolic leaf extract of PHF were tested for their in *vitro* antioxidant activity by using Nitric oxide scavenging model. It was observed that the free radicals were scavenged by the test compound in a concentration dependent manner up to the given in this model. The percentage scavenging values were calculated in Table20.

**Table-6: Effect of PHF on scavenging of Nitric Oxide.**

| S.No | Concentration (µg/ml) | Standard | Psidium.guajava extract | Cinnomum bark extract | Papaya leaf extract |
|---|---|---|---|---|---|
| 1 | 200 | 120.2±0.65 | 102.0±0.52 | 130.01±0.93 | 137.04±0.1 |
| 2 | 150 | 81.4±0.77 | 91.04±0.11 | 38.05±0.14 | 103.13±0.43 |
| 3 | 100 | 78.07±0.28 | 52.03±0.23 | 32.01±0.21 | 64.23±0.41 |
| 4 | 50 | 39.8±0.55 | 40.01±0.22 | 27.08±0.51 | 50.64±0.32 |
| 5 | 25 | 29.9±0.83 | 30.04±0.41 | 11.55±0.45 | 30.15±0.51 |

Values showing % inhibition of free radical scavenging activity are mean ± S.E.M.

**Graph-5: Effect of three different plant extracts on Nitric Oxide Scavenging Activity**




The % inhibition of free radical scavenging effect increased with the increasing concentrations of test compound. The ethanolic extract of PHF values were comparatively lower than the scavenging effect of ascorbic acid.

The results found in the present study show that the extract of PHF contains the highest amount of polyphenolic compounds and exhibits the greatest antioxidant activity through the scavenging of free radicals.

**4. DISCUSSION:**

The purpose of the work was to evaluate the traditional claims of polyherbal formulation on scientific basis in experimentally induced hyperlipidemia by employing models, Triton induced Hyperlipidemia and Fructose induced hyperlipidemia. The results of our present study clearly indicated that PHF of ethanolic extract at doses of 200 and 400mg/kg significantly lowered serum cholesterol and triglyceride levels i.e. antihyperlipidemic activity which was found to be more effective in higher dose as compared to lower dose when administered orally in triton induced hyperlipidemic models.

Triton, non ionic surfactant(isooctyl polyoxyethylene phenol/tyloxipal) to rats results in biphasic elevation of lipid levels. It acts as surfactant and supress action of lipases to block uptake of lipoproteins from circulation by extra hepatic tissue resulting in increased blood lipid concentration and increased cholesterol synthesis. The serum cholesterol lowering effect of PHF extract may be due to the inhibition of cholesterol biosynthesis.

The HDL-C levels is inversely related to the total body cholesterol and reduction of plasma HDL concentration may accelerate the development of atherosclerosis, leading to ischaemic heart diseases, by impairing the clearance of cholesterol from the arterial wall. In the PHF extract treated groups of animals showed slightly increase the serum HDL-C levels in triton and fructose induced hyperlipidemic model. The increased in HDL-C level may be due to the activity of LCAT and inhibition of the action of hepatic TG-lipase on HDL, which may contribute for rapid catabolism of blood lipids through extra hepatic tissues.

Total cholesterol/HDL-C ratio of >4.5 is associated with increased coronary heart disease risk. A significant decrease in the atherogenic index an ethanolic extract treatment shows that the protective efficacy of the extract against atherosclerosis.

In the present study, hyperlipidemia in rats is induced by feeding them with tritonx-100 and fructose. There was a significant increase in all the lipoproteins as well as triglyceride levels. However, absurdly, even HDL-C levels were elevated in the entire group that was fed fructose 10%. It has been well established that nutrition play an important role in the etiology of hyperlipidemias and atherosclerosis. Fructose diet model is used as a chronic model for induction of hyperlipidemia.

Diet containing polysaccharides increase the activity of HMG CoA reductase, the rate determining enzyme in cholesterol biosynthesis; this may be due to higher availability of CoA, which stimulated the cholesterogenesis rate. Moreover, this could be associated with a down regulation in LDL receptors by the cholesterol and saturated polysaccharides in the diet, which could also explain the elevation of serum LDL-C levels either by changing hepatic LDLR (LDL-receptor) activity, the LDL-C production rate or both. LCAT enzyme is involved in the transesterification of cholesterol, the maturation of HDL-C and flux of cholesterol from cell membrane in to HDL. The possible mechanism of PHF may involve increase of HDL-C, which is attributed to the

mobilization of cholesterol from pheripheral cells to the liver by the action of TG or cholesterol from serum to liver by pathway termed 'reverse cholesterol transport' where it is catabolised and excreted out of the body.

Preliminary phytochemical screening revealed the presence of flavonoids, terpenoids, phytosterols, alkaloids, saponins and tannins in PHF. It is found that some terpenoids and flavonoids were found to reduce blood cholesterol in several animal species by inhibiting intestinal absorption of cholesterol. Although compensatory synthesis were also reported, which was accompanied by increased secretion of cholesterol in bile, the net effect being lowering of cholesterol and Low Density Lipoprotein(LDL) in serum and elicitation of concomitant antihypercholesterolemic effect increase the permeability of mucosal cells in vitro, inhibit active mucosal transport and facilitate uptake of substances that are normally not absorbed. Phytosterols are reported to displace intestinal cholesterol and reduce cholesterol absorption from intestine. flavanoids have exhibited a variety of pharmacological activites, including the anti-atherogenesis and antioxidant effect. Thus the present study strongly suggests that the hypolipidemic activity of this medicinal plant could be attributed to the presence of flavanoids and sterols in the extract.

Nitric oxide is an important chemical mediator generated by endothelial cells, macrophages, neurons and involved in the regulation of various physiological processes. Excess concentration of nitric oxide is implicated in the cytotoxic effects observed in various disorders like AIDS, cancer, alzhemer's and arthritis. Oxygen reacts with the excess NO to generate nitrite and peroxy nitrite anions, which act as free radicals. From results of Nitric oxide method, it proved that the ethanolic extract of PHF had effective antioxidant activity. These extract compete with oxygen to react with NO and thus inhibit the generation of the nitrite and peroxy nitrite anions.

In the *in vitro* antioxidant studies, ethanolic extract of PHF had showed good nitric oxide scavenging activity with increasing concentrations of test compound may be due to the presence of polyphenols and flavonoids.

Thus, the data obtained from phytochemical analysis, pharmacological evaluation of ethanolic extract of PHF tend to suggests that the extract has shown significant antihyperlipidemic and antioxidant activity and safe administration of the extract, establishing the use of plant.

The polyherbal formulation of psidum guajava, carica papaya and cinnamomum verum are used in traditional medicine as a multiple remedy against many diseases and vectors. Despite the numerous scientifically proven pharmacological activities of PHF there is no data on its potential as antihyperlipidemic activity but results have been consistent. The present study is done to assess the antihyperlipidemic activity of PHF ethanolic extract in Triton induced and Fructose induced hyperlipidemia.

In Triton induced hyperlipidemia , administration ofTriton X 100 led to elevation of serum lipid levels. After 72 hrs lipid profile examined and these rats were given treatment with ethanolic extract of PHF at doses 200, 400 mg/kg for 7 days. Atorvastatin was employed as standard drug. At the end of experimental period lipid profile of the animals were measured and compared with positive control.

The chronic fructose diet induced experimental hyperlipidemia was produced by feeding the fructose (10%) for 7 days, the rats are then given test plant extracts i.e; p.guajava fruit extract, cinnamon verum bark and leaf extract of carica papaya (PHF) (200,400mg/kg p.o) once daily in the morning orally for next 7 consecutive days after induction of hyperlipidemia. During these days, all the groups also received fructose diet. At the end of the experimental period lipid profile of all the animals were observed and compared with positive control.

In Triton induced study results shows serum lipid parameters in animals were significantly reduced by 7 days treatment with PHF at dose levels 200,400mg/kg when compared with control group and there is also significant reduction in serum cholesterol 400 mg/kg of PHF group animals as shown significant compared with control group. At this time, an increased levels of HDL was also observed. There was significant difference in the mean lipid profile values of 200 and 400mg/kg, hence shows the dose dependent activity of the extract.

In fructose induced model administration of PHF at dose 200&400mg/kg showed significant reduction in the level of serum total cholesterol, Triglycerides, Low Density Lipoproteins, Very Low Density lipoprotein and High Density lipoprotein were increased. This study shows serum lipid parameters in animals were significantly reduced by 7 days treatment with PHF at dose levels 200&400mg/kg, when compared with control group.

In the present study ethanolic extract of PHF was assessed for its effect on *in vitro* antioxidant parameter like nitric oxide free radical scavenging at different concentrations, and the ethanolic extract of PHF had showed good nitric oxide radical scavenging activity with increasing concentrations of the extract.

The result of present study provides the evidence for the antihyperlipidemic and antioxidant activity of ethanolic extract of PHF as claimed in the traditional use. Safety and effectiveness in both Triton induced as well as fructose induced were established. The presence of phytosterols, flavanoids and terpenoids in the extract may be responsible for the antihyperlipidemic activity.

## 5. CONCLUSION

The results obtained from the pharmacological screeining have led to the conclusion that, ethanolic extract of PHF have significant antihyperlipidemic and anti-oxidant activity. Hence it can be exploited as an antihyperlipidemic therapeutic agent or adjuvant in existing therapy for the treatment of hyperlipidemia.

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