PHARMACOLOGICAL SCREENING OF AYURVEDIC ANTIHYPERLIPIDEMIC FORMULATION: AN AYURVEDIC APPROACH

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ABSTRACT

Doctrines of Ayurveda have momentous value even in the life of present day human life. These principles are based on the extraordinary observations and experiments at various levels. Hence one cannot easily deny the value in the life of present day human life. These principles are based on the extraordinary observations and experiments at various levels. Hence one cannot easily deny the presence in Ayurveda to maintain health of healthy people and to alleviate disorders in the diseased persons. The references of medicinal uses of herbs are recorded in Rgveda and Atharvaveda. Nighantus, the well-known compilations are the very rich sources of herbal drug data ranging from identification, collection to therapeutics uses of the drugs. Since previous two decades there has been an increasing status emphasized on screening of herbs for hypolipidemic actions in order to reduce the risk of heart and other related disease. The high expenses and side effects of hyperlipidemia medications have led many populaces to search for alternate treatments. Only a few studies have been conducted to evaluate the effect of herbs mentioned in Ayurvedic texts on hyperlipidemia. Capparis decidua F., Ricinus communis L., and Zizyphus jujuba L. 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 WR-1339 and High fat diet induced hyperlipidemia in rats. The probable mechanism of action of the extract may be inhibition of HMG-CoA reductase enzyme pathway.

KEY WORDS: Antihyperlipidemic action, Ayurveda, Capparis decidua, Ziziphus jujube, Ricinus communis

INTRODUCTION

Hyperlipidemia is a common predicament in society due to change of life style and food practice³⁴. It is an excess amount of fats, such as cholesterol, phospholipids, triglycerides and cholesterol esters. An excess amount of fats can cause significant health complications, particularly with the heart. Ayurvedic herbs are part of a traditional medicinal practice native to India. These herbs are variations of natural plants metallic preparations and animal products that aid in the treatment of disease, illness and imbalances within the body. Ayurvedic medicine is in practice traces back more than 4,000 years³. In the recent years, the interest in medicinal plants has increased in a great deal. The Ayurvedic concept of herbal medicine focuses on balancing three humors of body (Vata-Pitta-Kapha) and they are used to treat various ailments³⁴. Though the use of many indigenous drugs has been described in classics but still there is a need to find out more effective and safe drug, which not only controls the diseases but also tent to cure the complex conditions. The main aim of the study conducted is to evaluate the antihyperlipidemic activity of the poly-herbal formulation containing three herbal drugs using various experimental models of rats. The three herbal drugs are Capparis decidua F. Edgew. Ricinus communis Linn. Zizyphus jujuba Lam.

AYURVEDA & HYPERLIPIDEMIA:
The disease management approaches in Ayurveda have two fundamental principles: nourishment of the body tissues (Brimhan) or the depletion (Karshan) of them⁶. In Bhavaprakasha Nighantu (16⁸ Century text) emphasizes many herbs for above mentioned properties⁷. Hyperlipidemia, Cholesterol, triglycerides etc. are comes under the preview of Santaranathianya (Over-nourished Diseases) Vyadhi in Ayurveda⁸. Ayurvedic texts converse Meda Dhatu (lipid tissue) and explain how to maintain healthy quantity and quality of fat tissue in the body. When Meda Dhatu is balanced and healthy, that subsequently helps to maintain balanced cholesterol⁹. The body is a combination of the seven Dhatu (elements that hold and maintain the body), three Dosha (physiological dominating principles) and three Mala (metabolic excreta). Meda dhatu, fat tissue, is one of the seven Dhatus, or body tissues⁹. The principle factor behind balance in the body is balanced Agni (digestive fire), Dhatu & Dosha¹⁰. Proper digestion is the basis for good health & for every part of the body. It’s imperative to understand that fat tissue (cholesterol) in itself is not bad, and is actually essential for the body to function properly. So in the Ayurvedic perspective, the formation of cholesterol does not necessarily need to be tapering, but it configure to be at equilibrium. When the digestive fire is at equilibrium stage, then the body will form the right amount of lipids / cholesterol, to nourish the body. To understand how to maintain healthy Meda Dhatu, balance is the main principle behind it. There are 13 Agnis that work jointly in the digestive process. Initially the food is metabolized by the main digestive fire (Jathar-Agni), located in the stomach.
and duodenum. Next it is metabolized by the five elemental fires located in liver (Bhut-Agni), and finally by seven Dhatu-Agnis, located in the seven forms of tissues. These 13 types of Agnis collectively form the metabolism and digestive system in the body. When we eat fatty or oily food, it is metabolized by these 13 Agnis in a chronological process. Jhataragni helps to break down the food. The Bhut-Agnis help to screen toxins and ensure that the food is transformed into healthy, good-quality body tissue. The Dhatu-Agns help to transform the food into their respective tissues.

So the strength of the various digestive fires is needed for the air tight container. Material was cleaned, shade dried, powdered and processed. The identity of leaves of Dhatvagni is imperative to understand that the liver plays a vital role in the digestive system. Out of 13 Agni, Panchabhutagni type of biotransformation done by Liver. In abnormal conditions when Meda Dhatu mixes with Ama (Endotoxins created due to wrong lifestyle and food habits), it changes the quality of fat tissue ultimate quality of cholesterol, making it detrimental rather than healthy. This amalgamation of Ama with fat tissue is the prime cause of imbalanced cholesterol ultimately the quality and purity of the fat tissue disturbs. This entire metabolism summarized under the Bhutagni concept where Vridhhi & Kshaya of individual Agni hamper the normal or abnormal Dhatu.

As mentioned earlier, one of the seven Dhatus is Meda Dhatu, fat tissue. All of the tissues are formed in a sequence of metabolic bio-transformations, and the health and strength of each type of tissue is based on the previous one. The taken food is converted into the Rasa (nutritive fluid) and from there is transformed into Rakta (blood plasma), and in a sequence converts to the Mamsa (muscle), Meda (fat), Asthi (bone), Majja (bone marrow), and finally, Shukra (reproductive fluid). If Ama has accumulated in the nutritive fluid, blood plasma or the muscle tissue, which are all raw material for forming fat tissue, then that Ama will also be present in the fat tissue. Ultimately Ama in the fat tissue, presence of Ama in the Rasa, Rakta or Mamsa tissues, un-nourishment of the body tissues are the main reasons of abnormal lipid levels. The functioning of Agni needs to be increased especially Dhatvagni & Panchabhoutikagni to encounter the lipid levels.

**MATERIAL AND METHODS**

**Plant Material:** The fresh roots of *Ricinus Communis linn.*, leaves of *Zizyphus jujuba lam* and aerial parts of *Capparis decidua* edgew were collected from Anand and submitted to Anand Agricultural University, Anand, Gujarat, India for identity. The plants were authenticated by Dr. G. C. Jadeja, Professor and Head of Department of Agriculture Botany. The material was cleansed, shade dried, powdered to mesh size 60 and equal proportions (100 gms) of each were mixed thoroughly to prepare the polyherbal formulation and stored in air tight container.

**Formulation of plant extract:** The powdered mixture was subjected to continuous, hot solvent-extraction using mixture of ethanol and water (70:30) in a Soxhlet apparatus. The crude hydroalcoholic extract was filtered and dried under reduced pressure.

**Animals:** Adult Sprague–Dawley male rats (200-250 gms) were fed pellet diet and given water ad libitum. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals CPCSEA, India after approval by the Institutional Animal Ethics Committee (IAEC-Protocol no. CPCSEA/IAEC/ARC/2009-10/06).

**Chemicals:** Tyloxapol (Triton WR-1339, Sigma Aldrich, USA), Atorvastatin (Zydus Research Centre, Ahmedabad). Enzymatic kits (Lab care diagnostic Pvt. Ltd. India), All other chemicals used were of analytical grade.

**ACUTE TOXICITY STUDIES**- Acute toxicity studies for the hydroalcoholic extract of polyherbal formulation were conducted as per OECD guidelines 423 using Sprague–Dawley rats. Each animal was administered the hydroalcoholic extract of polyherbal formulation by oral route. The animals were observed for mortality up to 72 hours. The hydroalcoholic extract of polyherbal formulation was found to be safe up to 2000mg/kg body weight.

**EXPERIMENTAL METHODS FOR HIGH CHOLESTEROL (HC)-DIET MODEL**

Male Sprague–Dawley rats weighing 200-250 gm, were used for a standard experimental method as high Cholesterol (Hc)-diet model to study the comparison in various groups. The collected samples were centrifuged for 10 minutes at 2000 r.p.m. and serum samples so collected were used for various biochemical tests. The animals were then sacrificed and the liver collected.

**BIOCHEMICAL ANALYSIS OF SERUM**

Serum samples were analyzed for total cholesterol, high-density lipoproteins and triglyceride levels using standard enzymatic assay kits: Total cholesterol Kit, HDL-Precipitating RGT Kit, Triglyceride Kit. Low density lipoprotein (LDL) and Very low density lipoprotein (VLDL) were calculated according to Friedwald formula, i.e. LDL = TC–HDL–VLDL and VLDL cholesterol = Triglycerides/5. Atherogenic index (A.I) was also calculated as per the formula. A.I=TC – HDL-C / HDL-C

**BIOCHEMICAL ANALYSIS OF LIVER**

A standard method for Biochemical Analysis of liver and Hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase activity was followed. The ratio between HMG CoA and Mevalonate is inversely proportional to HMG CoA reductase activity, i.e. an increase in ratio indicates decreased activity.

**STATISTICAL ANALYSIS**

Data were analyzed using one way ANOVA followed by Tukey test and p < 0.05 was considered significant. Values are expressed as Mean ±SEM for six rats per group.
RESULTS
1- Effect of polyherbal formulation on lipid profile in serum and liver of Triton induced hyperlipidemic rats- Oral administration of hydroalcoholic extract of polyherbal formulation (200 mg/kg and 400mg/kg, p.o.) to Triton induced hyperlipidemic rats, significantly reduced the serum and liver cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), VLDL-cholesterol levels and atherogenic index. Levels of serum and liver HDL-cholesterol were significantly increased in rats treated with polyherbal formulation as compared to Triton treated rats (Table 1, 2).

2- Effect of polyherbal formulation on lipid profile in serum and liver of High fat diet induced hyperlipidemic rats- Oral administration of hydroalcoholic extract of polyherbal formulation (200 mg/kg and 400mg/kg, p.o.) significantly increased reductase activity in liver increased serum and liver HDL-cholesterol formulations (200 mg/kg and 400mg/kg, p.o.) significantly increased in rats treated with polyherbal hydroalcoholic extract of polyherbal formulation (200 mg/kg and 400mg/kg, p.o.) to Triton induced hyperlipidemic rats as compared to Triton treated rats (Table 3.4).

3- Effect of polyherbal formulation on HMG-CoA reductase activity in liver — Oral administration of hydroalcoholic extract of polyherbal formulation (200 mg/kg and 400mg/kg, p.o.) significantly increased HMG-CoA/Mevalonate ratio in hyperlipidemic rats as compared with normal rats (Table 5, 6).

DISCUSSION:
CONCEPTUAL AYURVEDIC MECHANISM OF SELECTED HERBS
Ayurvedic properties of these three drugs: Ayurvedic Properties of Badara (Zizyphus jujuba Lam.)

करं मधुर स्निध्य भोज्य वातमुखितजीवः।
तत्व्यक्तिम् स्वस्थान्वन पिले सत्यस्यत्वेः।

Charaka Samhita Sutrasthana 27
Badara having Snigdha Guna (Quality), Madhur Rasa (Taste), Madhur Vipak (Metabolism) and Sheet Virya (Potency)

Ayurvedic Properties of Kareera (Capparis deciduas Edgew)

करेरेः स्वस्थसहिष्ठकः स्वेदणां भोज्यस्यस्यपुस्तः।
दुनिस्तिकीक्षागतार्थोद्धरणाम्।

Bhavaprakash Nighantu
Kareera having Katu, Tikta Rasa (Taste), Ushna Veerya (Potency) and Katu Vipaka (Metabolism).

Ayurvedic Properties of Eranda (Ricinus communis Linn)

उर्दुक्ष्यमिन्नश्च गुणस्तुलुणिलखिप्तम्।
वक्ष्यीमयोक्श्चिताः कटुकुश्चिताः परम्।

Bhavaprakash Nighantu, Guduchyadi Varga 64
Eranda having Snigdha, Tiksh, Suk sham (Quality), Madhur, Kashay (Taste), Madhur Vipak (Metabolism), Ushna Virya (Potency) and Vednaschapan Prabhav (Impact)

Ayurvedic science has its own parameters and planning to design the formulation. For hyperlipidemia, many plants and formulations have been described in the Ayurvedic texts and are also currently used by Ayurvedic physicians. The above mentioned herbs are chosen based on Ayurvedic pharmacology, which relies on taste and other physical-chemical properties for its action. Medicinal plants having bitter (Tikta), pungent (Katu), astringent (Kashay) tastes, and light (Laghu), dry (Ruksha), rough (Khara), subtle (Sukshma), sharp (Tikshna), hot (Ushna Veerya), and pungent (Katu Vipak) properties are used to treat obesity and associated hyper-lipid levels. On the contrary, Substances having sweet (Madhur), sour (Amla), and salty (Lavanya) tastes increase fat. Bitter tastes are dry, cold, and light (Ruksha, Sheeta, and Laghu); they stabilize skin and flesh in the body and absorb subtle liquid waste products (Kleda), excessive fat, excessive mucus, pus, sweat, urine, stool, and humor (Agni and Apa). Pungent tastes have similar properties like bitter, light, and dry tastes but are unlike hot tastes. They act on the fat tissue through scraping (Lekhan) channel and its excretion through sweat, urine, stool, etc. They also devastate coughing. Astringent tastes are dry, cool, and heavy; they basically suppress Pitta but also act on Kapha. The property of a substance, called Guna, is equally important when selecting it as a medicine. In obesity, substances having light, dry, and rough properties are used. It also should have minute and sharp properties. Substances that are light and easy to digest relieve Kapha and increase Vata and digestive power (Agni). They also cause depletion of tissues in the body, scrape out (Lekhan) excessive fat, and clear the channels of the body for waste. Together, this brings lightness in the body. Dry substances absorb water and create hardness and dryness. They aggravate Vata and reduce Kapha. The rough property of substances increases Vata, depletes the constituents of the body, and absorbs water. Substances having these three properties (Gunas) will reduce Kapha and increase Vata in obese patients; combined action of these properties on fat will be through scraping (Lekhan), drying, and depleting through various channels in the form of waste. Sharp (Tikshna) substances act as sharp-edged weapons and cause depletion of tissues and thereby emaciation of the body-this process is called Lekhana. The hot quality and bitter taste of a substance has light, dry, and sharp and subtle (Sukshma) properties that act on obesity as described above.

The ingredients of selected and designed formulation possess the all above parameters and qualities. It was intended to exhibit the antilipidemic activity and so on was selected for experiment purpose. Apart from this all above herbal medicines are easily available, non controversial, eco-friendly and simple to manufacture. The results obtained from the experiment validate the expected positive activity of the formulation as well as basic concepts of Ayurveda.

CONCLUSION
Conceptual designing of pharmaceutical formulation considering traditional medicine especially Ayurveda helps to create novel drugs in industry.

ACKNOWLEDGEMENT
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Table 1. Effect of oral administration of hydroalcoholic extract of polyherbal formulation on serum Cholesterol, Triglyceride, HDL-C, LDL-C, VLDL-C and Atherogenic index.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TC (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>VLDL-C (mg/dl)</th>
<th>Atherogenic index (A.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>70.28±2.24</td>
<td>65.58±2.11</td>
<td>22.68±1.51</td>
<td>34.48±3.16</td>
<td>13.12±0.42</td>
<td>2.17±0.28</td>
</tr>
<tr>
<td>Triton treated</td>
<td>157.73±2.62</td>
<td>139.9±2.29</td>
<td>18.35±1.08</td>
<td>110.2±2.71</td>
<td>29.19±0.59</td>
<td>7.73±5.51</td>
</tr>
<tr>
<td>Triton + PHE (400 mg/kg)</td>
<td>109.7±2.31</td>
<td>117.03±2.84</td>
<td>22.85±0.89</td>
<td>63.45±2.66</td>
<td>23.4±0.57</td>
<td>3.75±0.18</td>
</tr>
<tr>
<td>Triton + PHE (200 mg/kg)</td>
<td>96.12±2.01</td>
<td>92.47±2.37</td>
<td>24.3±1.11</td>
<td>53.4±2.54</td>
<td>18.49±0.47</td>
<td>2.99±0.21</td>
</tr>
<tr>
<td>Triton + Atorvastatin</td>
<td>84.33±1.48</td>
<td>89.87±1.76</td>
<td>25.07±1.56</td>
<td>41.29±2.51</td>
<td>17.97±0.35</td>
<td>2.44±0.26</td>
</tr>
</tbody>
</table>

P value: ** p<0.001, * p<0.05 compared with normal group; † p<0.001, † † p<0.0005 compared with control group Triton WR 1339 treated rats.

Table 2. Effect of oral administration of hydroalcoholic extract of polyherbal formulation on liver Cholesterol, Triglyceride, HDL-C, LDL-C, VLDL-C and Atherogenic index.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TC (mg/gm)</th>
<th>TG (mg/gm)</th>
<th>HDL-C (mg/gm)</th>
<th>LDL-C (mg/gm)</th>
<th>VLDL-C (mg/gm)</th>
<th>Atherogenic index (A.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>62.45±1.723</td>
<td>61.37±1.61</td>
<td>30.78±1.14</td>
<td>19.39±1.31</td>
<td>12.27±0.32</td>
<td>1.03±0.05</td>
</tr>
<tr>
<td>Triton treated</td>
<td>163.75±3.52</td>
<td>125.58±2.13</td>
<td>25.45±1.24</td>
<td>113.18±3.19</td>
<td>25.12±0.42</td>
<td>5.51±0.31</td>
</tr>
<tr>
<td>Triton + PHE (200 mg/kg)</td>
<td>119.97±2.31</td>
<td>105.78±2.08</td>
<td>31.67±1.18</td>
<td>67.14±2.13</td>
<td>21.16±0.46</td>
<td>2.8±0.13</td>
</tr>
<tr>
<td>Triton + PHE (400 mg/kg)</td>
<td>102.82±3.05</td>
<td>95.97±1.43</td>
<td>37.92±1.59</td>
<td>45.7±2.44</td>
<td>19.19±0.29</td>
<td>1.72±0.09</td>
</tr>
<tr>
<td>Triton + Atorvastatin</td>
<td>91.91±2.26</td>
<td>84.97±3.39</td>
<td>40.7±1.12</td>
<td>34.86±2.51</td>
<td>16.99±0.68</td>
<td>1.3±0.06</td>
</tr>
</tbody>
</table>

P value: ** p<0.001, * p<0.05 compared with normal group; † p<0.001, † † p<0.0005 compared with control group Triton WR 1339 treated rats.

Table 3. Effect of oral administration of hydroalcoholic extract of polyherbal formulation on serum Cholesterol, Triglyceride, HDL-C, LDL-C, VLDL-C and Atherogenic index.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TC (mg/dl)</th>
<th>TG (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>VLDL-C (mg/dl)</th>
<th>Atherogenic index (A.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>66.45±1.69</td>
<td>51.7±2.98</td>
<td>29.38±0.98</td>
<td>25.26±1.63</td>
<td>10.34±0.59</td>
<td>1.28±0.05</td>
</tr>
<tr>
<td>HCD treated</td>
<td>109.93±3.09</td>
<td>95±2.83</td>
<td>24.28±0.85</td>
<td>66.31±3.52</td>
<td>18.99±0.57</td>
<td>3.52±0.18</td>
</tr>
<tr>
<td>HCD + PHE (200 mg/kg)</td>
<td>87.59±2.57</td>
<td>74.88±5.42</td>
<td>30.88±1.02</td>
<td>41.91±5.48</td>
<td>14.98±1.08</td>
<td>1.87±0.23</td>
</tr>
<tr>
<td>HCD + PHE (400 mg/kg)</td>
<td>70.53±0.66</td>
<td>56.77±2.47</td>
<td>32.28±2.11</td>
<td>26.9±2.44</td>
<td>11.35±0.49</td>
<td>0.98±0.20</td>
</tr>
<tr>
<td>HCD + Atorvastatin</td>
<td>85.46±4.43</td>
<td>61±7.39</td>
<td>34.6±1.99</td>
<td>37.59±1.89</td>
<td>12.38±1.48</td>
<td>1.48±0.08</td>
</tr>
</tbody>
</table>

P value: ** p<0.001, * p<0.05 compared with normal group; † p<0.001, † † p<0.0005 compared with control group High cholesterol diet (HCD) rats.
Table 4. Effect of oral administration of hydroalcoholic extract of polyherbal formulation on liver Cholesterol, Triglyceride, HDL-C, LDL-C, VLDL-C and Atherogenic index.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TC (mg/gm)</th>
<th>TG (mg/gm)</th>
<th>HDL-C (mg/gm)</th>
<th>LDL-C (mg/gm)</th>
<th>VLDL-C (mg/gm)</th>
<th>Atherogenic index (A.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>44.22±1.87</td>
<td>42.13±2.43</td>
<td>27.14±0.67</td>
<td>9.46±1.08</td>
<td>8.43±0.49</td>
<td>0.6±0.04</td>
</tr>
<tr>
<td>HCD treated</td>
<td>63.6±2.87**</td>
<td>54.92±2.38*</td>
<td>23.14±1.07**</td>
<td>29.46±3.09**</td>
<td>10.98±0.46*</td>
<td>1.6±0.10**</td>
</tr>
<tr>
<td>HCD + PHE (200 mg/kg)</td>
<td>54.26±0.54*</td>
<td>46.57±1.13*</td>
<td>28.8±1.56*</td>
<td>16.22±1.78*</td>
<td>9.26±0.23*</td>
<td>1±0.11**</td>
</tr>
<tr>
<td>HCD + PHE (400 mg/kg)</td>
<td>46.12±2.90**</td>
<td>43.57±1.94*</td>
<td>30.4±1.27</td>
<td>8.12±1.60</td>
<td>8.71±0.46*</td>
<td>0.51±0.09**</td>
</tr>
<tr>
<td>HCD + Atorvastatin</td>
<td>53.57±1.25*</td>
<td>47.05±1.05*</td>
<td>32.47±1.01**</td>
<td>11.69±1.01**</td>
<td>9.41±0.21*</td>
<td>0.65±0.04**</td>
</tr>
</tbody>
</table>

P value: ** p<0.001,* p<0.05 compared with normal group; ** p<0.001, * p<0.05 compared with control group High cholesterol diet (HCD) rats.

Table 5. Effects of hydroalcoholic extract of polyherbal formulation on HMG-CoA enzyme reductase activity on Triton WR 1339 model.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HMG-CoA / Mevalonate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.36±0.05</td>
</tr>
<tr>
<td>Triton + PHE (200 mg/kg)</td>
<td>2.08±0.06**</td>
</tr>
<tr>
<td>Triton + PHE (400 mg/kg)</td>
<td>2.26±0.04*</td>
</tr>
<tr>
<td>Triton + Atorvastatin</td>
<td>2.48±0.05**</td>
</tr>
</tbody>
</table>

P value: ** p<0.001,* p<0.05 compared with normal group.

Table 6. Effects of hydroalcoholic extract of polyherbal formulation on HMG-CoA enzyme reductase activity on High cholesterol diet (HCD) model.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HMG-CoA / Mevalonate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1.27±0.05</td>
</tr>
<tr>
<td>HCD + PHE (200 mg/kg)</td>
<td>1.47±0.06*</td>
</tr>
<tr>
<td>HCD + PHE (400 mg/kg)</td>
<td>1.56±0.03*</td>
</tr>
<tr>
<td>HCD + Atorvastatin</td>
<td>1.7±0.10*</td>
</tr>
</tbody>
</table>

P value: ** p<0.001,* p<0.05 compared with normal group.