PROTECTIVE EFFECT OF A COMBINATION OF ETHANOLIC RHIZOME EXTRACT OF ZINGIBER OFFICINALE ROSC., AND ROSUVASTATIN IN HIGH CHOLESTEROL DIET INDUCED HYPERLIPIDEMIC RATS

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ABSTRACT
Cardiovascular diseases continue to be the leading cause of death in the industrialized nations. Hyperlipidemia with subsequent coronary atherosclerosis is the major trigger for ischemia and other cardiovascular diseases. Combination therapy often takes advantages of complementary effects of different agents. The present study is aimed at elucidating the beneficial effects of combined administration of ethanolic rhizome extract of Zingiber officinale (ERZO) 200 mg/kg & 400mg/kg p.o and Rosuvastatin (RSV) 10 mg/kg p.o, on high cholesterol diet induced hyperlipidemic rats. Adult rats were fed with a cholesterol- rich diet for 8 weeks and received either ERZO (400mg/kg p.o) or RSV (10mg/kg p.o) or a combination daily starting from sixth week of cholesterol diet administration for three weeks. Body weight was measured daily. On 57th day of the study, lipid profile (TC, TG, LDL, VLDL, HDL), AST and ALT were measured in serum. SOD and Catalase were quantified in cardiac homogenates and aortic lesions were examined by histopathology of aorta. Three weeks treatment with ERZO (400mg/kg p.o) and RSV (10 mg/kg) alone showed reduction in body weight, significant decrease in lipid levels and increase in SOD and catalase levels and reduction in the aortic lesions. But the combination of ERZO (200 mg/kg p.o 400mg/kg p.o) and RSV(10 mg/kg p.o) produced more significant reduction in body weight, normalized the lipid levels, significant reduction in the AST and ALT levels elevated by high cholesterol diet. It also showed a more significant increase in SOD and catalase levels and normalized the aortic lesions. These changes were found to be more significant than monotherapy. This study provides evidence that combination regimens containing Ginger and low dose of rosuvastatin...
could be advantageous in treating hyperlipidemia and atherosclerosis than monotherapy with either of the drugs.

**KEYWORD:** *Zingiber officinale* (ERZO), Rosuvastatin (RSV).

**INTRODUCTION**

Currently, combination therapy of allopathic drugs with herbal medicine has become popular all over the world. The usage of herbal therapies along with prescription and Over-The-Counter (OTC) medications is increasing day by day.\(^1\) Mono-substance therapy model has gradually shifted toward the adoption of combination therapies, in which multiple active components are employed. Recent evidence has demonstrated that combination therapy could provide greater therapeutic benefits to diseases such as AIDS, cancer, hyperlipidemia, atherosclerosis and diabetes, all of which possess complex etiology and pathophysiology and therefore are difficult to treat using single a drug target approach\(^2\).

Cardiovascular diseases continue to be the leading cause of death in the industrialized nations.\(^3\) According to a study commissioned by the Indian Council of Medical Research (ICMR) at least 3/4th of the Indian population has abnormal levels of cholesterol that increases the risk of cardiovascular disease.

Hyperlipidemia is a major risk factor for all cardiovascular diseases. It refers to elevated levels of cholesterol, Triglycerides, Low density lipoproteins and decreased levels of high density lipoprotein. The causes of hyperlipidemia are mainly lifestyle changes (poor diet, smoking, alcohol). The hyperlipidemia may be primary ie. Genetic (monogenic or polygenic) or secondary which is associated with diabetes, myxedema, nephrotic syndrome, chronic alcoholism, use of drugs such as corticosteroids and oral contraceptives.\(^4\) Hyperlipidemia induced atherosclerosis is the main hidden cause of coronary artery disease.

Statins are effective therapeutic tools for dyslipidemia and reduce the risk of cardiovascular morbidity and mortality in patients with or at risk for coronary heart disease. Rosuvastatin is a potent drug among the statins that reduces the levels of cholesterol and increases High-Density Lipoprotein cholesterol (HDL-C) levels in patients with dyslipidemia.\(^1\) Though it is projected as a promising drug for monotherapy, it is also associated with some side effects like liver damage, kidney failure and muscle weakness. Usage of herbal medicines along with allopathic drugs may help to overcome these drug induced side effects.
Zingiber officinale commonly known as ginger, is one of the commonly used spices around the world. Ginger, a well known herb is found to have antioxidant principles, mainly gingerols and shogaols and some related phenolic ketone derivatives. Ginger extract possesses antioxidative characteristics, since it can scavenge superoxide anion and hydroxyl radicals. It has been targeted for its hypotensive and hypocholesterolemic activity, as its constituents are claimed to elevate the activity of hepatic cholesterol 7 hydroxylase, the rate limiting enzyme in bile acid biosynthesis, thereby stimulating cholesterol conversion to bile acid resulting in elimination of cholesterol from the body.\(^5\)

In view of the popularity of a combination therapy and based on the fact that ginger has been shown to have beneficial antihyperlipidemic potential, the present study seeks to evaluate whether a combination of Rosuvastatin and ginger extract would improve the antihyperlipidemic and antiatherogenic potential as compared to individual treatment.

**MATERIALS AND METHODS**

**Preparation of ethanolic extract of Zingiber officinale\(^5\)**

The rhizomes of Zingiber officinale Rosc., were purchased from the local market at Hosur, Krishnagiri (District), Tamilnadu in the month of August, 2016. The Rhizomes was identified and authenticated by Prof. Sasikala Ethirajulu, Botanist, Siddha Central Research Institute, Arumbakkam, Chennai-600106.

Five kilogram of fresh ginger was cleaned, washed under running tap water, peeled, cut into small pieces, shade dried and then subjected to size reduction to a coarse powder by using electrical blender. 200g of this powder was macerated in 1000ml of 99% ethanol for 72 hours with occasional shaking at room temperature. The extract was filtered using muslin cloth. The filtrate was concentrated to dryness and this concentrated ethanolic rhizome extract of Zingiber officinale Rosc. (ERZO) was used for the in vivo studies.

**Acute toxicity study for ginger\(^6\)**

Acute toxicity study has already been performed on the rhizome of Zingiber officinale Rosc. Ethanolic rhizomes extract of Zingiber officinale Rosc., was administrated as a single dose to rats at different dose levels of 250,500,1000,2000 and 5000 mg/kg BW. Animals were observed periodically for the symptoms of toxicity and death within 24h and then daily for 14 days. Rhizomes of Zingiber officinale Rosc., produced no mortality at 5000mg/kg.
Experimental animals\[^7\]
Healthy wistar albino rats (150-200g) were used in this study. Animals were maintained as per the guidelines of the CPCSEA. All the animals were housed in polypropylene cages at standard husbandry conditions (Temperature: 23 ± 2°C, Relative humidity: 55-60%, 12h: 12h light / dark cycle) in the Animal Experimental Laboratory, MMC, Chennai-03. They were provided with standard pellet diet and water *ad libitum*. They were initially acclimatized for the study. The experimental protocol was approved by the Institutional Animal Ethics Committee, MMC, Chennai (IAEC Approval No. IAEC/MMC/02/2016).

Chemicals
Rosuva statin was a gift sample from Fourrts (India) Laboratories Pvt Ltd, Chennai. Cholic acid and cholesterol powder were purchased from Microfine Chemicals, Chennai. All the chemicals used in study were of analytic grade.

Induction of hyperlipidemia
In addition to the standard diet, the rats were fed with cholesterol diet twice a day for 8 weeks. Cholesterol diet was prepared by mixing cholesterol 12%, cholic acid 1%, sucrose 40% in 10ml of coconut oil along with the normal diet. All the animals were weighed and divided into six groups, each group containing six animals.\[^8,9\]

EXPERIMENTAL GROUPS
Group I - (Normal control) : Standard pellet diet for 8 weeks.
Group II - (Disease control) : High cholesterol diet for 8 weeks.
Group III - (Ginger group) : High cholesterol diet for 8 weeks and ERZO 400mg/kg p.o from 6\(^{th}\) to 8\(^{th}\) week.
Group IV (Rosuvastatin group) : High cholesterol diet for 8 weeks and RSV 10mg/kg p.o from 6\(^{th}\) to 8\(^{th}\) week.
Group V (ERZO + RSV group) : High cholesterol diet for 8 weeks and ERZO 200mg/kg + RSV 10 mg/kg p.o from 6\(^{th}\) to 8\(^{th}\) week.
Group VI (ERZO + RSV group) : Rats were fed with high cholesterol diet for 8 weeks and ERZO 400mg/kg + RSV 10 mg/kg from 6\(^{th}\) to 8\(^{th}\) week.
EVALUATION PARAMETERS

Body weight changes\textsuperscript{[10]}

The body weight of each animal in every group was recorded once weekly till the end of the study and percentage change in body weight was determined.

Biochemical analysis

At the end of the study, i.e. on the 57\textsuperscript{th} day, after overnight fasting, blood was collected from the retro-orbital plexus using microcapillary tubes and serum was separated by centrifugation at 3000rpm for 15mins. The serum was used for biochemical evaluation of Total cholesterol (TC), Triglyceride (TG), Low density lipoprotein cholesterol (LDL-C), Very low density lipoprotein cholesterol (VLDL-C), High density lipoprotein Cholesterol (HDL-C), Alkaline phosphatase (ALT), and Aspartate aminotransferase (AST).

Estimation of cardiac antioxidant enzyme levels\textsuperscript{[11]}

The rats were then sacrificed by cervical dislocation and the heart was removed. Antioxidant enzyme levels were determined in cardiac tissue. Approximately 100 mg cardiac tissue homogenized with phosphate buffer, pH7.4 using Teflon homogenizer in ice cold condition. The homogenate was centrifuged at 5000 rpm for 10mins. The supernatant was taken up for evaluation of antioxidant enzyme Superoxide dismutase (SOD) and Catalase.

Histopathology of aorta\textsuperscript{[12]}

Histopathology was carried out according to Carleton and Drury (1973). Cuts were made at a right angle to aorta and fixed in 10% buffered formalin. Sections of 4 μm thickness were stained with hematoxylin and eosin. Aorta with uniform thickness throughout its circumference have been selected for morphometric measurements.

STATISTICAL ANALYSIS\textsuperscript{[11]}

All the values are expressed as mean ± SD. The data was statistically analyzed by one way ANOVA followed by Dunnet’s multiple comparison test. One way analysis of variance (ANOVA) was used to correlate the statistical difference between the variables. P<0.05 was considered to be significant. Statistical analysis was done by using Graph Pad prism 7.3.

RESULTS

1. BODY WEIGHT CHANGES

The body weight of each animal in every group was recorded once weekly till the end of the study and percentage decrease in body weight are given in Table 1.
Table 1: Body weight of rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Induction period</th>
<th>Treatment period</th>
<th>% change in body weight (35th Vs 56th day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Day</td>
<td>7th Day</td>
<td>14th Day</td>
</tr>
<tr>
<td>Control</td>
<td>130.8±5.8</td>
<td>130.8±5.4</td>
<td>135.8±5.8</td>
</tr>
<tr>
<td>Diseased control</td>
<td>137.5±2.7</td>
<td>162±6.57</td>
<td>169.3±7.1</td>
</tr>
<tr>
<td>ERZO</td>
<td>142.5±2.7</td>
<td>154.5±3.1</td>
<td>162±3.8</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>115±5.47</td>
<td>130.3±3.9</td>
<td>140.7±5.2</td>
</tr>
<tr>
<td>Low dose ERZO+RSV</td>
<td>116.7±5.1</td>
<td>131.7±2.7</td>
<td>141±4.60</td>
</tr>
<tr>
<td>High dose ERZO+RSV</td>
<td>125±5.4</td>
<td>145.5±3.8</td>
<td>156.3±1.9</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ± SD (n=6), One way ANOVA followed by Dunnet’s multiple comparison test a - vs 0 day, b- vs 35th day ***p< 0.001, NS- Non significant.
It is seen that in all the group of animals, fed with high cholesterol diet, there was a significant increase in body weight. In the control group there was a marginal increase in body weight (9.23%) at the end of 35th day. After the induction period, treatment in the following 3 weeks with ERZO or RSV alone showed a reduction in body weight. The percentage decrease in body weight was 21.81% and 22.22% respectively. The combination of ERZO and RSV showed greater reduction in body weight (28.16% and 36.50%) when compared to the monotherapy. In the animals fed with cholesterol rich diet, the increase in body weight continued to be significant over the entire period. The weight showed an increase from 229g on 35th day to 248g on 56th day.

2. BIOCHEMICAL ANALYSIS

A. Assessment of Lipid levels

The lipids levels in normal, untreated hyperlipidemic and treated rats are given in Table.2.

Table 2: Lipid levels of rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total cholesterol (mg/dl)</th>
<th>Triglyceride (mg/dl)</th>
<th>HDL  (mg/dl)</th>
<th>LDL (mg/dl)</th>
<th>VLDL (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>96±10.81</td>
<td>71±6.84</td>
<td>34.17±2.6</td>
<td>61.67±3.26</td>
<td>12.33±1.96</td>
</tr>
<tr>
<td>Diseased control</td>
<td>248±19.79 a***</td>
<td>177.6±7.03 a***</td>
<td>14±2.0 a***</td>
<td>190±5.32 a</td>
<td>35.67±3.26 a***</td>
</tr>
<tr>
<td>ERZO</td>
<td>181.3±18.04 b***</td>
<td>138±8.85 b***</td>
<td>23.67±3.20 b**</td>
<td>165.3±8.50 b</td>
<td>27.5±1.64 b**</td>
</tr>
<tr>
<td>RSV</td>
<td>150±16.35 b***</td>
<td>91±9.97 b***</td>
<td>28±2.19 b***</td>
<td>122.7±7.89 b</td>
<td>22±2.89 b***</td>
</tr>
<tr>
<td>Low dose ERZO+ RSV</td>
<td>122.3±13.19 b***, c**,</td>
<td>80±6.72 b***, c**,</td>
<td>31.83±2.31 b***, c*</td>
<td>87.17±6.79b***, c***</td>
<td>14.83±2.48 b***, c***</td>
</tr>
<tr>
<td>High dose ERZO+ RSV</td>
<td>97.17±7.6 b***, c**,</td>
<td>69.66±3.32 b***, c**</td>
<td>35±2.68 b***, c***</td>
<td>61.5±6.83b***, c***</td>
<td>11.5±1.76b***, c***</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ± SD (n=6), One way ANOVA followed by Dunnet’s multiple comparison test a-Vs Group I, b-Vs Group II, c- Vs Group IV, * p<0.5 **p< 0.01, ***p< 0.001.

It is seen that in all group of rats, animals fed with high cholesterol diet, there was a significant increase in TC, TG, LDL, VLDL levels and decrease in HDL cholesterol levels when compared to the control group of rats. The oral administration (ERZO) 400mg/kg and Rosuvastatin (RSV) 10mg/kg along with high cholesterol diet for 3 weeks showed significant reduction in TC, TG, LDL, VLDL levels and increase in HDL cholesterol levels as compared to the diseased control group of rats. The combined administration of ERZO 200mg/kg and RSV 10mg/kg and ERZO 400mg/kg and RSV 10mg/kg showed a more significant reduction in lipid levels and increase in HDL levels as compared to the diseased control rats. The
combination also showed a significantly more reduction in lipid levels as compared to the Rosuvastatin treated group.

B. Assessment of liver biomarker enzyme levels
The AST & ALT levels in normal, untreated hyperlipidemic and treated rats are given in Table 3.

Table 3: AST and ALT levels in rats.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>26.5±2.168</td>
<td>81±2.44</td>
</tr>
<tr>
<td>Disease</td>
<td>57.83±2.99 a ***</td>
<td>142.7±3.55 a ***</td>
</tr>
<tr>
<td>ERZO</td>
<td>42±2.53 b ***</td>
<td>91±4.51 b ***</td>
</tr>
<tr>
<td>RSV</td>
<td>56.5±3.20 b NS</td>
<td>141.3±3.14 b NS</td>
</tr>
<tr>
<td>Low dose ERZO+ RSV</td>
<td>40.33±2.50b***,c***</td>
<td>91.8±2.78b***,c***</td>
</tr>
<tr>
<td>High dose ERZO+ RSV</td>
<td>33.67±2.85b***,c***</td>
<td>78.17±6.30b***,c***</td>
</tr>
</tbody>
</table>

Values are expressed in Mean ± SD (n=6), One way ANOVA followed by Dunnet’s multiple comparison test, a-Vs Group I, b-Vs Group II, c- Vs Group IV, ***p< 0.001, NS- Non significant.

It is seen that in all group of rats fed with high cholesterol diet, there was a significant increase in AST and ALT levels when compared to the control group of rats. The oral administration (ERZO) 400mg/kg decreased the AST and ALT levels due to its antioxidant potential when compared with the disease group of rats. Rosuvastatin (RSV) 10mg/kg treatment did not show further elevation in the AST and ALT levels in the rats. The combined administration of ERZO 200mg/kg + RSV 10mg/kg and ERZO 400mg/kg + RSV 10mg/kg showed a significant reduction in AST levels when compared with mono therapy of Rosuvastatin.

3. ESTIMATION OF ANTIOXIDANTS IN CARDIAC TISSUE
Effect of high cholesterol diet on antioxidant enzyme levels and the effect of Rosuvastatin and ERZO alone and in combination on antioxidant enzyme levels of hyperlipidemic rats are given in Figure 1 and Figure 2.
It is seen that in all the group of rats fed with high cholesterol diet, there was a significant decrease in SOD and catalase levels when compared to the control group of rats. The oral administration of (ERZO) 400mg/kg or Rosuvastatin (RSV) 10mg/kg separately for 3weeks showed significant increase in SOD and catalase levels when compared to the disease control rats. The combined administration of ERZO 200mg/kg + RSV 10mg/kg and ERZO 400mg/kg + RSV 10mg/kg showed a more significant increase in SOD and catalase levels when compared with the mono therapy of Rosuvastatin.

4. HISTOPATHOLOGY OF AORTA
The histopathological sections of aorta of all the groups of animals are shown in Fig.3.
Consumption of cholesterol enriched diet for 8 weeks lead to the formation of foam cells which are indicative of the oxidation of LDL. ERZO administration along with the cholesterol diet showed a reduction in the number of foam cells and rosuvastatin treated rats also showed reduced foam cells and mild thickened intima. The combined administration of ERZO and Rosuvastatin showed absence of foam cells. This is an indicative measure that the combination therapy of rosuvastatin and ERZO is better in prevention of development of atherosclerosis than the monotherapy with rosuvastatin.
DISCUSSION
The advantage of combination therapy of statins with other kinds of lipid altering agents is to enhance the lipid lowering effect, reduce side effects and reduce the dosage of statins. The present study focuses on the combination of ginger and rosuvastatin on the cholesterol lowering efficacy of rosuvastatin as compared with monotherapy of rosuvastatin and envisages protective role against the development of atherosclerotic lesions. Biochemical parameters and antioxidants levels were evaluated to conclude the synergistic lipid lowering effect and protective effect of combination therapy against development of atherosclerosis.

The body weight of animals were measured once weekly for 8 weeks. During the induction period, all the rats which were fed with cholesterol rich diet showed a significant increase in body weight. Reduction in body weight were observed in rats given with ERZO and Rosuvastatin separately and in combination. A greater reduction in body weight was seen in combination therapy of ginger and rosuvastatin group of rats.

The rats were made hyperlipidemic by administration of high cholesterol diet for 8 weeks. These caused a significant elevation in the lipid levels. Administration of Zingiber officinale (400mg/kg) showed significant reduction in lipid levels like LDL, TC, TG and VLDL and an increase in HDL cholesterol in rats. This finding is consistent with the previous reports demonstrating the hypocholesterolemic and anti-atherosclerotic effects of ginger. It has been reported that ginger stimulates the conversion of cholesterol to bile acids, an important pathway for the elimination of cholesterol from the body. This is due to the elevation of hepatic cholesterol-7alpha–hydroxylase, the rate limiting enzyme in cholesterol biosynthesis. Based on the definition and effect of synergy, administration of rosuvastatin (10mg/kg) with ginger produced a synergistic effect on reduction lipid levels compared to the monotherapy of Rosuvastatin. When ERZO is combined with Rosuvastatin, the reduction in TC, TG, LDL, VLDL were lowered more significantly and the HDL levels showed a significant rise. The values were brought back to near normal values especially when higher dose of ERZO was used. It is known that Rosuvastatin is a HMG CoA reductase inhibitor. Perhaps on combining with ginger there is a synergistic reduction in the lipid levels.

Most of the HMG-CoA reductase inhibitors are metabolized by the liver. Damage to the liver is assessed by a persistent elevated levels of its aminotransferases. The consumption of high cholesterol diet leads to the formation of free radicals. These free radicals causes damage to the liver. In our study also, the consumption of high cholesterol diet for 8 weeks, led to
elevated levels of AST and ALT indicating the damage to the liver. But administration of rosuvastatin (10mg/kg) along with high cholesterol diet did not further elevate the AST and ALT levels. Previous studies have investigated the hepatoprotective effects of ginger against liver toxicity induced by ethanol, carbon tetrachloride, bromobenzene and acetaminophen. In these studies Ginger has shown a significant decrease in the levels of AST and ALT. The hepatoprotective effect of ginger was also observed in our study. Administration of ERZO 400mg/kg for 3 weeks along with cholesterol diet showed reduction in the elevated AST and ALT levels. The combined administration of Rosuvastatin and low and high doses of ERZO showed a significant decrease in AST and ALT levels indicating combination of ERZO with rosuvastatin is beneficial than the monotherapy of rosuvastatin.

Cholesterol enriched diet has been shown to markedly reduced cardiac nitric oxide levels and enhances formation of superoxide and peroxynitrite in cardiac tissues. This causes the imbalance in the antioxidant level leading to the damage of the cardiac tissues. SOD is a first line anti-oxidant defence enzyme which rapidly catalyzes the dismutation of superoxide ion. In case of SOD deficiency or increased superoxide ion production, it reacts with nitric oxide to produce peroxynitrite which is a potent oxidant that can cause direct damage to proteins, lipids and DNA. The major pungent constituent of ginger is 6-gingerol which is reported to exhibit inhibitory effect on xanthine oxidase which is responsible for the formation of reactive oxygen species, such as superoxide anion. Rosuvastatin is reported to have antioxidant effect. In our study also, the administration of cholesterol diet for 8 weeks reduced the SOD and Catalase levels. On treatment with ginger and Rosuvastatin separately, there was an increase in the declined SOD and Catalase levels but the combination of ERZO and RSV showed a significant increase in the SOD and Catalase levels indicating the protective effect of the combination against development of atherosclerosis which would be more beneficial than the monotherapy of Rosuvastatin.

Regarding the histopathology of aorta, the administration of cholesterol enriched diet for 8 weeks showed the formation of atherosclerotic lesions which is the initial stage in the development of atherosclerosis. Such lesions are known to be due to the formation of free radicals. Arterial wall macrophages plays a major role during the early atherogenesis. Oxidative stress induces macrophages responses such as increased capacity to oxidize LDL, increased OxLDL cellular uptake, as well as macrophage lipid peroxidation. LDL oxidation can also lead to atherogenic modification of LDL i.e. LDL aggregation. Aggregated
LDL are taken up by macrophages at enhanced rate, leading to cholesterol accumulation and foam cell formation. The anti-atherogenicity of ginger and rosuvastatin is attributed to its direct antioxidant effects on macrophages as well as on plasma LDL.

In the present study, consumption of cholesterol enriched diet for 8 weeks lead to the formation of foam cells which are indicative of the oxidation of LDL. ERZO administration along with the cholesterol diet showed a reduction in the number of foam cells and Rosuvastatin treated rats also showed reduced foam cells and mild thickened intima. The combined administration of ERZO and Rosuvastatin showed absence of foam cells. This is indicative of the fact that the combination therapy of Rosuvastatin and ERZO extract is better in prevention of development of atherosclerosis than the monotherapy with Rosuvastatin.

CONCLUSION

Combined administration of ethanolic rhizome extract of *Zingiber officinale* and rosuvastatin is far more superior to individual therapy with either ethanolic rhizome extract of *Zingiber officinale* or rosuvastatin in reversing the changes in lipid profile and antioxidant enzyme status in rats fed on high cholesterol diet. In addition, combination was also able to improve the hepatic function.

It is concluded that this combination may prove beneficial in treating hyperlipidemia and reducing the risk factors for cardiovascular disease in a clinical set up.

REFERENCES


7. CPCSEA guidelines for laboratory animals facility.


