Beneficial effects of *Zingiber officinale* Roscoe on fructose induced hyperlipidemia and hyperinsulinemia in rats

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Fructose supplementation produced cardinal features of Syndrome-X including significant elevations in serum cholesterol, triglyceride, glucose and insulin and also in body weight. While treatment with methanolic extract of dried rhizomes of *Zingiber officinale* produced a significant reduction in fructose induced elevation in lipid levels, body weight, hyperglycemia and hyperinsulinemia, treatment with ethyl acetate extract of *Z. officinale* did not produce any significant change in either of the last two parameters. However, it produced a significant reduction in elevated lipid levels and body weight. The concentration of 6-gingerol was found to be higher in methanolic extract and less in ethyl acetate extract. The results suggest that the methanolic extract of *Z. officinale* produces better effects as compared to ethyl acetate extract in fructose induced hyperlipidemia associated with insulin resistance. The extent of activity appears to be dependent on the concentration of 6-gingerol present in the extracts.

**Keywords:** Hyperlipidemia, Insulin resistance *Zingiber officinale.*

The prevalence of obesity is increasing worldwide. In the last few decades there has been a shift in the types of nutrients included in the diet. The consumption of fructose has increased, largely because of an increased consumption of soft drinks and many other beverages that are high in fructose and also because of the consumption of foods such as breakfast cereals, baked goods, condiments and prepared desserts sweetened with sucrose and high-fructose corn syrup. Fructose consumption induces insulin resistance, impairs glucose tolerance and produces hyperinsulinemia, hypertriglyceridemia and hypertension in animal models. This cluster of changes appears to be major risk factor in the pathogenesis of coronary artery disease.

*Zingiber officinale* Roscoe, (Zingiberaceae) commonly known as ginger is one of the commonly used spices in India and around the world. It belongs to Zingiberaceae family. Ginger is reported to possess antiallergic, antinauseant, antiemetic, antihepatotoxic, anti-inflammatory, antipyretic, antiseptic, antitussive, hypoglycemic, antioxidant, antiplatelet, and hypolipidemic activities. It also has carminative, aromatic, stimulant, stomachic, and tonic activities. For the first time Akhani et al. have shown that ginger possesses anti-diabetic activity by virtue of 5-HT modulators present in *Z. officinale*.

Hyperlipidemia is generally associated with elevated levels of blood glucose and insulin levels. Until now observations on beneficial effects of *Z. officinale* in experimental animal models are studied only for lipid profile in hyperlipidemic states representing atherosclerosis. Studies on the effects of *Z. officinale* in conditions associated with elevated glycemic and insulin levels representing dyslipidemia and syndrome X are scanty. Hence, the present study has been undertaken to explore the possible beneficial effects of *Z. officinale* on syndrome X and to correlate with 6-gingerol concentrations in extracts for their effects in fructose induced hyperlipidemia, hyperinsulinemia and hyperglycemia in rats.

**Materials and Methods**

**Plant material**—Dried rhizomes of *Zingiber officinale* were collected locally, rhizomes identified and authenticated by Prof. O. P. Saxena, Head of the Department of Botany, Gujarat University, Ahmedabad, and the identification tests were done as per United States Pharmacopeia 2000.

**Preparation of extracts**—Dried rhizomes of *Z. officinale* Roscoe were powdered and used for extraction. Powder of dried rhizomes (500 g) was...
taken in a round bottom flask and extracted twice with methanol (1L x 2) under reflux for 6 hr each time. The extracts were filtered and collected each time were pooled and concentrated to dryness under reduced pressure. The yield obtained was 4.3%. Again, 500 g powder of dried rhizomes was taken in a round bottom flask and extracted with ethyl acetate (1L x 2) as above. The extracts were filtered, pooled and concentrated to dryness under reduced pressure. The yield obtained 4.6%. For feeding the extracts (250 mg/ml) were prepared by mixing them with polyethylene glycol 400 using a magnetic stirrer.

Standardization of extract—Standardization of methanolic and ethyl acetate extracts for 6-gingerol content, a marker substance was carried out by HPLC analysis using 8-methyl-n-vanillylnonamide as a reference standard. The analysis was carried out as per He et al

Experimental animals and induction of hyperlipidemia—Male albino Wistar rats weighing 200-250 g, used for the study were fed on pellet diet (Pranav Agro Pvt. Ltd, India) and water ad libitum. Hyperlipidemia was induced by supplementing their drinking water with 10% fructose. All the procedures were performed in accordance with the Institutional Animal Ethics Committee constituted as per the directions of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), under Ministry of Animal Welfare Division, Government of India, New Delhi, India.

Treatment—Rats (24) were divided into following 4 groups of 6 each:

Group I: normal diet and water ad libitum and received vehicle solvent.
Group II: normal diet and water with 10% fructose and received vehicle solvent (control)
Group III: normal diet and water with 10% fructose and received methanolic extract (250 mg/ kg)
Group IV: normal diet and water with 10% fructose and received ethyl acetate extract (250 mg/ kg).

Each group of animals were administered vehicle or drugs daily for 3 weeks by gavage using oral feeding needle. Feeding of animals by fructose and extracts were done simultaneous from the beginning. At the end of the 3 weeks period, animals were kept for overnight fasting and the blood samples were collected from the tail vein in the centrifuge tubes.

The blood samples were allowed to clot for 30 minutes at room temperature, and then centrifuged at 5000 rpm for 15 min. Serum samples thus obtained were stored at -20°C until biochemical estimations were carried out.

Biochemical analysis—The serum parameters were analyzed spectrophotometrically by using double beam UV-Visible spectrophotometer (Shimadzu UV-Visible spectrophotometer, model 1601). Estimation of serum glucose (GOD-POD method)16, cholesterol (enzymatic method)17, triglyceride (enzymatic method)18 and HDL-cholesterol (phosphotungstate method)19 were carried out using respective diagnostic kits from Bayer Diagnostic Ltd, India. Serum insulin was estimated by radioimmunoassay method using the kit from Bhabha Atomic Research Center, Mumbai, India. In addition to the above parameters, daily body weight, food intake and water intake of the animals were recorded. VLDL-cholesterol and LDL-cholesterol in serum were also calculated as per Friedewald's equation20.

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\text{VLDL-cholesterol} = \frac{\text{total serum triglycerides}}{5} \\
\text{LDL-c} = \frac{\text{total serum cholesterol} - \text{total serum triglycerides-HDL-c}}{5}
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Statistical analysis—Results were analyzed statistically using one way analysis of variance (ANOVA) followed by Tukey's test. Values of P<0.05 were considered as significant.

Results and Discussion
The results are presented in Table 1.

6-gingerol content in the extracts—Standardization of the methanolic and ethyl acetate extracts of Z. officinale for 6-gingerol content showed the presence of 6-gingerol in methanolic extract (3.08% w/w) and ethyl acetate extract (1.64% w/w), respectively.

Hyperlipidemic control rats showed significant increase in body weight, serum cholesterol, triglyceride, LDL and VLDL-cholesterol levels and no significant change in serum HDL-cholesterol levels and significant increase in fasting serum glucose and insulin levels as compared to normal control rats.

In recent years the populations suffering from syndrome X are increasing. In the present world approximately 20% of the world population are suffering from syndrome X and this syndrome involves various disorders into its fold namely
diabetes, coronary artery disease, atherosclerosis and hypertension. The hallmark of all these disorders is that it is associated with hyperlipidemia with or without hyperinsulinemia. Conventional drugs and allopathic drugs were evaluated for their beneficial effects in such conditions. Drugs from traditional system of medicine are also evaluated for their efficacy in such conditions. Z. officinale is among such drugs obtained from traditional systems of medicine. Studies until now on Z. officinale were evaluated for its usefulness in reducing experimentally induced hyperlipidemia that causes atherosclerosis, hypertriglyceridemia, and hyperinsulinemia representing syndrome X.

Numerous human and animal studies have demonstrated myocardial alteration in conditions of hyperinsulinemia associated with elevated VLDL and triglyceride levels. It is also shown that people with hyperinsulinemia are more likely to experience dyslipidemia. Several other studies have also demonstrated that in conditions of hyperinsulinemia, hypertriglycerideremia becomes the strongest indicator of cardiovascular disease. A strong correlation exists between insulin resistance and dyslipidemia. Insulin resistance at the adipocyte leads to release of free fatty acids and their increased flux to the liver, which leads to stimulation in liver for synthesis and release of VLDL with consequent hypertriglycerideremia.

Fresh juice of Z. officinale reduced elevated lipid levels in streptozotocin induced diabetes a condition with hypoinsulinemia. The present study involving a condition of hyperglycemia, hyperlipidemia and hyperinsulinemia shows that treatment with an extract of Z. officinale is effective in reducing both elevated lipid profile and elevated glucose levels. Methanol extract of Z. officinale also prevented partially but significantly the elevated insulin levels in fructose fed rats. The present results show significant reduction in body weight on treatment with both the extracts of Z. officinale tested for their efficacy.

5-HT modulators are reported to possess significant beneficial effects on dyslipidemia in conditions of syndrome X. 5-HT receptor modulators like sibutramine are reported to possess significant lipid lowering activity associated with hyperglycemia and hyperinsulinemia. Sibutramine also reported to reduce body weight in conditions of syndrome X. Extracts of ginger are reported to possess 5-HT modulatory effect. It appears that the beneficial effects obtained by ginger extracts on hyperlipidemia associated with hyperglycemia and hyperinsulinemia are similar to 5-HT receptor modulator sibutramine. However, further experiments are required to be done in this direction.

The results of the present study show that Z. officinale may be useful in conditions of syndrome X and associated disorders as it can reduce the elevated hypertriglyceride, VLDL-cholesterol levels and hyperinsulinemia. This is the first study with Z. officinale, which correlates its usefulness in syndrome X.
Standardization of the methanolic extract and ethyl acetate extract of *Z. officinale* for 6-gingerol content showed the presence of 3.08% w/w and 1.64% w/w of 6-gingerol in each of them respectively. This shows that higher concentration of 6-gingerol present in the methanol extract as compared to ethyl acetate extract may be responsible for the better efficacy of methyl extract as compared to ethyl extract.

In conclusion, the present data suggest that treatment with methanolic extract of *Zingiber officinale* is better in controlling the elevated glycemic levels and elevated lipid profile in experimentally induced hyperlipidemia representing syndrome X in animals as compared to its ethyl acetate extract, which correlates with the concentration of 6-gingerol a marker compound in *Z. officinale*.

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References