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RESEARCH ARTICLE

PROTECTIVE EFFECT OF GAMMA TERPINENE AGAINST HIGH FRUCTOSE DIET AND STRESS INDUCED METABOLIC SYNDROME IN RATS

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ABSTRACT

The present study was designed to evaluate the protective effect of **gamma terpinene** against metabolic syndrome in rats. Metabolic syndrome was induced by a combination of high fructose diet along with Chronic Unpredictable Stress (CUS) protocol of 21 days duration and the complete induction was evident from a significant increase in blood pressure, elevated blood glucose, triglycerides and uric acid levels. Furthermore, it was also associated with oxidative stress as depicted by an increase in serum Thiobarbituric Acid Reactive Substances (TBARS) levels. Moreover, there was a significant decrease in serum GSH levels. The rats in the drug treated groups were treated with gamma terpinene (50 & 100 mg/kg orally) once daily for 21 days. Treatment of rats with low and high doses of gamma terpinene resulted in prevention from the development of metabolic syndrome as indicated by a significant and dose dependent reduction in above mentioned metabolic syndrome markers. Furthermore, there was marked decrease in TBARS, along with the induction in GSH at levels ($p < 0.001$). The antioxidant potential of gamma terpinene was also evaluated by *in vitro* experimentation using DPPH method. Gamma terpinene also showed potent antioxidant activity *in vitro*. The results indicate the protective role of **gamma terpinene** against the metabolic syndrome.

INTRODUCTION

Lifestyle behaviors may influence the maintenance of energy in human body over the long term (Dariush *et al.,* 2011). However, lifestyle and dietary modifications can effectively control the risk factors of many disorders. The increasing trends of major chronic diseases such as cardiovascular diseases, diabetes, respiratory disorders, autoimmune disorders, cancers and many of which are unique to the civilized cultures has been attributed partially or wholly to the "western diet" that includes high quantities of carbohydrates and processed foods (Kolb and Mandrup Poulsen, 2010; Miller, 2009). The major risk factor associated with the diet in this growing world is the metabolic syndrome, characterized by insulin resistance, hypertension, abdominal obesity, dyslipidemia and hyperuricemia (Figure 1). It also results in reduced quality of life and increased risk of mortality and morbidity over the past three decades (Schor and Borges, 2014).

Fructose is a naturally occurring monosaccharide, an epimer of glucose found in fruits, honey and sap, the fluid that carries nutrients throughout a plant (Hallfrisch, 1990; Guthrie and Morton, 2000). Fructose has been implicated in the pathogenesis of MS and Non alcoholic fatty liver disease (NFALD) by the number of investigators (Lim *et al.,* 2010). The phenomenon of metabolic syndrome can also be induced by fructose because of its metabolic resemblance to ethanol (Lim *et al.,* 2010).

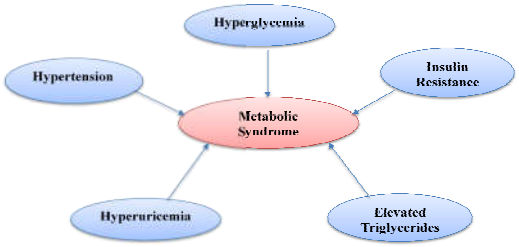

Figure 1 Representation of complications collectively implicated in Metabolic Syndrome

Stress is a state of disturbance in the homeostasis occurs due to internal or external sources like physical or psychological stimuli or known as stressors (Axelrod and Reisine, 1984) Chronic exposure to stress plays a major role increase in the generation of reactive oxygen species (ROS) which can directly damage cellular proteins, DNA and lipids, furthermore alter the prooxidant-antioxidant balance, which might lead to the development of various human pathological states like metabolic syndrome. Gamma Terpinene, a monoterpene hydrocarbon is one of the components of essential oils in certain plants (Figure 2).

The availability of gamma terpinene in the citrus essential oils ranges from zero to 21.3%. It is one of the most important aromatic isolates used widely in food, flavours, soaps, cosmetics, pharmaceuticals, tobacco, confectionary and are

used in perfume industries. Gamma terpinene has a characteristic lemon odour of rather low tenacity (Akgul and Kivanc, 1988). It has slightly bitter, herbaceous and citrus like taste at concentrations. Gamma terpinene having boiling point 182°C occurs in various plant oils including those of coriander, cumin, lemon, ajowain, and samphire. Already reported activities of compound containing gamma terpinene encouraged us to evaluate its activity against metabolic syndrome.

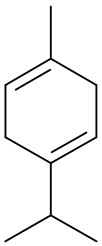

Figure 2 Gamma terpinene

MATERIAL AND METHODS

Animals

Male wistar albino rats weighing 175±25 grams were employed in the present study. Animals were fed with the standard laboratory chow (Kisan Feeds Ltd., Chandigarh, India) with tap water *ad libitum* and fasted overnight before the experiments. The experimental protocol was approved by institutional Animal Ethics Committee and the care of the animals out as per the guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environmental and Forests Government of India (Registration No. 1753/PO/E/S/14/CPCSEA).

Drugs and Chemicals

Gamma terpinene was purchased from Sigma-Aldrich Corp. New Delhi, India. Nitroblue tetrazolium (NBT), triss buffer carboxymethyl cellulose (CMC), sodium carbonate and thiobarbituric acid (TBA), alpha tocopherol, mannitol, ethylene glycol, hydroxylamine, sodium fluoride, starch corns, choline chloride cyanocobalamine, casein were obtained from Central Drug House (CDH) Pvt. Ltd., New Delhi, India. 1, 1-diphenyl-2-picryl-hydrazyl (DPPH), Glutathione, copper sulphate, trisodium citrate, potassium sodium tartarate and ethylene diamine tetraacetic acid (EDTA) were purchased from Himedia Pvt. Ltd., Mumbai.

Preparation of Feed

A high fructose diet of 31% was prepared and fed to rats employed in the present study. Diets were freshly prepared by mixing the ingredients in small amounts every 2–3 days.

Experimental protocol

Eight groups were employed in the present study, each comprising of 6 rats. Gamma terpinine was administered to rats after 14 days up to 35th day of protocol.

Group I (Normal diet)

No drug was administered to rats. The rats were given a standard chow diet.

Group II (Unpredictable stress)

Chronic unpredictable stress was given to rats for 35 days (i.e. 3 and half cycles). The rats were given a standard chow diet.

Group III (Fructose 31%)

Fructose diet having 31% fructose was administered to rats' *ad libitium* for 35 days.

Group IV (Fructose 31% + Unpredictable stress)

Fructose diet having 31% fructose and chronic unpredictable stress were given to rats for 35 days.

Group V (Fructose 31% + Gamma terpinene, 50 mg/kg)

Fructose 31% along with Gamma terpinine 50 mg/kg was administered orally to rats.

Group VI (Fructose 31% + Gamma terpinene, 100 mg/kg)

Fructose 31% along with Gamma-terpinine 100 mg/kg were administered orally to rats.

Group VII (Fructose 31% + Unpredictable stress + Gamma-terpinene, 50 mg/kg)

The rats were given chronic unpredictable stress. Fructose 31% along with Gamma-terpinine 50 mg/kg were also administered orally to rats.

Group VIII (Fructose 31% + Unpredictable stress + Gamma-terpinene, 100 mg/kg)

The rats were given chronic unpredictable stress. Fructose 31% along with Gamma-terpinine 100 mg/kg were also administered orally to rats.

Chronic Unpredictable stress protocol

Chronic unpredictable stressors were given to rats for 10 days per cycle up to 5 weeks i.e. 3 and half cycles. To prevent the development of resistance, chronic unpredictable stress models were employed, which involve the use of various physical and psychological stressors in a predetermined manner so that the animals were unable to adapt to the stressor and to prepare the animal's perfect models for metabolic syndrome. In chronic unpredictable stress protocol for 10 days, the animals were subjected to different stressors over a period of 10 days. One of the following stressors were administered daily (in random order) over a period of 10 days, like restraint stress, cold isolation, swim stress, sleep deprivation, food/water deprivation etc (Bhatia *et al.,* 2011).

Estimation of Blood glucose

Blood glucose was measured by gluconometer, Accu check®. Blood samples were obtained after an overnight fast from the tail vein and recorded weekly in all groups. Base fasting blood glucose was recorded after 2 weeks of acclimizaion of rats in test groups.

Estimation of Systolic Blood pressure (SBP)

The systolic blood pressure of the rats was measured in conscious rats by tail cuff sphygmomanometer i.e., Non Invasive Blood Pressure (NIBP) (LE-5001, A-panlab, Letica, Barcelona, Spain) everyday from 14th day of experimental protocol. Rats were pre-warmed at 36°C for 10 min and allowed to rest quietly in a chamber before blood pressure measurement. The tail was passed through a miniaturized cuff connected to an amplifier. The amplified pulse was recorded during automatic inflation and deflation of the cuff, where Systolic Blood Pressure (SBP) was defined as the inflation pressure at which the waveform became indistinguishable from baseline noise. Final SBP readings were obtained by averaging three successful readings. For each animal an average of at least three consecutive measurements was taken to reduce variability by the same animal, in a similar peaceful environment with special precautions to minimize stress induced fluctuations in BP (Reims *et al*., 2005).

Estimation of Serum Triglycerides

The triglycerides levels were estimated in the serum sample using commercially available kit by Beacon diagnostics Pvt. Ltd., India. This method was based upon the principle that, the glycerol released from the hydrolysis of triglycerides by lipoprotein lipase is converted by glycerol kinase into glycerol-3-phoshate which was oxidized by glycerol phosphate oxidase to hydroroxyacetone phosphate and hydrogen peroxide in the presence of peroxidase, hydrogen peroxide oxidizes phenolic chromogen to a red coloured compound. The absorbance of standard and samples were observed against 505 nm on the spectrophotometer. The triglyceride levels were expressed as milligram per decilitre of serum (Trinder *et al.,* 1969).

Estimation of Serum Uric Acid

The uric acid was estimated in the serum sample using commercially available kit by Beacon diagnostics Pvt. Ltd., India. This method was based upon the principle that uricase converts uric acid to allantoin and hydrogen peroxide the hydrogen peroxide formed further reacts with a phenolic compound and 4 –aminoantipyrene by the catalytic action of peroxidase to form a red coloured quinonemine dye complex. Intensity of the coloured formed is directly proportional to the amount of uric acid present in the sample was measured by spectrophotometer at 505 nm. The uric acid levels were expressed as milligram per decilitre of serum (Isdale *et al*., 1966).

Estimation of TBARS

The quantitative measurement of TBARS, an index of lipid peroxidation in liver tissue was performed according to method of Niehaus and Samuelsson, (1968). In this method, malondialdehyde and other TBARS were measured by their reactivity with thiobarbituric acid in an acidic condition to generate pink colored chromophore which was measured spectrophotometrically at 535 nm. To 1.0 mL of tissue homogenate, 2 mL of trichloroacetic acid-thiobarbituric acid-hydrochloric acid (TCA-TBA-HCl) reagent was added and mixed thoroughly. The mixture was kept in a boiling water bath for 15 min. After cooling the tubes were centrifuged at 10000 g for 10 min. And the color developed in the supernatant was measured at 535 nm against blank reagent. A series of standard solutions of tetra methoxy propane in the concentration of 1 to 10 nM was treated in the similar manner. Values are expressed as nano moles per mg of protein (Niehaus and Samuelsson, 1968).

***In vitro* Studies**

DPPH Assay for free radical scavenging

The DPPH is a stable free radical and is widely used to assess the radical scavenging activity of antioxidant compounds. This method is based on the reduction of DPPH in methanol solution in the presence of a hydrogen–donating antioxidant due to the formation of the non radical form DPPH-H (Blois, 1958). This transformation results in a color change from purple to yellow, which is measured spectrophotometrically. The disappearance of the purple color is monitored at 517 nm. The free radical scavenging activity can be measured by using 2, 2-diphenyl-1picryl-hydrazyl or 1, 1- diphenyl-2-picryl-hydrazyl (Hunsaker and Schenk 1983). The reaction mixture (3.0 ml) consists of 1.0 ml of DPPH in methanol (0.3 mM), 1.0 ml of the extract and 1.0 ml of methanol. It is incubated for 10 min in dark and then the absorbance is measured at 517 nm on UV spectrophotometer. In this assay, the positive controls can be ascorbic acid, gallic acid, Butylated hydroxyanisole (BHA), α-tocopherol, quercetin, Butylated hydroxytoluene (BHT), rutin, catechin, or glutathione (Alagumanivasagam *et al*., 2002).

Statistical analysis

The results were expressed as Mean ± SEM. The data obtained from various groups were statistically analysed using one way analysis of variance followed by Tukey-Kramer post hoc test. The $p<0.05$ was considered to be statistical significant. All the comparisons were made with respect to the control in various parameters employed in the present study

RESULTS

Effect of gamma terpinene on Systolic Blood Pressure (SBP)

A significant increase in systolic blood pressure was

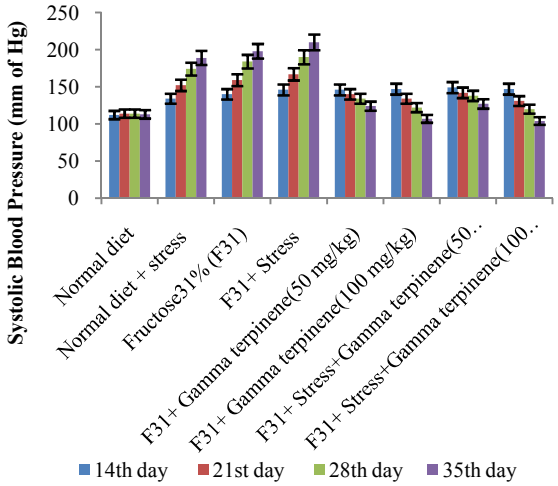

Figure 3 Effect of Gamma terpinene on systolic blood pressure at level ($p<0.05$) vs Stress, Fuctose 31% and Fructose 31% with stress Values are expressed as Mean ± SEM.

demonstrated in stress, Fructose 31% and Fructose 31% with stress treated groups when compared to normal diet group. The administration of Gamma terpinene in two different doses (50 mg/kg and 100 mg/kg) once daily after 14 days up to end of protocol showed significant reduction at level ($p<0.05$) in the elevated systolic blood pressure. The gamma terpinene at 100 mg/kg was found to be highly effective as it corresponds nearly to the normal diet group. The administration with gamma terpinene (50 mg/kg and 100 mg/kg) demonstrated the active protection against fructose and stress induced elevation in systolic blood pressure in a dose dependent manner respectively. (Figure3).

Effect of gamma terpinene on Blood glucose

A significant increase in systolic blood glucose levels were demonstrated in stress, Fructose 31% and Fructose 31% with stress treated groups when compared to normal diet group. The administration of gamma terpinene in two different doses (50 mg/kg and 100 mg/kg) once daily after 14 days up to end of protocol showed significant decrease at level ($p<0.05$) in the elevated systolic blood glucose. The treatment with gamma terpinene (50 mg/kg and 100 mg/kg) demonstrated the active protection against fructose and stress induced elevation in blood glucose (Figure 4)

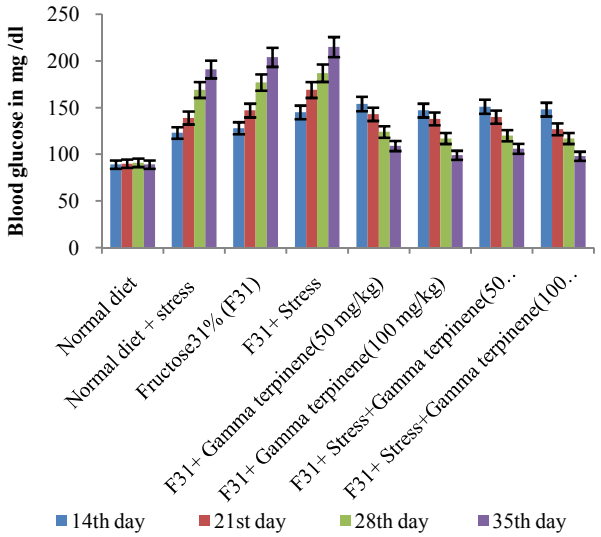

Figure 4: Effect of Gamma terpinene on Blood glucose at levels ($p<0.05$) vs Stress, Fructose 31% and Fructose 31% with stress. Values are expressed as Mean ± SEM

Effect of Gamma terpinene on Serum Triglycerides

A significant increase in triglyceride levels was demonstrated in stress, fructose 31% and fructose 31% with stress treated groups as compared to normal diet group. The administration of gamma terpinene (50 mg/kg and 100 mg/kg) progressively declined at level ($p<0.05$) the elevated status of triglycerides as compared to fructose and stress group; however the significant effects were demonstrated only at 100 mg/kg of dose. The data demonstrates the protection by gamma terpinene against fructose and stress induced increase in serum triglyceride in rats (Figure 5).

Effect of Gamma terpinene on Uric Acid

A significant increase in uric acid levels were demonstrated in stress, fructose 31% and fructose 31% with stress induced groups as compared to normal diet group. No significant change was observed between the fructose 31% and fructose along with the stress tested groups. The treatment with gamma terpinene (50 mg/kg and 100 mg/kg) demonstrated the protection at level ($p<0.05$) against fructose and stress induced increase in serum uric acid levels (Figure 6).

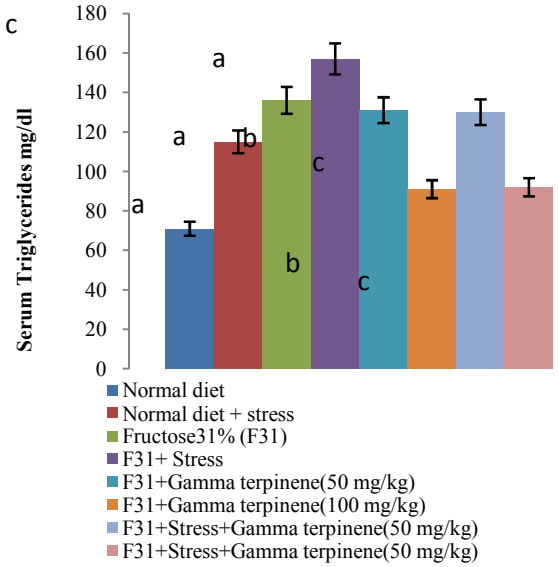

Figure 5: Effect of Gamma terpinene on serum triglyceride . Values are expressed as Mean ± SEM. a=$p<0.05$ Vs normal diet; b=$p<0.05$ Vs Fructose31%; c=$p<0.05$ Vs Fructose31% + stress

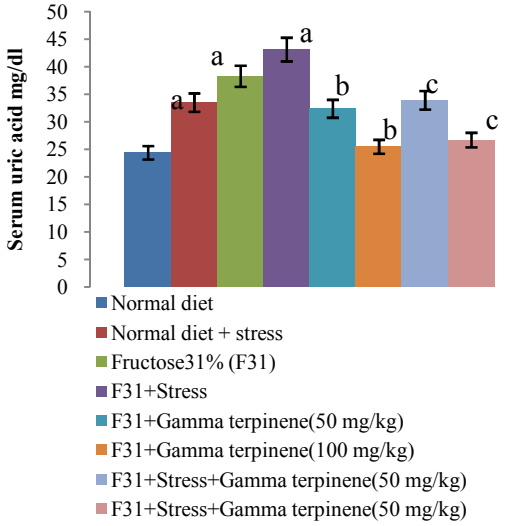

Figure 6: Effect of Gamma terpinene on serum uric acid level. Values are expressed as Mean ± SEM. a=$p<0.05$ Vs normal diet; b=$p<0.05$ Vs Fructose 31%; c=$p<0.05$ Vs Fructose 31%+ stress

Effect of Gamma terpinene on hepatic TBARS

Fructose and stress treated groups have shown a remarkable increase in the hepatic TBARS as compared to the group having normal diet. No significant change was observed in the fructose 31% and stress treated groups. The treatment with gamma terpinene (50 mg/kg and 100 mg/kg) demonstrated the significant reduction in TBARS level. The values are found to be very close to normal. Therefore protection against fructose and stress induced increase in hepatic TBARS in rats has been demonstrated (Figure 7).

Effect of Gamma terpinene on hepatic GSH

A significant decrease in the hepatic GSH was demonstrated in

fructose and stress treated groups as compared to the group having normal diet. The treatment with gamma terpinene (50 mg/kg and 100 mg/kg) demonstrated the protection against fructose and stress induced decrease in hepatic GSH by increasing the levels of GSH at level ($p<0.05$) in rats in dose dependent manner respectively (Figure 8).

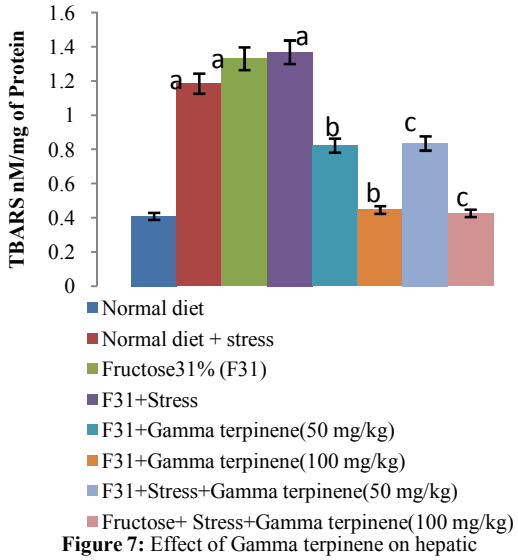

Figure 7: Effect of Gamma terpinene on hepatic thiobarbituric acid reactive substances. Values are expressed as Mean ± SEM. a=p<0.05 Vs normal diet; b=p<0.05 Vs Fructose31%; c=p<0.05Vs…

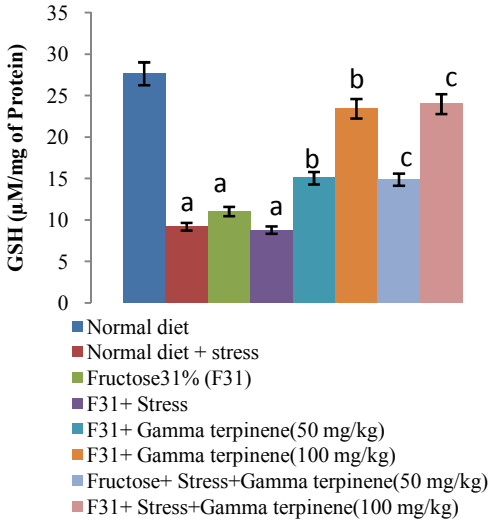

Figure 8: Effect of Gamma terpinene on hepatic reduced glutathione level. Values are expressed as Mean ± SEM. a=p<0.05 Vs normal diet; b=p<0.05 Vs Fructose 31%; c=p<0.05 Vs Fructose 31% + stress

In vitro antioxidant potential of Gamma terpinene

In the DPPH assay the radical scavenging ability of gamma terpinene was measured spectrophometrically against positive control ascorbic acid (7.2×10^{-3} mg/ml). The compound was able to reduce the stable radical DPPH to the yellow coloured DPPH-H with IC_{50} value of 1.8 mg/ml.

DISCUSSION

Consumption of fructose 31% alone and along with chronic unpredictable stress (5 weeks) progressively achieve a condition which is associated with elevated blood pressure, glucose, dyslipidemia, hyperuricemia and oxidative stress. These findings are convincingly similar to metabolic syndrome. The results of present study reveals that administration of gamma terpinene after 14 days up to end of protocol in both doses (50 mg/kg and 100 mg/kg) was successfully counter the metabolic syndrome condition.

It was revealed in the study that elevated body weight in fructose (31%) and stress models was protected by administration of gamma terpinene in both doses. The mechanism might be associated with lipolytic effect of gamma terpinene that could be attributed to interfere with inhibition of adipocytes which lead to decrease body weight (Takahashi *et al.,* 2003). The results support that increased blood pressure and glucose levels were reversed by the administration of gamma terpinene in dose dependant manner. The mechanism associated with the elevated blood pressure and glucose is the generation of ROS. Increased levels of ROS triggers the activation of serine threonine cascade such as C-Jun-N-Kinase and nuclear factor κβ that in turn phosphorylate multiple targets including the insulin receptor substrate (IRS) proteins causing hyperglycemia (Evans *et al.,* 2005 and Reddy *et al.,* 2009) and insulin resistance with impaired vasodilation that leads to elevate blood pressure (Evans *et al.,* 2005; Muoio and Newgard, 2008; Reddy *et al.,* 2009).

The current study indicates that abnormal levels of triglycerides are well countered by administration of gamma terpinene after 14 days upto the end of the study. This might be a result of lipoprotein activity secondary to reduced plasma insulin level. Gamma terpinine reduces the TGs levels in Triton WR 1339 treated rats by stimulating lipoprotein lipase activity (Takahashi *et al.,* 2003). The present study reveals that Gamma terpinene ameliorates elevated levels of urea, uric acid and creatinine in serum occurred due to oxidative stress and fructose metabolism induced renal damage (Pasko *et al.,* 2010). Therefore gamma terpinene might be attributed as renoprotective.

The current study shows that administration of gamma terpinene is able to reverse the decreased levels of glutathione and increased levels of superoxide anion generation occurred due to excessive oxidative stress and cellular damage (Reddy *et al.,* 2009). Gamma terpinene was found to improve these hepatic antioxidant activities. Furthermore elevated blood pressure, glucose, triglycerides, urea, uric acid becomes near to normal may be due to the antioxidant potential of gamma terpinene. The current study becomes witness of protective mechanism of Gamma terpinene against fructose and stress induced metabolic syndrome and the antioxidant effect of gamma terpinene is further supported by the decrease in MDA level. The *in vitro* antioxidant potential of gamma terpinine confirmed the protection of hepatic anti oxidant enzymes and decreases lipid peroxidation.

CONCLUSIONS

The current study indicates that the rats fed with a high fructose diet and subjected to chronic unpredictable stress resulted in development of hyperglycemia, hypertension, hyperuricemia, dyslipidemia as well as oxidative stress. Supplementation of Gamma terpinine in the diet of rats of treatment groups for 35 days significantly prevented the increase in above-mentioned parameters indicating a decrease in the major complications associated with a common syndrome called as metabolic syndrome. The present study

also provides additional evidence in support of the use of gamma terpinine for prevention and or management of diabetes and the pre-diabetic state of insulin resistance.

Acknowledgement

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