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Ginseng *Malva Verticillata* Tea (GMVT) Improve Glucose and Lipid Metabolism by Up-regulation of Leptin Hormone in Overweight Rats

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ABSTRACT: *Hyperglycemia plays a main role in the pathogenesis of cardiovascular diseases, fatty liver disease and insulin resistance in Diabetes mellitus type 2 (T2DM). Excess adipose tissue is the main risk factor for developing T2DM. Numerous drugs have been approved to reduce body weight and these medicines act by increasing lipolysis, decreasing satiety level, and increasing thermogenesis. But due to their adverse effects they are withdraw from the market. People are interested in using herbs and herbal drugs to achieve the best effect with fewer side effects. Traditionally in Asia, cinnamon (Cinnamomum verum), bitter gourd (Momordica charantia), dill (Anethum graveolens), black cumin (Nigella sativa). Turmeric, Ginger, green cardamom, Fenugreek and Ginseng use to improve hyperlipidemic and hypoglycemic conditions. In the current study, we treated overweight rats to ginseng tea. Results demonstrated a significant decrease in glucose, LDL-C, and cholesterol while increase in the HDL-C and leptin levels. Leptin is belonging to cytokine release from adipose tissue exhibit decrease satiety, increase energy expenditure and reduce fat by inhibiting lipogenesis and increasing lipolysis. Thus, it was concluded Ginseng Malva Verticillata tea (GMVT) can be suggested as a possible alternative treatment to improve lipid profile, hyperglycemia and related pathogeneses.*

Key words: *Leptin, hyperglycemia, hyperlipidemia, insulin resistance, T2DM, Fatty liver*

INTRODUCTION

Deaths from diabetes increased by 70% globally between 2000 and 2019. Ninteen million people in Pakistan are living with diabetes, and numbers are continuously increasing. In Pakistan, the diabetes mortality rate is twice as compared to another region of WHO. Obesity and diabetes have increased the chance of developing T2DM (Malon et al., 2019). Hyperlipidemia is the main leading risk factor for cardiovascular disease in hyperglycemic patients. High concentration of triglycerides (TG), low density lipoprotein cholesterol (LDL-C), Cholesterol (CHO) and low concentration of high density lipoprotein cholesterol (HDL-C) are the main components of hyperlipidemia (Bano et al., 2013). Metabolic syndrome, Obesity and T2DM increase the chance to develop non-alcoholic fatty liver diseases (NAFLD). Dysregulation of hepatic lipid metabolism is an established marker for alcoholic liver diseases (ALD) and non-alcoholic fatty liver disease (NAFLD). Many factors like inflammation of liver, imbalance food intake and utilization of lipid and lipoperoxidative stress are involved in progress hepatic steatosis (Li et al., 2020).

The hormone leptin is secreted from white adipose tissue in response to lipid storage. This facilitates the phosphorylation of the enzyme hormone-sensitive lipase (HSL), provoking lipolysis which results in fat loss (Zeng et al., 2005). Over the past century, herbal medicine, herbal extract, and a combination of herbs and natural products get increased attention as alternative therapeutic agents due to more beneficial effects and fewer side effects. Ginseng is the oldest and famous traditional medicinal herb with eleven different varieties and is being used for over two centuries. Ginseng leaves and stem contain many bioactive constituents, namely ginsenosides, polysaccharides, triterpenoids and flavonoids. Ginsenosides are more important in ginseng effectiveness (Wang et al., 2009).

In the present study, we investigated the effect of Ginseng Malva Verticillata tea (GMVT) on lipid profile, glucose and leptin levels in overweight rats.

MATERIALS AND METHODS

Preparation of Tea and Selection of Animals

One tea bag (2.26gm) boiled in 100 ml of water for five minutes by following the methods of Bano and Akhter (2017). Albino Wistar male rats whose weight was between 280-320 gm were used for three week in this study. Animals were divided into two groups. Each group have twelve rats.

a. Test group or treated rats (receive herb)

b. Control group or untreated rats (receive tap water).

Experimental Protocol

Test group received 2ml Ginseng Malva verticillata tea and at the same time, 2ml of tape water was given to control animals. Rats were sacrificed by using guillotine when the body weight of the test animals decrease up to 15-19% (obtain after three weeks). Untreated rats were also decapitated at the same time. Blood was obtained at the end of 3rd week serum was centrifuged and preserved at -70°C for estimation of lipid profile and leptin levels. Biochemical estimation was performed by using respective Kits on a chemistry analyzer. ELISA kits use for the estimation of leptin hormone.

Statistical Analysis

Data were analysis by using SPSS 16. The significant differences between the mean of the treated and untreated groups were analyzed by the student's t-test. Values of $p<0.05$ considered as significant. Data express in figures as mean ± standard deviation (SD).

RESULTS

Effect on Leptin hormone

Fig. 1 showed the effect of oral administration of GMVT on serum leptin hormone. Statistical analysis by student's *t*-test show a significant increase ($P<0.01$) in serum leptin hormone level in test as compared to untreated rats.

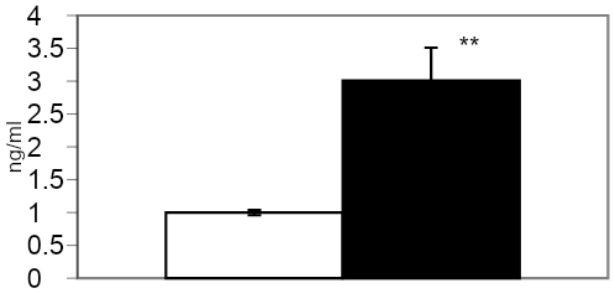

Fig. 1: Effect of oral administration of GMVT on serum leptin levels. Values are mean ± SD (n=12) significant difference **p<0.01

Effect on serum lipid profile:

Fig. 2 showed the effect of oral administration of GMVT on lipid profile. A significant decrease ($p<0.01$) in cholesterol, triglyceride, low density lipoprotein cholesterol and a significant increase ($p<0.01$) in high density lipoprotein cholesterol in test as compared to untreated rats.

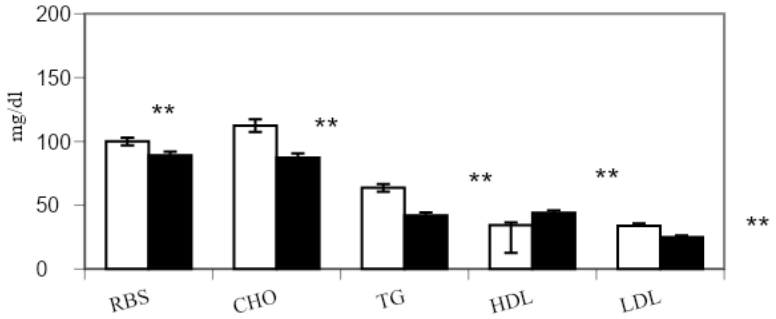

Fig. 2: Effect of oral administration of GMVT on lipid profile. Values are mean ± SD (n=12) significant difference **p<0.01

Effect on body weight of rats

Fig. 3 showed the effect of oral administration of GMVT on body weight. A significant decrease ($p<0.01$) in body weigh in test as compared to untreated rats.

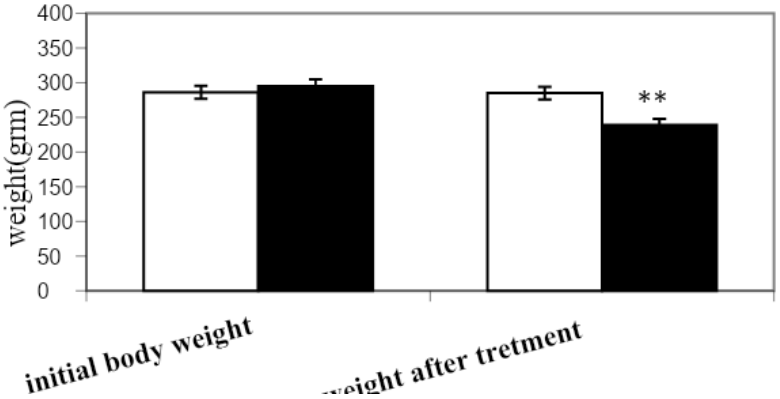

Fig. 3: Effect of oral administration of GMVT on body weight. significant difference **p<0.01

DISCUSSION

Obesity is a worldwide health problem that contributes to developed osteoarthritis, obstructive sleep apnea, Cholelithiasis, hepatic steatosis, genital and gastric cancer, hyperlipidemia, high blood pressure, T2DM, heart failure, arteriosclerosis, and stroke (Park et al., 2008). Correlation between deposition of lipid and insulin resistance is well establish metabolic syndrome is associated with obesity (Mungle et al., 2012).

In the present research, repeated administration of ginseng herbal tea significantly increased (100.249%) leptin (Fig. 1) and decreased glucose level 12% (Fig. 2) as compared to control animals. Leptin's importance in research is increasing day by day on account of its role in appetite control, energy expenditure, glucose metabolism. Both insulin and leptin produce negative effect on adiposity by acting on the brain (Schwartz et al., 1996). Leptin increases insulin sensitivity in hyperglycemia and hyperinsulinemia (Kamohara et al., 1997).

Leptin deficient mice reveal an increase in body weight besides hyperglycemia, hyperglycemia and hyperphagia, which can be corrected by treatment with leptin (Mantzoros et al., 1999).

Herbal extract might increase leptin level by positive regulation of leptin from adipocytes and other tissues. It could be a possible effect of the herbal extract on hypoglycemia.

Obesity and inflammation are the main factors in developing insulin resistance. The release of free fatty acid, cytokines and other factors from adipose tissue cause inflammation, which inhibits insulin signal transduction and develops insulin resistance. (Perseghin et al., 2003). Many studies show higher levels of Tumor Necrosis Factor-α (TNF), Interleukin-6 (IL-6) and Interleukin (IL-8) in diabetic and insulin-resistant states (Hotamisligi et al., 1995; Roytblat et al., 2000)

Leptin has medicinal importance in obesity and diabetes. Transgenic animals exhibit increases in body weight, insulin resistance, hyperinsulinemia, impaired glucose homeostasis and diabetes due to inhibition of leptin synthesis or defect in leptin receptor function. (Schwartz et al., 1996; McMinn et al., 2005). The leptin resistance due to different factors like a defect in the transport of leptin hormone through blood-brain barrier, defect in leptin signal transduction in neurons, and inflammation in hypothalamus, endoplasmic reticulum stress and defective autophagy are suggested to be involved in it (Amitani et al., 2013).

Hypoglycemic effect of Ginseng tea could be possible by different ways by enhancing insulin secretion, increasing uptake of glucose by tissue, inhibiting

intestinal glucose absorption and hepatic glucose synthesis (Xie et al., 2011).

Ginseng improves fasting blood glucose in people with and without diabetes (Esra et al., 2014). Ginsenosides have antioxidant, anti-inflammatory, antioxidant, anti-apoptotic and immune-stimulant properties. (Xiang et al., 2008). All these properties increase medicinal importance of ginseng. These properties contribute to the release of insulin from their cells.

Anti-inflammatory properties could be responsible for increasing insulin sensitivity and release of leptin hormone in overweight rats and decreased glucose level and improved lipid profile. Continuously administering a dose of leptin prevents decrease in leptin levels, decreases hyperphagia and insulin resistance (Denroche et al., 2012).

Dong et al. demonstrated anti-inflammatory effects of ginseng extracts were proven with purified ginsenosides. The downregulation of pro-inflammatory cytokine expressions (TNF-α, IL-1β, and IL-6) and enzyme expressions was found as the anti-inflammatory mechanism of ginsenosides (Dong et al., 2012). These effects may contribute to increased insulin and leptin release from their tissues leading to lipolytic and hypoglycemic effects of Ginseng tea.

Another important finding in the present research work is the lipid-lowering effects of Ginseng. Ginseng tea decrease cholesterol (24.22 %), LDL-C (29.93%),), triglyceride (41.05: %) fig. 2, body weight decrease (20.96%, Fig. 3) after three-week treatment while the increase in serum HDL-C level (24.48%). It is consistent with the reported dose of 8 g/day of Panax Ginseng extract- induced hypolipidemic effects (Delui et al., 2013).

Lipid and glucose metabolism co-relate one another in many directions in diabetic mellitus. High concentration of TG and low concentration HDL-C major risk factors in inflammation and atherosclerosis (Welty et al., 2013) decreased levels of HDL-C decrease or inhibit reverse cholesterol transport developed cardiovascular disease (Girona et al., 2019). Our study showed increased level of HDL-C, which has beneficial effects on cardiovascular disease. Atherogenic index value also calculated. Ginseng treated rats (AI = 1.984) as compared to controls (AI = 3.27). This implies that Ginseng provides protective effects on heart. In the present study, decreased levels of TG, and higher levels of HDL-C were observed.

Increase LDL-C in control animals might be due to Insulin resistance. Insulin resistance increases degradation of LDL receptors by up-regulation of hepatic lipase. Lipoprotein Lipase remove triglyceride from intermediate density lipoprotein (IDL-C) and produce LDL-C also effect LDL-C metabolism by increasing hepatic lipase synthesis and LDL receptors degradation (Miksztowicz et al., 2012). Insulin

resistance inhibits HDL-C synthesis by enhancing the phosphorylation and degradation of ATP-Binding Cassette transport (ABCA1) and decreasing ABCA1 activity (Nonomura et al., 2011).

Elevated TG increases free fatty acid move toward insulin resistance and beta-cell dysfunction. Hypoglycemia is achieved by higher HDL-C concentrations (Barter et al., 2011). Drew and coworkers reported intravenous injection of recombinant HDL-C ameliorates glucose metabolism in Type 2 diabetes mellitus. (Siebel et al., 2015). HDL-C decreases inflammation and increases cholesterol efflux by increasing Insulin sensitivity and secretion (Lehti et al., 2013).

Another study reported decreased level of TG and increased level of HDL-C after treatment of 100 mg and 200 mg doses of Ginseng (Sotaniemi et al., 1995) which has a beneficial effect on cardiovascular diseases. Liver synthesized triglyceride (TG) and secreted in blood, high level of TG develop dyslipidemia.

Triglycerides (TG) synthesized in the liver were secreted into the plasma circulation as very low-density lipoproteins (VLDL), causing dyslipidemia in liver. In addition, both alcoholic and non-alcoholic fatty liver diseases have excessive fat deposition in the liver (Alves et al., 2019), which may be considered in studies on liver dyslipidemia. Decreased level of triglyceride in present research might be involved in increase level of HDL-C in similar as reported by Sotaniemi et al., (1995).

CONCLUSION

The present research results showed the hypoglycemic effect of Ginseng tea by increasing leptin level. There could be many postulated mechanisms of these results and there is a need for further studies to find out the mode of action, such as insulin and leptin synthesis and resistance and anti-inflammatory markers. Due to hypoglycemic, hypolipidemic properties Ginseng tea can be used to reduce the chance to develop diabetes mellitus type II and could possibly inhibit the progression of steatosis by improving lipid profile.it can be used to reduce body weight due to lipolytic effects.

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