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Comparison of Protective Effects of Omega3 Fish Oil and Aqueous Extract of Glycyrrhiza glabra Root on Thioacetamide Induced Lipid Toxicity in Male Rats

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ABSTRACT

Thioacetamide(TAA) is an organic compound and is a potentotoxin.TAA has dyslipidemic effects because of its rapid elimination and cumulative injury when it is given intermittently,presumably by free radical-mediated lipid.Glycyrrhiza glabra is a well-know medical plant.Glycyrrhiza glabra root reduce the risk of coronary heart disease.Omga3 fatty acids are widely used to treatment hypertriglyceridema.Omega3 fatty acid are know to act as hypolipidaemics.The current investigation was designed to explore the possible protective effects of omega3 fish oil and glycyrrhiza glabra aqueous extract on TAA-induced dyslipidemia in male rats.63 wistar male rats were divided into 9 group. Control group.Sham group1.each rat of the group received 0.4ml olive oil as a solvent omega3 fish oil supplements orally per day for 3 months. Sham group2.each rat of the group received 150 mg/kg of TAA intrapertionealy in a single dose for 3 months. Experimental group 1,2,3. each rat of the 100,200,300 mg/kg of omega3 fish oil supplements orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months. Experimental group 4,5,6.each rat of the group received 100,200,300 mg/kg of aqueous extract of glycyrrhiza glabra root orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months.The provided blood samples were tested for total cholesterol, HDL, LDLcholesterol, triglyceride and FBS serum levels.pretreatment with 100,300mg/kg of aqueous extract of glycyrrhiza glabra or by 300mg/kg omega3 fish oil supplements significantly reduced thioacetamide-induced elevation in plasma levels of total cholesterol. Pretreatmen with the omega3 fish oil and aqueous extract of glycyrrhiza glabra root at all doses showed no significant difference in serum levels of triglyceride,LDL,HDL cholesterol and FBS comparing with thioacetamide group($P<0.05$).In conclusions,The study suggests that thioacetamide-induced lipid toxicity in male rats can be ameliorated by oral administration of aqueous extract of glycyrrhiza glabra root and omega3 fish oil.

Key words: Glycyrrhiza Glabra,Omega3 Fish Oil,Thioacetamide, Dyslipidemia.

INTRODUCTION

Thioacetamide (TAA) is an experimental hepatoxin[1]which is a thiono-sulfur containing compound with liver damaging and carcinogenic activity.Shortly after administration,TAA undergoes metabolism to acetamide and thioacetamide-S-oxide by the mixed function oxidase system[2].TAA is the most potent nephrotoxic substance because of its repid elimination and cumulative injury when it is given intermittently,presumably by free radical-mediated lipid[3,4].Metabolic studies of TAA-induced tissue damage suggest that TAA is metabolized by the mixed function oxidase system to its toxic metabolites sulfine(sulfoxide) and sulfene(sulfone) which then distributed among serveral organs including plasma,liver,kidney,bone marrow, adernals and other tissues[5].

Alpha-linolenic acid(ALA), ecosapentaenoic acid(EPA) and docosahexaenoic acid (DHA) are grouped together as the omega3 PUFA,there is substantial evidence suggesting that the individual fatty acids may have selective and potentially independent effects on cardiovascular health[6,7].Omega3 fatty acids led to management of diverse disease such as psychiatric[8],inflammatory bowel disease and cystic fibrosis[9].The omega3 Fatty acid,present in fish oil,interfere with the arachidonic acid pathway of inflammation[10]and can also modulate the response of macrophage to endotoxin by inhibition of TNF-alpha production in vitro[11].

Glycyrrhiza glabra,papilionaceae/ fabaceae family grows in various parts of the world. Glycyrrhiza glabra,also know as licorice,is a herbaceous perennial,with pinnate leaves and purpule to whitish blue flowers.It roots posses some nutritive value and medical properties[12]. Phytochemical analysis of glycyrrhetinic acid and liquirtic acid ,flavonoids and other constituents such as coumarins,simple sugar and polysaccharide like starch,pectin,amino acids, choline, phytosterol,mineral salts and various other substance[13].Many biological activities such as anti-genic activity,anti-ucler effects,protective action against hepatotoxicity,anti tumor promoting activity,antimicrobial effects[14,15].

Due to the high incidence of cardiovascular diseases and the numerous side effects of chemical drugs, it is needed to look for safer drugs with lower side effects and higher effectiveness. In the present study ,with respect to the low side effects of omega 3 polyunsaturated fatty acids and glycyrrhiza glabra root,the protective effects of omega-3 fish oil supplement and aqueous extract of glycyrrhiza glabra root against lipid toxicity in thioacetamide induced male rats were investigated.

MATERIALS AND METHODS

63male white wistar rats with a weight of 210±10 gr provided from laboratory animal center shiraz azad university were divided 9 equall groups.Control group.each rat of the group underwent no stress such as injection ,oral gavage and etc. Sham group1.each rat of the group received 0.4ml olive oil as a solvent omega3 fish oil orally per day for 3 months.Sham group2.each rat of the group received 150 mg/kg of TAA intrapertionealy in a single dose for 3months. Experimental group 1. each rat of the group received 100 mg/kg of omega3 fish oil supplements orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months.Experimental group 2. each rat of the group received 200 mg/kg of omega 3 fish oil supplements orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months. Experimental group 3 . each rat of the group received 300 mg/kg of omega 3 fish oil supplements orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months.Experimental group 4. each rat of the group received 100 mg/kg of aqueous extract of glycyrrhiza glabra root orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months.Experimental group 5. each rat of the group received 200 mg/kg of aqueous extract of glycyrrhiza glabra root orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months. Experimental group 6 . each rat of the group received 300 mg/kg of aqueous extract of glycyrrhiza glabra root orally per day for 3 months and 150 mg/kg of TAA intrapertionealy in a single dose for 3months [16-18].

By the end of experimental periods,rats were scarified under diethyl ether anesthesia at fasting state.The portion of blood samples were collected and allowed to coagulate at room temperature;other portion of blood added to it,EDTA(ethylene diamine tetracetic acid) and centrifuged at 5000r.p.m for 15 minutes.The clear,none-haemolysed supernatant sera and plasma were quickly removed divided into four portions for each individual,and stored at -20c for subsequent analysis[19,20].

Levels of plasma low density lipo-protein cholesterol(LDL), high density lipo protein cholesterol (HDL),total cholesterol,triglyceride(TG) and fasting blood sugar(FBS) were assayed using clinical test kits and anzymatic methods.

All of the valves are reported as mean ±SEM.The statistical significance of variations

between groups was analysed employing one-way ANOVA pursued by Tukey test analysis using SPSS version 18 with a value of P<.05 was regarded significant when compared to the control and sham groups.

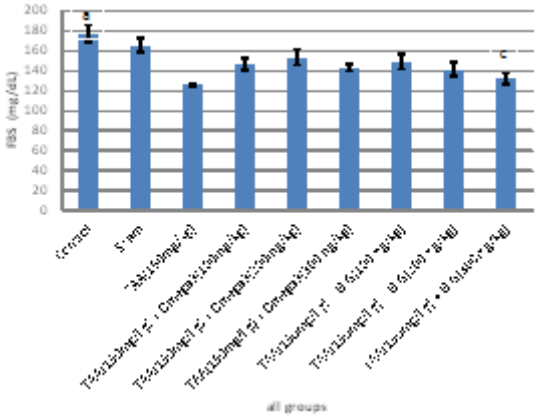
RESULTS AND DISCUSSION

Administration of thioacetamide let to significant increase the serum level of total cholesterol compared to the control group. Pretreatmen with 300 mg/kg of omega3 fish oil supplements significant increased the serum levels of total cholesterol comparing with thioacetamide group. Pretreatmen with 100,300 mg/kg of aqueous extract of Glycyrrhiza glabra root significant increased the serum levels of total cholesterol comparing with thioacetamide group (P<.05).

Administration of thioacetamide let to significant reduced the serum level of FBS compared to the control group . Pretreatmen with the omega3 fish oil supplements at all doses increased the serum levels of FBS comparing with thioacetamide group but there was no significant difference. Pretreatmen with the aqueous extract of Glycyrrhiza glabra root at all doses increased the serum levels of FBS comparing with thioacetamide group but there was no significant difference(P<0.05).

Administration of thioacetamide showed no significant difference in serum levels of LDL,HDLCholesteol, and triglyceride in compared to the control group . Pretreatmen with the omega3 fish oil supplements at all doses showed no significant difference in serum levels of LDL,HDLcholesterol and triglyceride comparing with thioacetamide group. Pretreatmen with the aqueous extract of Glycyrrhiza glabra root at all doses showed no significant difference in serum levels of LDL,HDLcholesterol and triglyceride comparing with thioacetamide group.

Various useful drugs like acetaminophen, gentamicin and some environmental and industrial toxin can cause severe renal damage through activation of these drugs to highly reactive free radicals[21].One of the most extensively studied chemical and industrial toxicants is TAA. TAA is know to induce centrilobular hepatic necrosis,liver cirrhosis,hepatocellular carcinoma



Values significantly different between control and sham groups with TAA group.[a]P<.05
Values significantly different between experimental groups with TAA group. [b]P<.05
Values significantly different between experimental groups with control and sham groups. [c]P<.05

Fig. 1: Effects of omega3 fish oil and aqueous extract of glycyrrhiza glabra root on serum levels of FBS

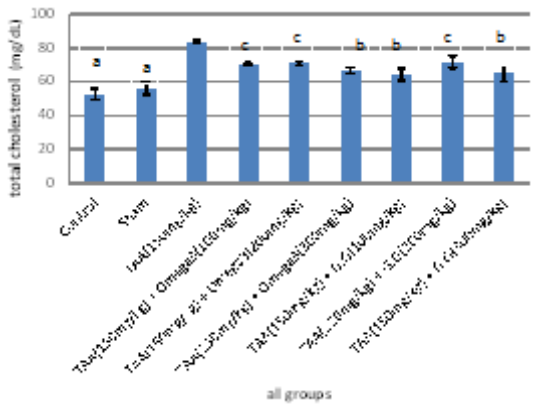


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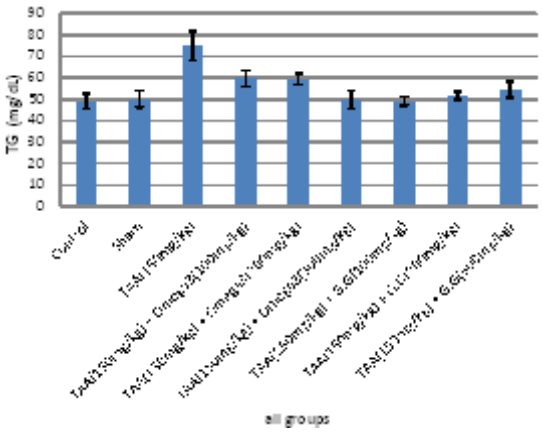
Fig. 2: Effects of omega3 fish oil and aqueous extract of glycyrrhiza glabra root on serum levels of total cholesterol

and bile duct proliferation[22,23]with injury to the terminal portion of the proximal renal tubule and dyslipidemia.

Pretreatmen with 100,300 mg/kg of aqueous extract of Glycyrrhiza glabra root significant increased the serum levels of total cholesterol comparing with thioacetamide group. Pretreatmen with the aqueous extract of Glycyrrhiza glabra root at all doses decreased the serum levels of triglyceride comparing with thioacetamide group but there was no significant difference(P<0.05).

Glycyrrhizic acid a constituent of glycyrrhiza glabra,reduces plasma cholesterol by down-regulating hepatic HMG COA reductase (HMGR) mRNA expression in hamster fed a high fructose-fat diet. Glycyrrhizic acid treatment significantly decrease apolipoprotein B(APO B),lipase a(LP a) and cholesteroliester-transport protein(CETP) concentrations but increased APO A-1 levels and APO A-1 / APO A-2 ratio.The contents of cholesterol and triglyceride in hepatic tissue were significantly lower in the glycyrrhizic acid group than in the control group[24].Glycyrrhizic acid improved insulin sensitivity and lipid profiles and induced up-regulation of total PPAR gamma and lipoprptein lipase(LPL) expression level in rats and decrease in triacylglycerol , total cholesterol and a elevation in HDL cholesterol[25]. Licochalcone A(LA) a constituent of glycyrrhiza glabra, suppressed hepatic triglyceride accumulation through modulation of AMP-SREBP pathway. LA inhibited lipogenesis via supperession of sterol regulatory element-binding protein1 (SREP1C) and target enzymes (stearoyl-COA desaturase1, fatty acid synthase and glycerol-3-phosphate acyltransferase) transcription.LA up-regulated gen expression of proteins such as PPAR alpha and fatty acid transport(FAT/CD36) which are responsible for lipolysis and fatty acid transport[26]. Chalcones of glycyrrhiza glabra roots decrease that levels of plasma total cholesterol and triglyceride. Chalcones showed strong inhibition against pancreatic lipase[27]. Glabrol from glycyrrhiza glabra roots act as antihypercholesterolemic agent.Glabrol inhibited acyl-coenzyme A cholesterol acyltransferase(ACAT) and decreased cholesterol ester formation[28].Beta-sitosterol from glycyrrhiza glabra roots reduced intracellular levels of triglyceride and cholesterol in L6 cells.Benefical



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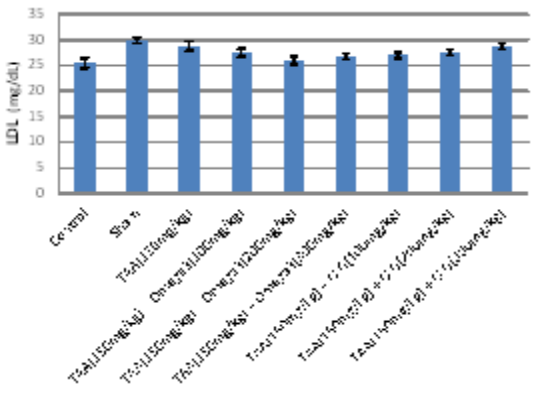
Values significantly different between experimental groups with TAA group. [b]P<.05
Values significantly different between experimental groups with control and sham groups. [c]P<.05

Fig. 3: Effects of omega3 fish oil and aqueous extract of glycyrrhiza glabra root on serum levels triglyceride



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Values significantly different between experimental groups with TAA group. [b]P<.05
Values significantly different between experimental groups with control and sham groups. [c]P<.05

Fig. 4: Effects of omega3 fish oil and aqueous extract of glycyrrhiza glabra root on serum levels of LDL cholesterol

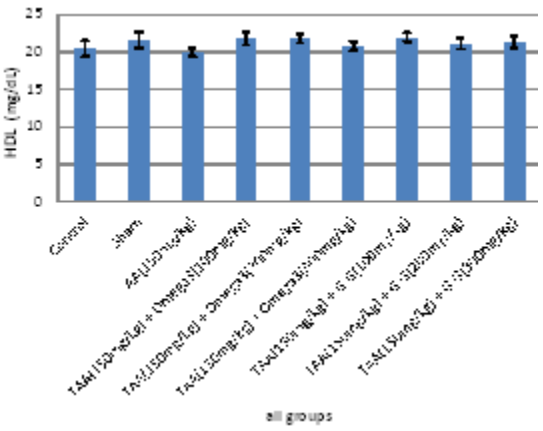
effects of beta-sitosterol on lipid metabolismIn L6 myotube cells are mediated by AM-activated protein kinase[29].Glabirdin from glycyrrhiza glabra roots showed inhibitory effect on adipogenesis in a dose dependent manner.The inhibitory effects of glabirdin resulted from inhibiting the induction of transcription factor CAAAT enhancer binding protein alpha and PPAR gamma[30].

Pretreatmen with 300 mg/kg of omega3 fish oil supplements significan increased the serum levels of total cholesterol comparing with thioacetamide group. Pretreatmen with omega3 fish oil supplements at all doses decreased the serum levels of triglyceride comparing with thioacetamide group but there was no significant difference($P<0.05$).

Omega3 polyunsaturated ameliorated diet-induced hyperlipidemia and fatty liver through induction of CYP7A1 expression and activation of cholesterol catabolism to bile acid[31]. Omega3 readly incorporated into hepatic phospholipids,reduced stearoyl-COA desaturase16 , stearoyl-COA desaturase,delta 6 desaturase,delta5 desaturase activities and reduced the lipogenesis index[32].Both caloric restriction and omega3 supplement diets are able to prevent hypercholesterolemia,by regulating HMG-COAR activation state by controlling ROS production and P38 phosphorylation.Moreover also the age-dependent less of LDL membrane exposition in prevented[33].Combination of fish oil and fish protein hydrolysate decrease the plasma cholesterol level[34].Omega3 fatty acid negatively regulate triglyceride biosynthesis.Omega3 fatty acid deficiency increase stearoyl-COA desaturase(sd1)and suggest that down regulation of sd1 is a mechanism by which omega3 fatty acid repress constitutive triglyceride biosynthesis[35].DHA supplementation reduced APO C III concentrations which inhibits the activity lipoprotein lipase(LPL) that control triglyceride(TG) clearance from blood. Thus,a reduction in the concentrations of APO C III increased activity of LPL and hence increased clearance of plasma TG[36].Omega3 regulate APO C III there effects on PPAR alpha which down regulates APO C III expression and NF-KB which up regulated APO C III expression[37]. Docosahexanoic acid(DHA) is an FXRa ligand has been shown to decreases the expression of hepatic lipase and APO C III and increase APO C II and VLDL-receptor gene expression in HPG2 cells[38].Omega3 fatty acids reduced activity of key enzymes in TG biosynthesis such as phosphatidic acid phoshohydrolase and diacylglycerol acyltransferase.

Pretreatmen with the aqueous extract of Glycyrrhiza glabra root at all doses increased the serum levels of FBS comparing with thioacetamide group but there was no significant difference.

18 beta-glycyrrhetinic acid.a glycine of glycyrrhizin possesses a potential anti hyperglycemia effects that is comparable with glibenclamide[39].Glycyrrhizic acid inhibit 11 beta-hydroxysteroid dehydrogenase1 activity[40].Glycyrrhizin improved significantly the diabetogenic effects of streptozotocin namely enhanced blood glucose level,glucose intolerant behavior,decreased seum insulin levels[41].Glycyrrhizic acid improved insulin sensitivity and lipid profile and induced up



Values significantly different between control and sham groups with TAA group.[a]$P<.05$

Values significantly different between experimental groups with TAA group. [b]$P<.05$

Values significantly different between experimental groups with control and sham groups. [c]$P<.05$

Fig. 5: Effects of omega3 fish oil and aqueous extract of glycyrrhiza glabra root on serum levels of HDL cholesterol

regulation of total PPAR gamma and lipoprotein lipase expression levels in rats[42].Glabridin,a polyphenolic flavonoid from licorice significantly decreasing fasting blood glucose.These results demonstrated that glabridin possesses hypoglycemic effects[43].Glycyrrhizin ameliorates insulin resistance, dyslipidemia and oxidative stress in fructose-induced metabolic syndrome X in rat model.The decrease levels of PPAR gamma and glucose transport(GLUT4) proteins in slekeletal muscle of metabolic syndrome were elevated by glycyrrhizin,indicating improved fatty acid oxidation and glucose homeostasis[44].

Pretreatmen with the omega3 fish oil supplements at all doses increased the serum levels of FBS comparing with thioacetamide group but there was no significant difference.

Omega3 fattty acids may increase the plasma glucose level through other mechanism. Long-chain omega3 can decrease glucose utilization and increase glucagon-stimulated C-peptide[45] or could increase hepatic gluconeogenesis by increase uptake and oxidation of free fatty acids in liver[46].Thus,omega3 fatty acid and fish consumption may increase the diagnosis of T2DM by increasing circulating concentration of glucose but whithout causing other adverse metabolic abnormalities.

The overall result from this study demonstrated TAA-induced lipid toxicity by biochemical analysis.The concurrent treatment with omega3 fish oil and or by aqueous extract of glycyrrhiza glabra root clearly provided a considerable degree of protection in a dose-dependent manner against the deleterious lipid side effects of TAA.

CONCLUSION

In conclusion,omega3 fish oil and aqueous extract of glycyrrhiza glabra root could act on the lipid metabolism as potent antioxidant to prevent ongoing TAA-induced lipid toxicity.

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