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Anti-diabetic, anti-oxidant and anti-hyperlipidemic Activity of *Fomitopsis pinicola*

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Abstract

Fomitopsis pinicola is a traditional medicinal mushroom used traditionally in the folk medicine of both China and Korea. Polysaccharides are the principal constituents of the fruiting body of *F.pinicola*. In the current study 3 different extracts were prepared, Polysaccharide Extract (FPP), Alkali Extract (AE) and Chloroform Extract (FPC). *F.pinicola* extracts anti-diabetic, anti-oxidant and effect on lipid metabolism was checked by using diabetic rats, diabetes induced by streptozotocin (STZ) injection. Five groups were made with nine rats in each group. Parameters were compared with normal control (NC), diabetes control (DC) and FPC treatment groups. With the induction STZ, all diabetic rats showed disturbed fasting blood glucose (FBG), lipid profile and reduced activities of anti-oxidant enzymes such as CAT, SOD, and GSH-Px. Throughout the procedure, DC rat's body weight deprived, while NC gains bodyweight from beginning to end. Results of the current study revealed that FPP showed superior effect than the other groups, showed more reduced FBG levels and more gain in body weight. With the STZ, serum insulin levels were significantly dropped, FPP also exhibited a rehabilitation effect on serum insulin levels. The biochemical study disclosed that FPP showed significant lipid metabolism than other treatments by declining the levels of TC, TG, and LDL-C with elevated levels of HDL-C. FPP further manifested that CAT, SOD, and GSH-Px activities were increased substantially with dangerous MDA activity suppression. The study endorsed that FPP extract at dose of 300mg/kg/day gave more anti-diabetic, anti-oxidant and anti-lipidemic effects than AE (300mg/kg) and FPC (300mg/kg).

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Introduction

Recently many studies have demonstrated that extracts from mushrooms fruiting bodies are giving numerous pharmacological impacts on the body. (Konno *et al.*, 2002; Tsai *et al.*, 2014; J. Wu *et al.*, 2016) Mushrooms are more abundantly used in foods item because of their well-known flavor and texture. In recent years, mushrooms got more attraction because of possessing numerous biologically active compounds such as terpenes, steroids and polysaccharides. (Cai *et al.*,1993; Kim *et al.*, 2006; JS. Lee *et al.*, 2006). Normally mushrooms roughly own 3-21% and 3-35% carbohydrates and fiber respectively by its dry mass. Thus mushroom carbohydrate dry weight contains a substantial amount of fiber that humans are unable to digest easily. This makes mushrooms a low caloric diet for most of the medical situations. (Breene, 1990).

Due to various biological reactions, free radicals and reactive oxygen species (ROS) production, and their elevated levels in the human body lead to tissue damage and various diseases. (Sies, 1997).

Foreign available anti-oxidants are induced to reduce the lethal effect of ROS and free radicals. In recent years, medicinal edible mushrooms are widely used because of having natural anti-oxidant activity. Furthermore, it was found that polysaccharides from mushroom sources had a counter effect on free radicals as well as ROS. (Ge *et al.*, 2009; Sun *et al.*, 2009).

Furthermore, revealed that polysaccharides exhibited anti-hyperglycemic effect when produces by alkali or water extracts of *F.pinicola* fruiting bodies. (SI. Lee *et al.*, 2008).

F.pinicola associated with Basidiomycota and has been extensively farmed in japan, also part of folk medicine to traditionally treat diabetes and also considered as health food. (Högberg *et al.*, 1999). *F.pinicola* is a wood-decaying medicinal mushroom, used traditional medicine in north and east china to make leg circulation better in elders. (X. Zhao *et al.*, 2010). Moreover, 11 species of Fomitopsis were found in china, including *F.pinicola*.(Dai, 2012) Research established the fact that *F.pinicola* had an anti-oxidant effect, biological activities of extracts of *F.pinicola* were checked on GSH-Px, CAT, acetaldehyde dehydrogenase and alcohol dehydrogenase. (Cha *et al.*, 2009a). Lanostane triterpene glycosides and lanstane triterpenoids have been extracted from *F.pinicola* and their anti-cyclooxygenase 1 and 2 effects were also determined.(Yoshikawa *et al.*, 2005). Studies have also proved that extracts from the fruiting body of *F.pinicola* exhibited the anti-diabetic as well as anti-lipidemic effect.(Cha *et al.*, 2009b; SI. Lee *et al.*, 2008) However, the present study designed to demonstrate the anti-diabetic, anti-oxidant and anti-lipidemic effects of *F.pinicola*. We observed the body weight, FBG, serum insulin, hepatic glycogen and total protein (TP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triacylglycerol (TG) and anti-oxidant effect among treatment groups.

Materials and methods

Experimental specimens

Dried fruiting bodies of *F.pinicola* were used. The mushroom is collected from Changbaishan Mountains (China), identified by Prof. Bao Haiying and Prof. Tolgor Bao, Engineering Research Centre of the Chinese Ministry of Education for edible and medicinal fungi, Jilin Agricultural University, Changchun, Jilin, China.

Chemical reagents and ELISA kits

For the evaluation of all experimental parameters, various chemicals and reagents were purchased from reputed companies. STZ was provided by Changchun huayi biotechnology Co. Ltd, located in Changchun, China. For the analysis of insulin, Glycogen, TC, TG, LDL-C, HDL-C, catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxide (GSH-Px) and TP, commercial kits were bought from Changchun nuojin Instrument Co. Ltd (Changchun, China).

Experimental animals

In the current experiment, Male Sprague-Dawley rats (20g) are used provided by Changchun yisi experimental animal's technology Co. Ltd (China). The experimental protocol followed for laboratory animal care is according to approved conditions set by Traditional Chinese Medicine School, Jilin Agricultural University, Changchun, China. Controlled environmental conditions were given to all experimental animals, as 12h light and 12h dark cycle, temperature range from 25-30°C and humidity range from 30-50%. All the rats had given free access to food and water.

Preparation of F.pinicola chloroform extract

Dried fruiting bodies of *F.pinicola* (300g) was powdered and then mixed thoroughly into ethanol (95%) at a temperature range of 45°C. This well-homogenized solution was subjected to 3 times the ultrasonic-assisted extraction (UAE). The solution then placed to vacuum filtration and further concentrated by using rotary evaporation, followed by lyophilization after freeze-drying.

The ethanol extracted specimen then stored at -20°C. Ethanol extract fractionated with $CHCl_3$ (chloroform), and uniformed with ethanol (70%) and centrifuged (3000rpm) for 15min with a temperature of 25°C. This homogenized solution was filtered with 0.45mm and 0.22mm filters.(Gao *et al.*, 2017).

Preparation of F.pinicola polysaccharide extract

Dried fruiting bodies powder of *F.pinicola* (300g) was soaked into 80% ethanol and then boiled it on 80°C for two hours by using reflux. After two hours filtered the solution and further dried by rotary evaporator and collected the residues. After drying, the dried residues were soaked into 1L of water and boiled at 100°C for two hours. Filter the solution and got two more extractions by using the same procedure. Mixed the three water extraction and protein was removed. The polysaccharides were precipitated by using ethanol (95%), followed by centrifugation (3000rpm) for 15min. The residues were then freeze-dried and collected.(Zhang *et al.*, 2013).

Preparation of F.pinicola alkali extract

Fruiting bodies were cut into small pieces, the size range was approximately 1 × 1 × 1-cm for cubes. AE was prepared to following the method of Jang *et al.* (Jang *et al.*, 2005) 100g of dried fruiting bodies were dipped into Potassium hydroxide (KOH)(2N) at room temperature for 1h. The solution was extracted by sieve (100-mesh). HCl was added to extract to make it neutralize and washed with water to make it alkali and salt-free. The *F.pinicola* AE then subjected to freeze-drying.

Experimental procedure

To set the model, all the rats were fed with a normal chow diet for seven days with free access to water. After seven days, all the rats were fed with a high-fat diet purchased from Beijing HFK Biosciences Co. Ltd, for eight weeks. After eight weeks, within 72h, all rats have injected with a freshly prepared injection of streptozotocin (STZ) (60mg/kg) in citrate buffer, interperitoneally. After the administration of STZ, again rats were given a high-fat diet for a further two weeks. After two weeks of STZ injection, blood glucose levels were monitored by taking a drop of blood from the tip vein of the tail for every rat with a glucometer. Those rats were selected whose blood glucose levels were greater than 11.1 mmol/L and considered them a diabetic model for pharmacological study. Five groups were made with nine rats in each group. Throughout the experiment, normal saline was given to DC and NC. Polysaccharide, Chloroform, and Alkali Extract administered at a dose of 300mg/kg/day to diabetic rats. The duration of the experiment was 4 weeks and all the specimen administration was done by using an orogastric cannula. Except for NC, all other experimental groups were fed with a high-fat diet throughout the procedure. All the rats fasted the whole night before the determination of FBG after every week.

Biochemical parameters analysis

After four weeks, rats of all experimental groups fasted overnight. Before sacrificed them, blood was collected from the orbital sinus; blood serum was

separated from blood by centrifuged at 4°C at 3000rpm for 15 minutes. Serum insulin levels, LDL-C, HDL-C, TG, and TC was determined from blood serum by using commercial/ELISA kits. All rats were dissected by cervical dislocation, a small part of the kidney and liver were homogenized with normal saline and then at 4°C centrifuged at 3000rpm for 15min.(Sun *et al.*, 2008).

The supernatant was separated for the analysis of TP, glycogen, GSH-Px, CAT, SOD, MDA levels with the help of commercial/ELISA kits.

Statistical analysis

All the data were statistically analyzed by using statistix (version 8.1). The variations that occurred between groups were calculated by one-way analysis of variance (ANOVA) test. Nine rats' results were expressed as mean ± SD for each group. Only those results were considered statistically significant whose $p < 0.05$.

Results and discussion

Effect on the bodyweight by F.pinicola Extracts

The weight of the body is shown in Table 1. The results exhibited that at the start body weights were 49.92, 45.62, 45.66, 44.12 and 41.86g for NC, DC, AE, FPP, and FPC treatment group respectively. At the end of 4 weeks, DC showed a significant reduction of 5.87% in the body weights than the beginning. After treatment with *F.pinicola* extracts, in comparison to DC the weight of other groups increased by 17.04%, 8.48%, 17.92% and 11.82% for NC, AE, FPP and FPC accordingly.

Results analysis revealed that FPP showed better gains than other groups. FPP showed a 15.67% gain in body weight as compared with initial weight. Moreover, 1.07%, 6.91% and 10.32% more procure bodyweight than NC, FPC and AE respectively.

Table 1. Effect of *F.pinicola* extracts on bodyweight.

Treatments	1st week body weight(g)	2nd week body weight(g)	3rd week body weight(g)	4th week body weight(g)
NC	$49.92^{B}\pm0.78$	$50.32^{A}\pm0.4$	$51.16^{A}\pm0.55$	$51.76^{A}\pm0.86$
DC	$45.62^{B}\pm1.87$	$44.62^{B}\pm1.56$	$43.58^{C}\pm1.43$	$42.94^{D}\pm1.1$
AE	$45.66^{B}\pm0.52$	$45.46^{B}\pm0.97$	$46.30^{B}\pm0.45$	$46.92^{C}\pm0.62$
FPP	$44.12^{B}\pm1.53$	$49.92^{A}\pm0.52$	$51.08^{A}\pm0.6$	$52.32^{A}\pm0.56$
FPC	$41.86^{C}\pm1.86$	$45.26^{B}\pm1.31$	$46.42^{B}\pm0.79$	$48.7^{B}\pm0.68$

Experiment data represent the mean ±S.D of 9 rats. Treatment groups (n=5). Significantly different at $P < 0.05$.

Table 2. Effect of *F.pinicola* extracts on anti-oxidant enzymes activity.

Treatments	CAT(ng/mL)	SOD(pg/mL)	MDA(nmol/L)	GSH-Px (pg/mL)
DC	$3.64^{C}\pm0.25$	$5.49^{C}\pm0.22$	$0.62^{AB}\pm0.05$	$10.68^{B}\pm1.65$
NC	$4.76^{AB}\pm0.39$	$8.15^{AB}\pm0.61$	$0.48^{C}\pm0.04$	$14.54^{A}\pm1.05$
AE	$4.16^{BC}\pm0.27$	$7.07^{B}\pm0.19$	$0.65^{A}\pm0.09$	$10.74^{B}\pm1.14$
FPP	$5.31^{A}\pm0.26$	$8.47^{A}\pm1.06$	$0.5B^{C}\pm0.02$	$17.07^{A}\pm1.52$
FPC	$3.56^{C}\pm0.38$	$7.56^{AB}\pm0.53$	$0.6A^{BC}\pm0.03$	$15.18^{A}\pm0.85$

Experiment data represent the mean ±S.D of 9 rats. Treatment groups (n=5). Significantly different at $P < 0.05$.

Weight loss is the usual distinctive of diabetes, especially T2DM.

This is caused by enhanced utilization of protein with reducing deposition in circumstances of non-accessibility of carbohydrates for glucose molecules generation. (Chung *et al.*, 2011) Furthermore, STZ-induced diabetes caused the destruction of muscles so that the weight of both organs and ultimately the weight of the body is reduced. (Kasetti *et al.*, 2010) Diabetes management is potently in correlation with bodyweight management.

Effect on serum insulin and FBG

After STZ-injection the rat's blood glucose levels increased as compared with NC that exhibited that the model is successfully established for the procedure. The FBG was determined at the end of every week. After the administration of *F.pinicola* extracts, the levels of FBG decreased after 4 weeks as compared to the beginning. As compared with DC the reduction was 57.81%, 8.06%, 65.04% and 51.93% for NC, AE, FPP and FPC individually. It was exhibited that FPP showed more control than the other groups, as 75% more control than initially, 17%, 27% and 61.97% more reduction than the NC, FPC and AE separately. (Fig. 1).

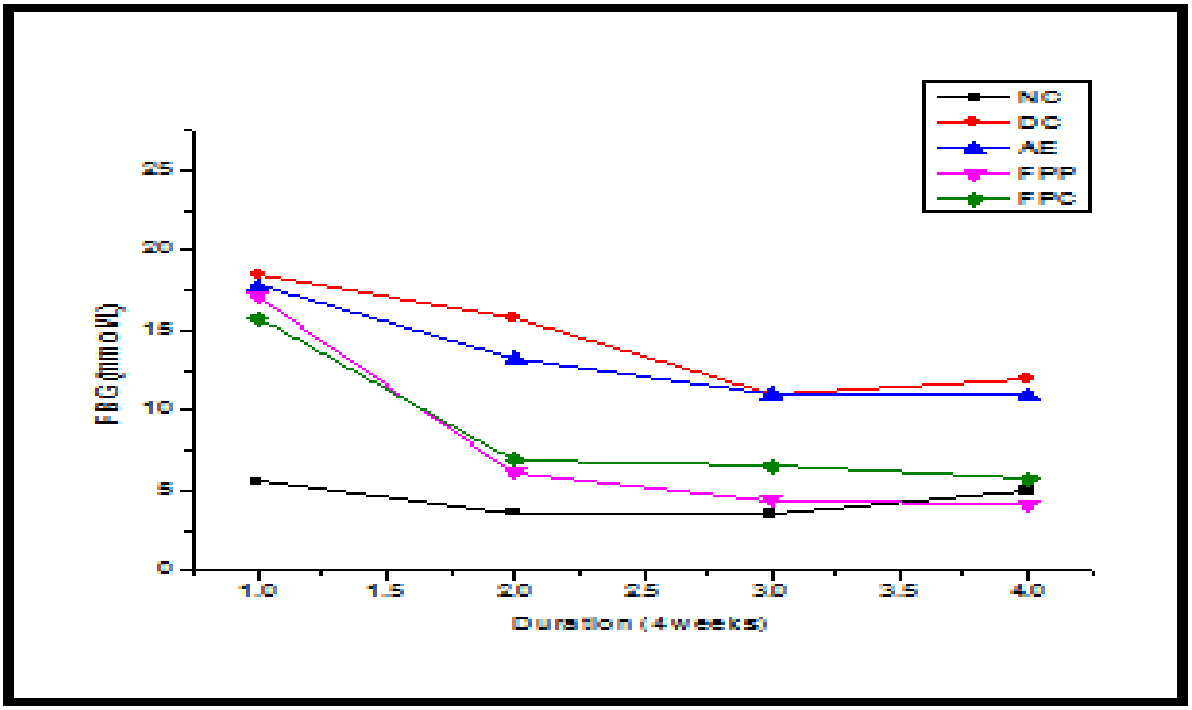

Fig. 1. Effect of *F.pinicola* extracts on FBG.

In the current study, serum insulin levels were also determined for 4 weeks. With the STZ-induction of diabetes, the diabetic rat's blood insulin levels were greatly reduced.

After 4 weeks of administration of *F.pinicola* extracts, the recovery effect was seen in the serum insulin levels of treated groups. According to the results and analysis with DC, serum insulin levels were increased by 14.17%, 51.12% and 42.93% for AE, FPP, and FPC respectively. The results further demonstrated that FPP showed more enhancement in insulin levels as compared with other groups. 5.38%, 14.34% and 43.04% more elevation in serum insulin levels as compared with NC, FPC and AE respectively. (Fig. 3).

T2DM is characterized by insulin deficiency. Insulin resistance plays an important role in T2DM that ultimately leads to the failure of homeostasis of glucose molecules metabolism and boosts the hepatic glucose omission. (Mazzola, 2012; Zhu *et al.*, 2013) Insulin deficiency for a long span induces hyperglycemia and hypoinsulinemia in diabetes, lead to damaging peripheral organs and tissues with life-threatening complications.(Baron, 1998; Xiao & Hogger, 2015) An effective procedure to treat T2DM is controlling both blood glucose as well as insulin levels. (Li *et al.*, 2012; Lo & Wasser, 2011) Insulin is a prime hormone that regulates glucose homeostasis in the body. Insulin resistance, insufficiency, and deficiency are the characteristics of T2DM.

Effect of F.pinicola on serum lipids profile

STZ-induction greatly disturbed the serum lipids profile of diabetic rats. After the administration of *F.pinicola* extracts, a notable reduction in TC, TG,

and LDL-C and a valuable increase in the HDL-C was seen in the serum of diabetic rats. According to the results the reduction in TC, TG and LDL-C were, (16.76%, 26.16%, and 19.48%), (36.95%, 47.72%, and 37.20%) and (17.73%, 20.65%, and 17.69%) for AE, FPP and FPC respectively. On the other hand, the HDL-C levels were enhanced by 1.05%, 27.64% and 2.77% for AE, FPP and FPC accordingly. The results demonstrated that FPP showed more reduction of TC, TG, and LDL-C as compared with other treatment groups, as (-15.04%, 8.29% and 11.35%), (1.68%, 16.74% and 17.07%), (4.49%, 3.6% and 3.55%) than NC, FPC and AE separately. HDL-C for FPP was increased as 19.87%, 25.57% and 26.87% for NC, FPC and AE individually. (Fig. 2).

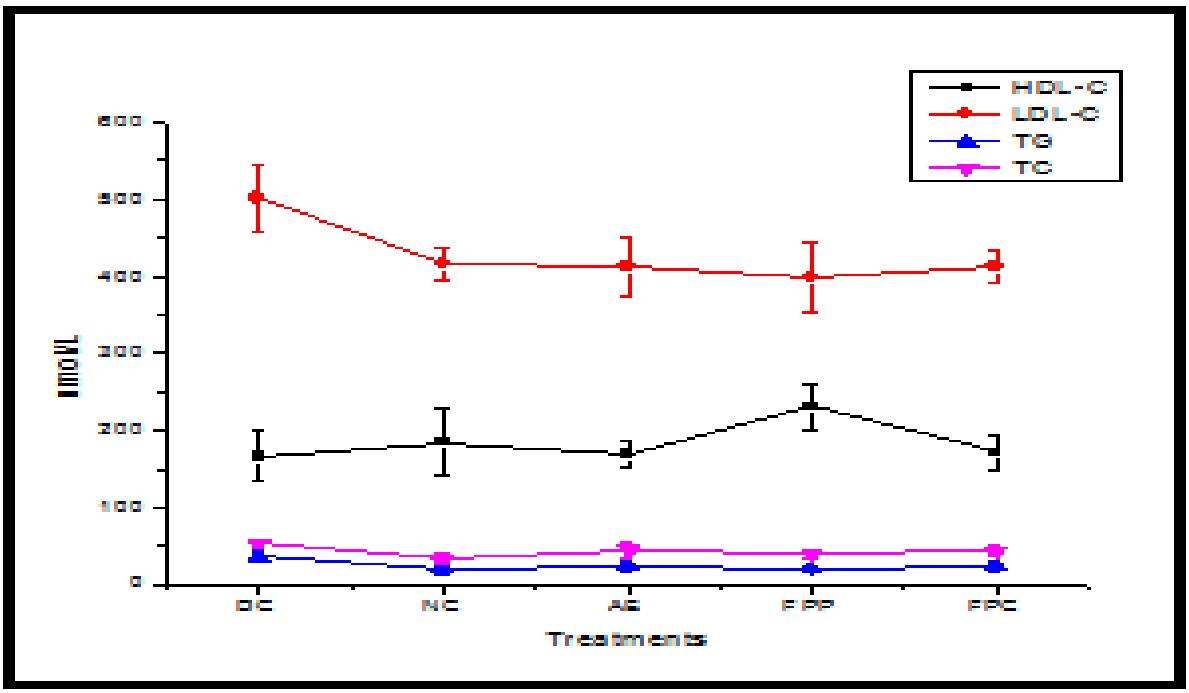

Fig. 2. Effect of *F.pinicola* on lipid metabolism of diabetic rats.

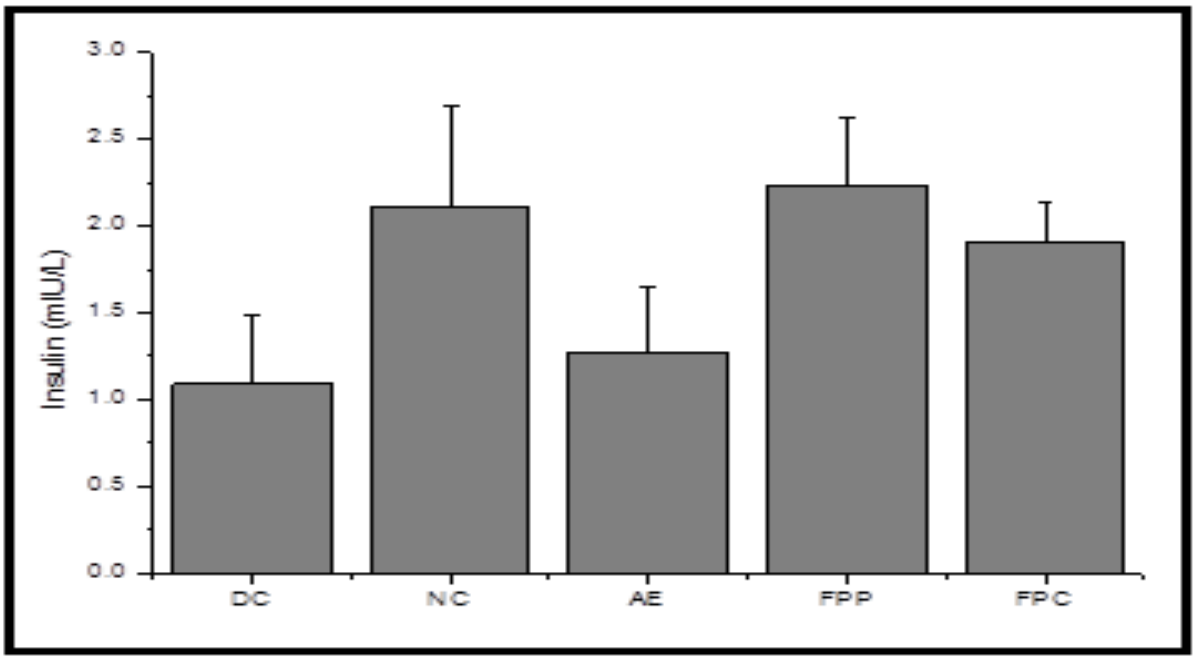

Fig. 3. Effect of *F.pinicola* extracts on Serum Insulin.

The liver is the primary vital organ in the body that carries out the metabolism of lipids and maintains a homeostatic level of cholesterol. (Adams *et al.*, 2011) Hyperlipidemia to a chronic stage causes a harmful effect on the hepatic tissues and ultimately leads to insulin resistance and cardiovascular complications in the body. (Association, 2013; Dey & Lakshmanan, 2013) Hyperlipidemia more frequently leads to a generation of a condition called dyslipidemia in the body and alternatively establish the insulin resistance in the periphery by increasing the free fatty acids. (Ginsberg, 2000; K. Wu *et al.*, 2013).

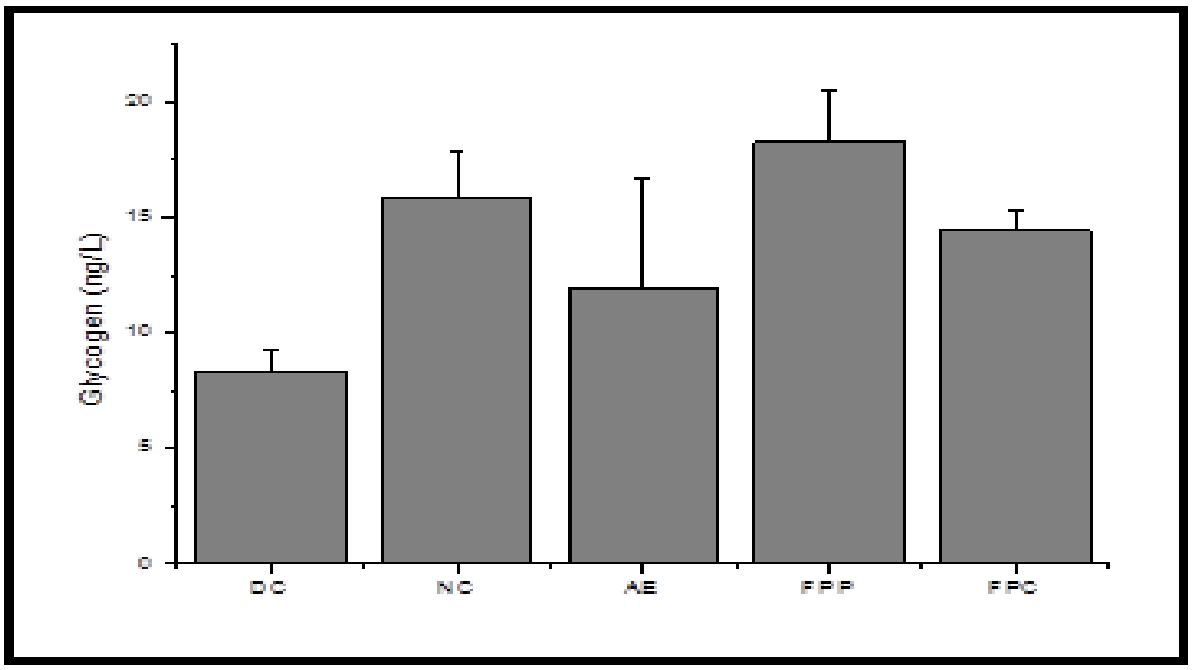

Fig. 4. Effect of *F.pinicola* extracts on Hepatic Glycogen.

Effect on anti-oxidants enzymes

As shown in Table 2, in the STZ-induced diabetic rats, liver CAT, SOD, and GSH-Px levels significantly reduced. In contrast, the MDA level in diabetic rats enhanced the toxic point. After treatment of 4 weeks, the diabetic rat's hepatic antioxidant enzymes levels increased with the decrease in toxic MDA levels. According to the results, the haptic anti-oxidant enzymes, CAT, SOD and GSH-Px levels increased by (12.5%, 31.45% and -2.24%), (22.34%, 35.18% and 27.38%) and (0.55%, 37.43% and 29.64%) for AE, FPP and FPC respectively. The reduction in lethal MDA levels was -4.61%, 19.35% and -3.33% accordingly. Analysis of results with other groups revealed that FPP satisfied all parameters effectively. CAT, SOD and GSH-Px enhanced rates for FPP were (10.35% > NC, 32.95% > FPC, 21.65% > AE), (3.77% > NC, 10.74% > FPC, 16.52% > AE) and (14.82% > NC, 11.07% > FPC, 58.93% > AE) respectively. Results further demonstrated that FPP group MDA reduction is more than NC, FPC and AE as 20%, 4% and 16.66% respectively.

Under severe hyperglycaemic conditions, the origination of ROS occurs, ROS production is caused by various biochemical reactions such as lipid peroxidation and non-enzymatic glycation as a result of decreased activity of antioxidant enzymes. (Singh *et al.*, 2005) Furthermore, ROS cause the destruction of body anti-oxidant defensive mechanism that ultimately set-up the vascular complications and pathogenesis. (Pham-Huy *et al.*, 2008).

Enzymes such as CAT, SOD, GSH-Px and inorganic compound MDA play a prime role in increasing the oxidative stress of the cell in vivo. (Meenatchi *et al.*, 2017; H. Zhao *et al.*, 2016) Hyperglycemia suppresses the antioxidant enzymes in the liver. MDA is a reactive compound and its high levels in the body lead to lethal effects on cells(Davey *et al.*, 2005).

Furthermore, MDA has used a parameter to monitor oxidative stress in an organism(H. Zhao *et al.*, 2016).

Effect on TP and Glycogen by F.pinicola extracts

In carbohydrate deficiency, the body targets the protein contents for glucose production as an energy source. So protein destruction is a common situation in diabetes. (Chung *et al.*, 2011; Kasetti *et al.*, 2010).

In the current study, TP contents of the liver and kidneys were determined. It was a determination of the accumulation of protein contents after *F.pinicola* extracts treatment. According to results, a significant reduction was seen in both hepatic and kidneys TP after STZ-induced diabetes. After *F.pinicola* extracts supplementation, a significant gain in TP was seen in both organs. Results confirmed that the FPP, TP gain for both organs was more than other treatment groups, in comparison with DC the gain was 50.76% and 23.22% for liver and kidney respectively. FPP group TP gain was also better than the NC, FPC and AE treatment groups. As shown by results hepatic TP gain was 21.3%, 4.07% and 41.46% more than NC, FPC and AE respectively, and kidneys TP gain was 23.22%, 0.54% and 20.28% accordingly. (Fig. 4).

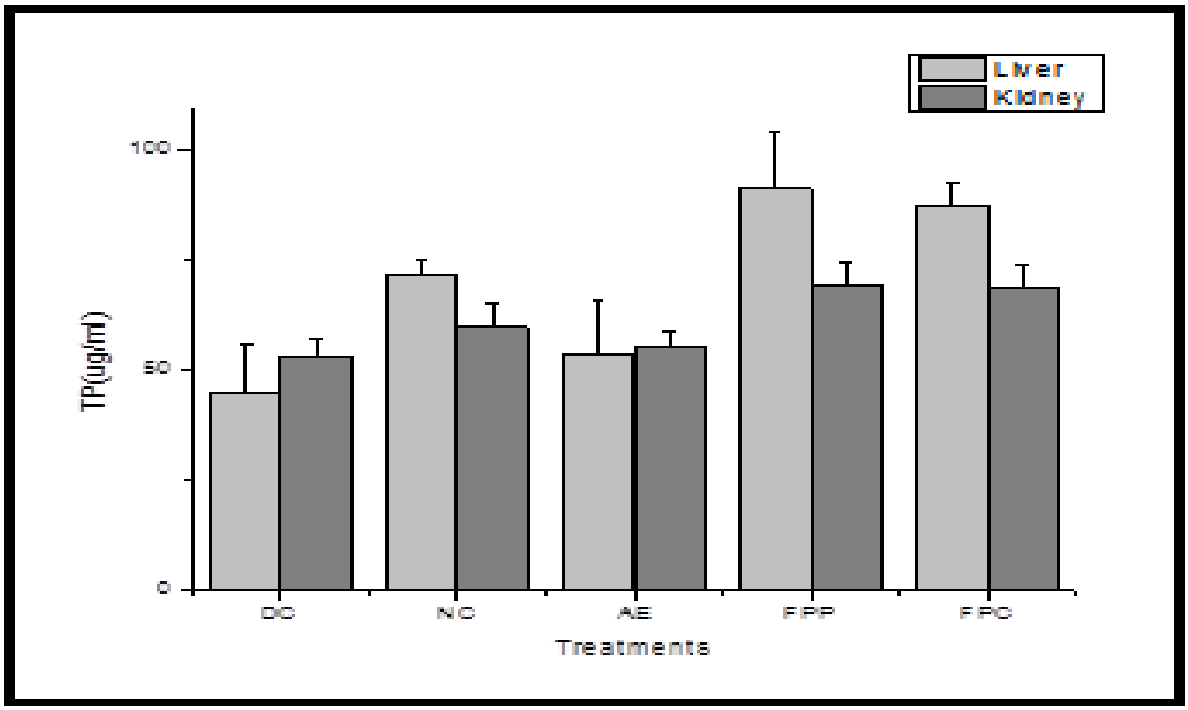

Fig. 5. Effect of *F.pinicola* on TP of liver and kidney.

On the intracellular level of the organism, glucose store in the form of glycogen in the liver and muscle. Glycogen production by the enzyme glycogen synthase is primarily performed by hormone insulin and inhibits glycogen phosphorylase. In a diabetic rat, the level of glycogen storage is directly related to the insulin level, and furthermore it is a key parameter to examine the insulin deficiency in T2DM. (Jung *et al.*, 2007; Li *et al.*, 2012) Glycogen storage at the hepatic level was prominently decreased after STZ-induced diabetes. After treatment with *F.pinicola* extracts for 4 weeks, a prominent increase in hepatic glycogen was seen. The storage ratio was 30.04%, 54.21% and 42.18% for AE, FPP and FPC respectively.

In comparison with NC, FPC and AE, the FPP group showed more hepatic deposition.

The deposition ratio was 13.08%, 20.81% and 34.55% more than NC, FPC and AE respectively. These results clearly stated that *F.pinicola* extracts treatment increased insulin production by β-cells that ultimately led to the accumulation of glycogen on the hepatic site. (Fig. 5).

Conclusion

Results of the study concluded that FPP showed more Anti-diabetic, anti-oxidant and anti-lipidemic effects than other treatment groups. FPP at a dose of 300mg/kg/day had a more antihyperglycemic effect with serum insulin deficiency rehabilitation. FPP showed a valuable gain in body weight and TP contents of both kidney and liver.

Additionally, FPP exhibited a significant lipid metabolism in diabetic rats by normalizing the increased levels of LDL-C, TC, and TG and by increasing the HDL-C. Furthermore, FPP prevented the cells and tissues from oxidative stress with enhanced activities of CAT, SOD, and GSH-Px and declined the lethal activity of MDA. All parameters indicated that *F.pinicola* polysaccharide (300mg/kg) extract had more anti-diabetic, anti-oxidant and anti-hyperlipidemic potential than FPC (300mg/kg) and AE (300mg/kg), revealed that *F.pinicola* is a promising approach to cure diabetes in future.

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Conflicts of interest

There are no conflicts to declare.

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