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# *Persea americana* seeds improve glycosylation and dyslipidemia in fructose-fed streptozotocin-injected type 2 diabetic male rats

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**Abstract**: This work explored the *in-vitro* phytochemical contents and antidiabetic activity of crude seeds powder of *Persea americana* (*CSSPa*) and their *in-vivo* biochemical effects on glycated hemoglobin, lipid profile and other parameters in type 2 diabetic rats (fructose-STZ model). There were 2 groups of over night fasted rats, control (normal diet) and diabetic (35% Fructose for 6 weeks followed with injection (i.p.) of streptozotocin (STZ) (40mg/kg bw). Diabetic group was further divided into diabetic control, positive control (pioglitazone 15mg) and test (*CSSPa* 500mg) groups. After the appropriate treatments in each group for 2 weeks fasting glucose level (FGL), serum lipids, insulin, alanine aminotransferase (ALT), creatine Kinase (CK) & uric acid were determined. *CSPPa* showed presence of alkaloids, flavonoids, phenols etc and potent antidiabetic activity with $IC_{50}$ 13.23±0.76µM. *CSPPa* treatment showed a significant ($p$<0.01) decline in lipid profile, while HDL showed significant increase ($p$<0.01) in test group as compared with positive and diabetic control groups. The serum ALT, CK, uric acid, bilirubin & fasting glucose (fbg) showed significant improvements in test group ($p$<0.01). Coronary risk index (CRI), Fasting insulin resistance index (FIRI), Percent glycemic change (PGC) and HbA1c values also significantly ($p$<0.01) improved.

**Keywords**: Insulin resistance, fructose, STZ, FIRI, *Persea Americana.*

## INTRODUCTION

The level of frequent generation of free radicals and the onset of various metabolic diseases can be associated in terms of utilization of dietary polyphenols (Poprac *et al*., 2017). Many secondary plant metabolites or polyphenolic herbs have been identified to treat many disorders (Balunas and Kinghorn, 2005) specially those which occur due to the presence of free radicals such as cardiovascular insufficiency, hypertension, inflammatory conditions, asthma, diabetes and Alzheimer's (Hosseini and Hosseinzadeh, 2015; Rouhi-Boroujeni *et al*., 2015;Manach *et al*., 2004). In addition to this, polyphenols have been used as preservatives, providing protection against the unusual growth of microorganisms (Sowa *et al*., 2016).

Biochemically fructose, a versatile fruit and plant origin sugar, is metabolized via de novo pathway in hepatocytes (Azmi and Qureshi, 2016). The biochemical transporter for the absorption of dietary fructose is also different from other sugars with differential specificity and metabolic sensitivity from others (Gorana *et al.,* 2012). The specificity of transporter specially in case when high dietary fructose intake, leads to subsequent generation of molecules like Acetyl Co-A (Feinman and Fine, 2013), which serve as a potential anabolic precursor for the biochemical synthesis of lipogenic molecule like cholesterol and other metabolites (Patel *et al.,* 2013). These biochemical consequences may result in sequential establishment of obesity and gradual implication of insulin resistance (through post receptors disability), impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia and hypertension and others (Bocarsly *et al*., 2010). From last decade over-use or administration of fructose has been worked in the experimental establishment of diabetes and other dyslipidemic problems in animal models (Tabeshpour *et al*., 2017).

Usually antidiabetic remedies are potent α-glucosidase inhibitors responsible for delayed carbohydrate digestion in order to maintain blood sugar by reducing its hydrolysis. To avoid unpleasant side effects researchers worked to find out plant based glucosidase inhibitors that potentially equals to synthetic antidiabetic drugs with less side effects (Benhabyles *et al*., 2015). *Persea americana* (family Lauraceae), its fruits are commonly used all over the world as it is a rich source of carotenoids, minerals, vitamins, fatty acids and phenolic compounds (Ezuruike and Prieto, 2014; Dabas *et al*., 2013). Seeds and fruits extract of this plant also reported to have lipid-lowering, antihypertensive, hypoglycemic, weight reducing, antithrombosis, and cardioprotective effects in various animal models (Tabeshpour *et al*., 2017). *P. americana* seeds showed the presence of many beneficial phytoconstituents like triterpenes, fatty acids, flavonol, saponins, amino acids, polyphenols etc. (Hussain *et al*., 2016; Mahmoed and Rezq, 2013). In the beginning of 21st century combination of STZ (low dose) lipid diet and sugars like sucrose, fructose were used to develop type 2

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diabetic features specially glucose intolerance in animal models in a narrow time frame (Skovso, 2014; Reed *et al., 2000)* to better understand beta-cells related metabolic consequences (Wilson and Islam, 2012; Barriere *et al*., 2018). Therefore the purpose of this study was to investigate active phytochemical, antidiabetic activity of crude seeds powder of *Persea americana* (*CSPPa)* first and then its ameliorative biochemical effects in fructose-fed single low dose STZ-injected diabetic rat model receptors disability), impaired glucose tolerance, hyperinsulinemia, hypertriglyceridemia and hypertension and others (Bocarsly *et al*., 2010). From last decade over-use or administration of fructose has been work in the experimental establishment of diabetes and other dyslipidemic problems in animal models (Bocarsly *et al*., 2010). Usually antidiabetic remedies are potent α-glucosidase inhibitors responsible for delayed carbohydrate digestion in order to maintain blood sugar by reducing its hydrolysis. To avoid unpleasant side effects researchers working to find out plant based glucosidase inhibitors that potentially equals to synthetic antidiabetic drugs with less side effects (Benhabyles *et al*., 2015). *Persea americana* (family Lauraceae), its fruits are commonly used all over the world as it is a rich source of carotenoids, minerals, vitamins, fatty acids and phenolic compounds (Ezuruike and Prieto, 2014; Dabas *et al*., 2013). Seeds and fruits extract of this plant also reported to have lipid-lowering, antihypertensive, hypoglycemic, weight reducing, antithrombosis, and cardioprotective effects in various animal models (Tabeshpour *et al*., 2017). *P. americana* seeds showed the presence of many beneficial phytoconstituents like triterpenes, fatty acids, flavonol, saponins, amino acids, polyphenols etc. (Hussain *et al*., 2016; Mahmoed and Rezq, 2013). The purpose of this study was to investigate active phytochemical, antidiabetic activity of crude seeds powder of *Persea americana* (*CSPPa*) and its ameliorative biochemical effects in fructose-STZ induced diabetic rat model.

## MATERIALS AND METHODS

***Preparation of plant material***

The crude seeds of *Persea americana* were purchased from local market, identified by the taxonomist of Federal Urdu University of Arts Science and Technology (FUUAST). The seeds were washed and shade-dried for 3 to 4 weeks then grounded into powder with a help of blender and stored in refrigerator as crude seeds powder of *Persea americana* (*CSPPa*).

***In vitro investigation***

Qualitative phytochemical study was done by the methods described (Harborne, 1973; Kodongala *et al.,* 2010) included alkaloids, carbohydrates, glycosides, triterpinoids, steroids, flavonoids, phenols, saponin, gallotanin, phalobotanin, resins, anthraquinones etc. For Anti-diabetic activity alpha glucosidase enzyme assay was performed by the method of (Oki *et al*., 1999). *Persea americana* seeds powder activity was carried against α-Glucosidase from *Sacchromyces Cerevisiae.* Standard drug Acarbose was used as competitive drug.

***Animals***

Male albino wister rats (body weight of 150-180gm) were purchased from The Agha Khan University Hospital and kept in the separate cages. Animals were kept for a week before inception of study in laboratory and divided into diabetic and control groups according to fig. 1.

***Induction of Type 2 diabetes in rats via fructose- fed insulin resistance***

Rats in both control and diabetic group were given standard diet during the study. For the diabetic group rats were fed with 35% fructose in drinking water in fasting state daily (approx.4-5ml) for 6 weeks to develop insulin resistance gradually and their body weight and fasting blood glucose fbg was observed from their tail veins through glucometer on weekly basis (Mudassir and Qureshi, 2015). The diabetic rats then were given intraperitoneal injection of a single low dose of streptozotocin STZ (40mg/kg bw), that was set in 0.1M citrate phosphate (pH-6.3) before utilized (Barriere *et al*., 2018). The impaired fbg >190-250mg/dl (just after 72 hrs) was the criterion to start treatment. Therefore from diabetic group further division was made into diabetic test group where rats were treated with Crude Seed Powder of *Persea americana CSPPa* @ 500mg/kg and Positive control group in which Pioglitazone treatment @ 15mg Zolid was given to rats for 2 weeks. The fbg reading of rats in all groups was done daily till the last day of treatment (fig. 1). Finally rats in all groups were sacrificed to collect blood and serum for biochemical investigations.

***In-vivo biochemical investigation***

Glycated haemoglobin (HbA1c)

HbA1c (percentage value) was done by automatic clinical analyzer (Roche/Hitachi 902), Turbidimetric Inhibition Immunoassay.

***Lipid profile***

Enzymatic kits (Randox, United Kingdom) were used to perform serum TC, TG and HDL while LDL and VLDL were done by formulas (Azmi and Qureshi, 2012a)

LDL = TC - (TG) / 5 - HDL

VLDL = (TG) / 5

Coronary risk index (CRI) was also done by (Misra and Fridovich, 1972)

CRI = TC / HDL

FIRI = Fasting Insulin (μU/ml) × Fasting glucose (mg/dl) / 25

***Percent glycemic change (Pgc)***
It was done by scheming fasting blood glucose fbg mg/dL, *via* glucometer by pricking tail veins of experimental rats on first and last day (Perfumi and Tacconi, 1996) as below

$$Pgc = \frac{(Ffbg - Ifbg)}{Ffbg} \times 100$$

where, Ifbg = glucose (mg/dl) of day 1
Ffbg = glucose (mg/dl) of last day.

***Ethical approval***
The experimental work (Rats) was done with the approval of Ethical Review committee (ERC) of FUUAST, followed the laboratory guidelines for animal reseach.

## STATISTICAL ANALYSIS

Results are expressed as mean ± SEM (standard error mean) and considered significant at $p<0.05$ when data were examined by *one-way* ANOVA followed by LSD (least significant difference) test (SPSS version 18).

***Fasting insulin and insulin resistance index***
Serum fasting insulin level was done by automated analyser (Cobas e411) Electro-chemiluminescence immunoassay (Sapin *et al*., 2001) further the fasting insulin resistance index (FIRI) was done according to (Duncan, 1995).

## RESULTS

***Phytochemical analysis of CSPPa***
Qualitative analysis showed the presence of alkaloids, phenols, carbohydrates, glycosides, flavonoids, gallotanin, phalobotanin, triterpinoids and resins in *CSPPa* (table 1)

***Antidiabetic activity of CSPPa***
*CSPPa* showed extremely good activity with $IC_{50}$ 13.23±0.76µM, as compared to standard drug Acarbose with $IC_{50}$ value 840±2.76µM that showed the presence of some of the most potent anti-diabetic compounds

***Effect of CSPPa on percent glycemic change and biochemical parameters in fructose-fed STZ-injected diabetic rats***
*CSPPa* treatment showed a significant ($p< 0.01$) decline in the values of serum TC, TG, LDL and VLDL than diabetic and positive control groups (fig. 1). Serum levels of HDL-c was increased ($p<0.01$) significantly in *CSPPa* treated test group as compared to positive and diabetic control groups (fig. 1). CRI value in *CSPPa* treated group significantly ($p<0.01$) decreased i.e. 4.2 than diabetic and positive control groups that showed a noticeable rise up to 5.44 in the same ratio (fig. 2). *CSPPa* was also found effective in normalizing blood glycemia as test group showed significant reduction (upto -13%) in percent glycemic values ($p< 0.01$) as compared to positive and diabetic control groups (fig. 3). The significant reduction ($p< 0.01$) in the values of HbA1c, serum fasting insulin (fig. 4) and glucose (table 2) in *CSPPa* treated test group was also endorsed by FIRI values that showed a significant decrease ($p< 0.01$) from 150 to 28 in the same group as compared to positive and diabetic control groups (fig. 3). The serum levels of alanine aminotransferase (ALT), creatine Kinase (CK) and uric acid were significantly ($p<0.01$) decreased in test group as compared to diabetic and positive control groups. The serum total and direct bilirubin concentrations was found increased in diabetic control group whereas *CSPPa* treated test group showed a significant decrease ($p<0.01$) better than pioglitazone treatment in the same parameters (table 2).

**Table 1**: Phytochemical investigation of *CSPPa*

| Metabolites | *CSPPa* |
|---|---|
| Alkaloids | ++ |
| Phenols | ++ |
| Carbohydrates | ++ |
| Glycosides | + |
| Flavonoids | + |
| Saponin | - |
| Gallotanin | + |
| Phalobotanin | + |
| Triterpinoids | + |
| Steroids | - |
| Resins | + |
| Anthraquinones | - |

## DISCUSSION

The cellular stability of macromolecules can be affected

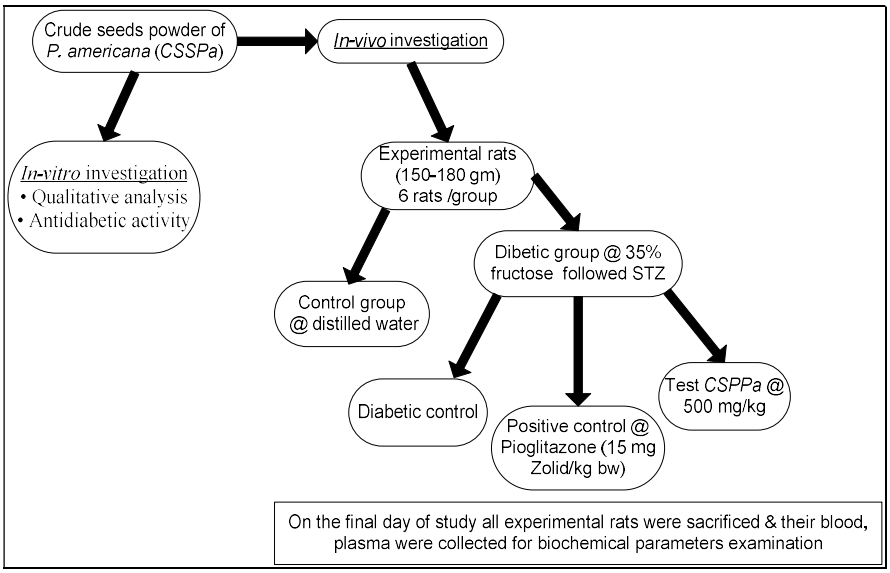
**Table 2**: Effect of *CSPPa* on Fbg & serum Total, Direct & Indirect Bilirubin in Fructose- STZ induced Type 2 Diabetic Rats

| | fbg(mg/dL) | Total Bilirubin | Direct Bilirubin | Indirect Bilirubin |
|---|---|---|---|---|
| C | 92±4.1 | 0.76±0.05 | 0.30±0.03 | 0.46±0.02 |
| PC | 131±8.7 | 0.90±0.09 | 0.47±0.12 | 0.43±0.005 |
| DC | 298±30.2 | 1.27±0.17 | 0.55±0.09 | 0.72±0.08 |
| *CSSPa* | 106±4.6 * | 0.66±0.11 * | 0.25±0.04 * | 0.41±0.07 |

Values are mean ± SEM (n=6). *$p<0.01$, when compared with Diabetic & Positive Control groups

by insulin resistance due to uneven glucose access (Henriksen *et al*., 2011). This alarmed metabolism given rise to postprandial hyperglycemia that is considered to be a first step of type 2 diabetes (H. Choudhury *et al*., 2018). Therapeutic stimulation prevents and managed metabolic risks but remain unsuccessful in restoring normoglycemia. Conventional folk medicines are considered to be a complimentary therapy in the form of herbal extracts to deal with diabetes and its related complications (Howard and White, 2013).The derivatives of several currently available treatments have been extracted from plant sources and provide an incomparable foundation of contemporary medicines (Ponnusamy *et al*., 2011). Polyhenols and antioxidants like thymoquinone and rutin (Razavi and Hosseinzadeh, 2014) have antidiabetic properties and found in many medicinal plants like *Cinnamomum cassia* (Anderson *et al.,* 2015)*, vitis vinifera* (grape), *allium sativum* (garlic), *crocus sativus* (saffron) (Akaberi and Hosseinzadeh, 2016; Hosseini and Hosseinzadeh, 2015; Hosseinzadeh and Nassiri-Asl, 2014). Natural plants are rich source of antioxidants against free radicals and its high consumption shields the degenerative mechanics by scavenging system (Tabeshpour *et al*., 2017).

The present work showed *CSPPa* treatment in fructose-fed STZ injected type 2 diabetic rats was effectively normalized all types of cholesterol levels including TC, TG, LDL, VLDL and HDL might be due to the presence of potential antioxidant in the form of phyto-constituents



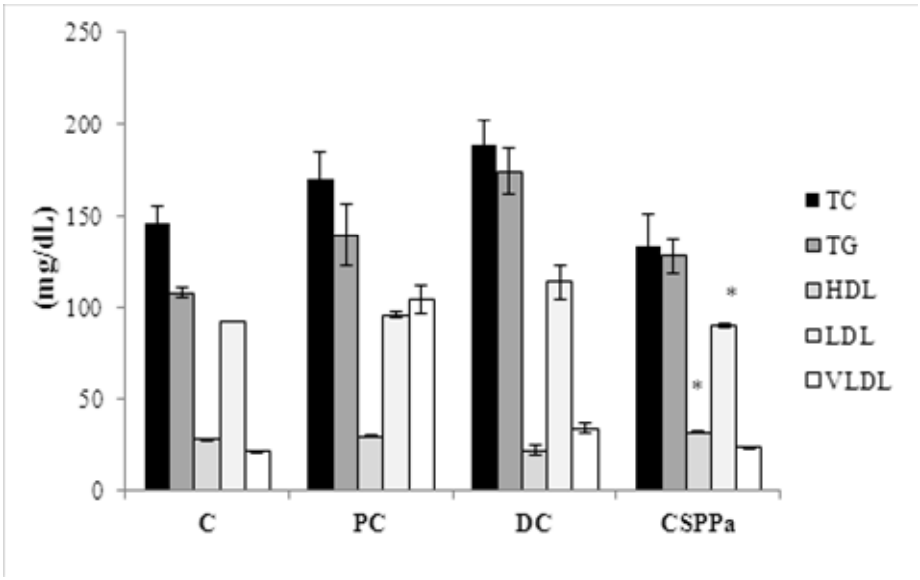




**Fig. 1**: Effect of *CSPPa* on Lipid Profile in Fructose- STZ induced Type 2 Diabetic Rats Values are mean ± SEM (n=6). **p*<0.01, when compared with Diabetic & Positive Control groups.

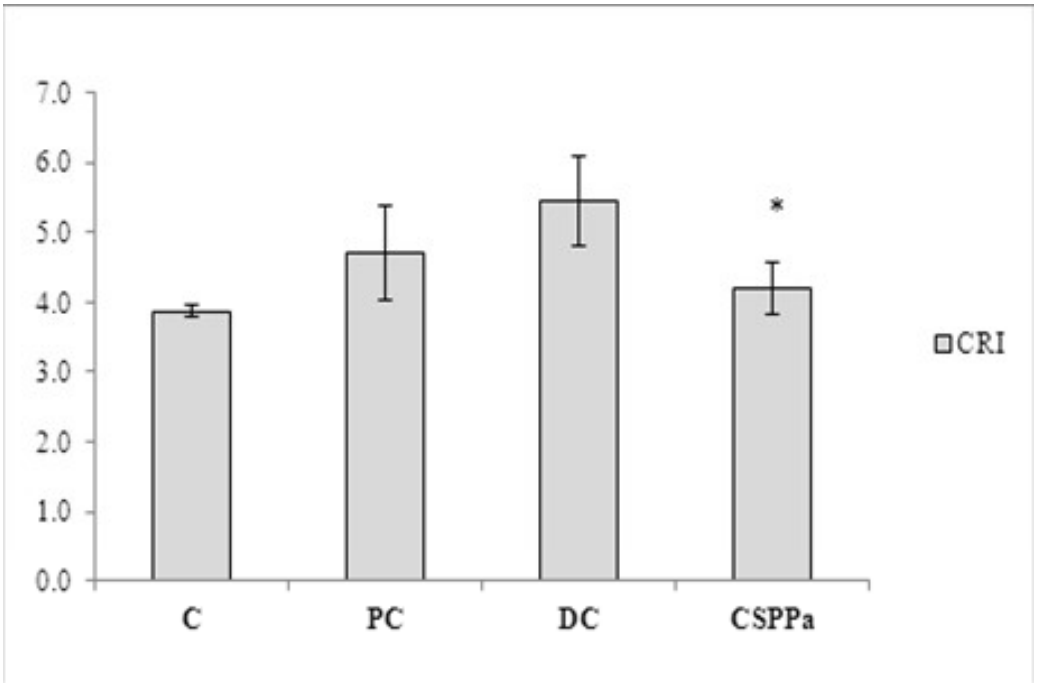



**Fig. 2**: Effect of *CSPPa* on Coronary risk index CRI values in Fructose- STZ induced Type 2 Diabetic Rats Values are mean ± SEM (n=6). *$p$<0.01, when compared with Diabetic & Positive Control groups

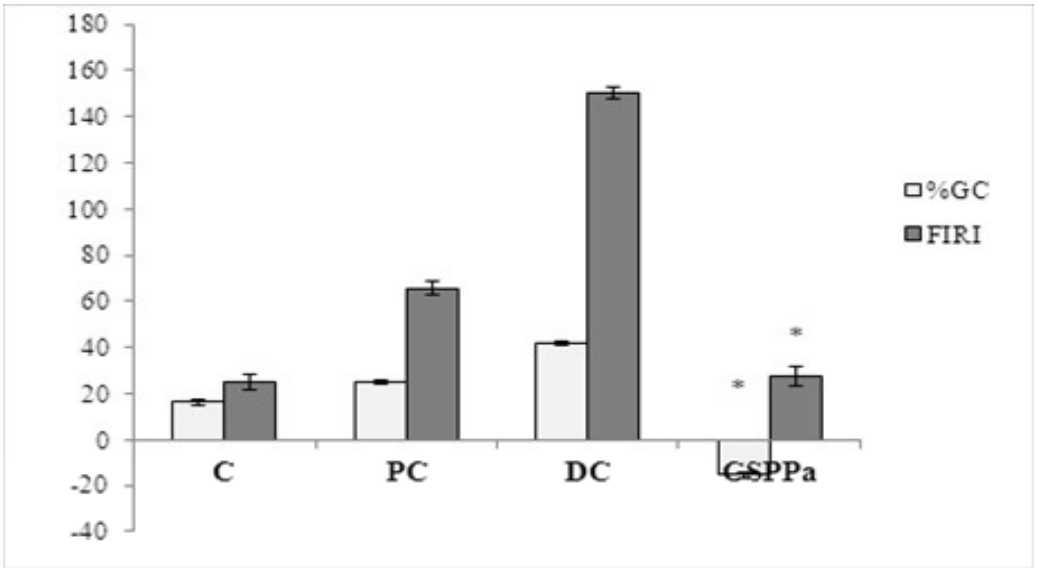



**Fig. 3**: Effect of *CSPPa* on Percent Glycemic Change & FIRI values in Fructose- STZ induced Type 2 Diabetic Rats Values are mean ± SEM (n=6). *$p$<0.01, when compared with Diabetic & Positive Control groups.

i.e. alkaloids, phenols, flavonoids, saponins carotenoids etc. (table 1) (Vinha *et al*., 2013 Adaramola *et al*., 2016; Oboh, 2014;). These results has been supported by coronary risk index (CRI) values in test group that provided a measuring tool to assess the risk of diabetic related atherosclerosis and CVD, which is the foremost reason of death in diabetes. *CSPPa* also brought improvement in fasting blood glucose levels in experimental rats (Tabeshpour *et al*., 2017) even better than pioglitazone treated positive control could be associated to the presence of polyphenols (Adaramola *et al*., 2016) that might involved to inhibit hexokinase activity and glycolysis (Sabate *et al*., 2015).

The relative amount of glucose in blood can be predicted in terms of HbA1c values (Farhan *et al*., 2012). *CSPPa* showed a highly potent *in-vitro* antidiabetic activity against α-glucosidase that supported the improved HbA1c

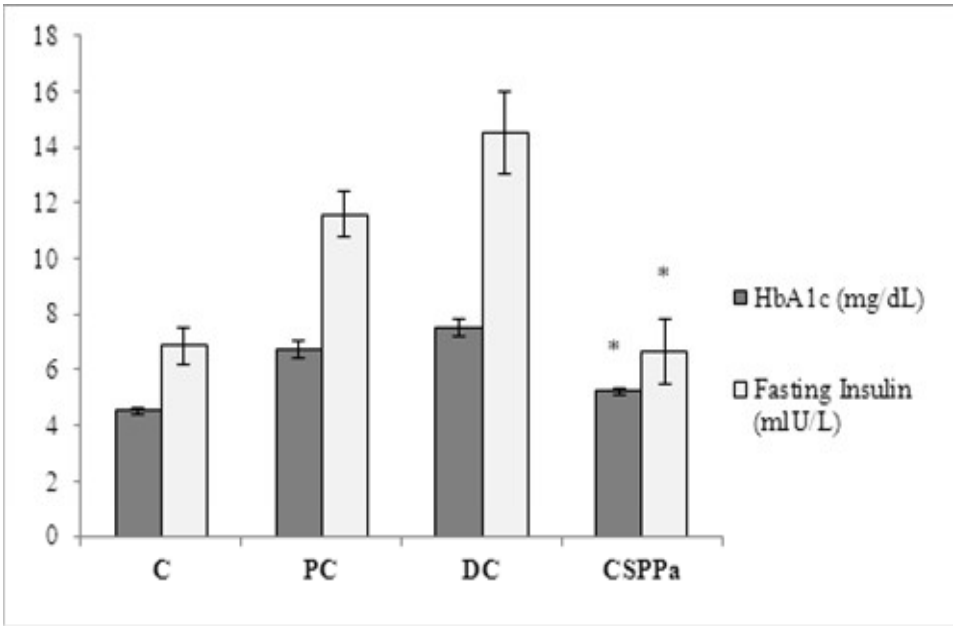



**Fig. 4**: Effect of *CSPPa* on HbA1c & Serum Fasting Insulin in Fructose- STZ induced Type 2 Diabetic Rats Values are mean ± SEM (n=6). **p*<0.01, when compared with Diabetic & Positive Control groups.

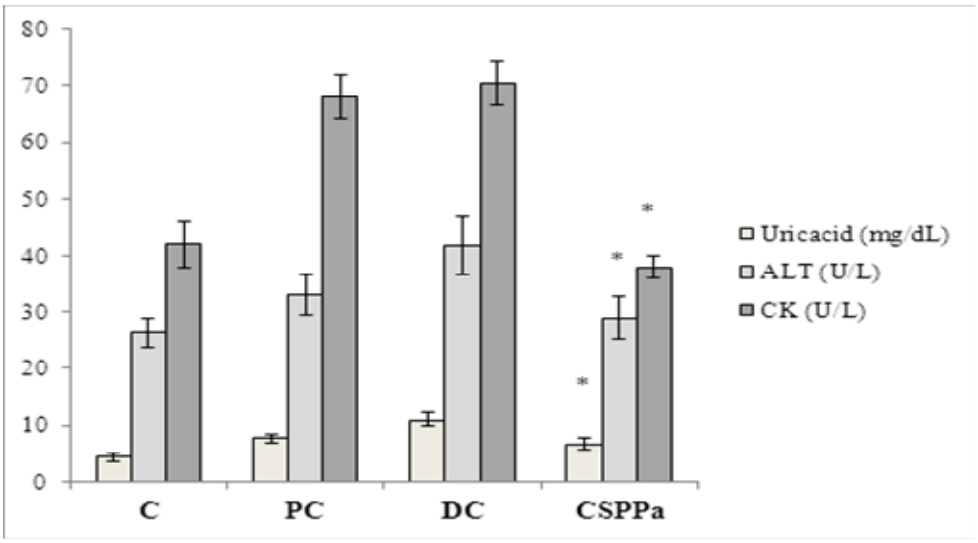



**Fig. 5**: Effect of *CSPPa* on Serum ALT, CK & Uric acid in Fructose- STZ induced Type 2 Diabetic Rats Values are mean ± SEM (n=6). **p*<0.01, when compared with Diabetic & Positive Control groups.

level in *CSPPa* treated diabetic rats far better than pioglitazone treated positive control. It showed potential hypoglycemic function of bioactive compounds of *CSPPa* that might be involved in delayed fructose absorption at intestinal level, while *CSPPa in-vitro* studies also confirmed the inhibitory effect on α- glucosidase enzyme many hundred times effectual ($IC_{50}$ 13.23±0.76µM) than acarbose (Thenmozhi *et al*., 2012) .

High serum insulin is the key feature of pancreatic beta cell deterioration normally seen in insulin resistance that was eminent in our present work. The revival of serum fasting insulin values in *CSPPa* treated diabetic rats indicated its better activity towards insulin secretary mechanism that also be seen by low FIRI ratio (Yang *et al*., 2016) (fig. 3) in the same group where as diabetic and pioglitazone treated positive control groups showed elevated values of this ratio.

The serum ALT levels reflect liver performance to identify any inflammation that caused enzymes leak into the blood and serum (Nasir *et al*., 2013). Inflamed

hepatocytes could be an aspect of type 2 diabetes (Ahsan *et al*., 2009) and was observed in current work in diabetic control rats showed elevated ALT values. On the contrary *CSPPa* treatment was found effective to normalize these values in test group (Thenmozhi *et al*., 2012; Elbadrawy and Shelbaya, 2013). In present study, the improved hepatocyte activityof *CSPPa* again showed by serum bilirubin values in the form of total and direct bilirubin in experimental diabetic rats (Pahua-Ramos *et al*., 2012) than pioglitazone that was ineffective in this regard. *CSPPa* also found defensive for CVDs (Tabeshpour *et al*., 2017), seen by improved serum CK levels in test group as compared to diabetic and positive control groups. Serum uric acid level in *CSPPa* treated test group showed notable decreased (Al-Dosari, 2011) than pioglitazone treated positive control group (fig. 5).

Overall the present study confirmed that *CSPPa* contained bioactive compounds that reflected by its antidiabetic, anti-triglyceridemic, anti-cholesterolemic, antioxidant activities in diabetic rats. Furthermore it restored serum ALT, CK and total bilirubin levels in type 2 diabetic rats.

## CONCLUSION

It is concluded that *CSPPa* of *P. americana* could be a strong hypoglycaemic mediator that showed bulk of bioactive compounds that might involved in the recovery of glycated Hb level, lipid profile along with liver and kidney functions in type 2 diabetic rats. To be inducted as novel ethno-medicinal and pharmaceutical formulations it would require to follow a line of investigations.

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