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SOME VEGETABLE PEEL EXTRACTS IN COMBINATION MAY PRODUCE SYNERGISTIC EFFECTS

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Abstract : The combined effect of peels of *Daucus carota* and *Ipoemia batatas*; *Cucurbita pepo* and *Cucumis sativus* as well as of *Lageneria siceraria* and *Solanum tuberosum* were studied for their protective effects in alloxan induced diabetic male mice (100 mg/ kg, i.p.). A comparison was made with the effects of individual peel extracts in previous studies. Alterations in serum glucose, insulin,T_3 and T_4 levels were studied as main parameters. Hepatic LPO, SOD and CAT were also studied to study the toxic effects if, any.

The combined effects of *C.pepo* and *C.sativus* at 500 mg/kg body wt. were more effective than when administered alone. Similarly, *L. siceraria* and *S. tuberosum* were also more effective in combination than individual peel administration at 100 and 500 mg/kg respectively. Our study therefore, suggests that *C. pepo* and *C. sativus* and *L. siceraria* along with *S. tuberosum* may be used in combination for better effects whereas *D. carota* and *I. batatas* were effective when used alone at 200 and 240 mg/kg respectively.

Key words: alloxan, lipid peroxidation , mice, vegatable peels

INTRODUCTION

Formulations of different plant extracts are very often prescribed in herbal medicines, believing that the herb extracts in combinations may prove to be more potent in comparison to single extract therapy. It is primarily because of the fact that combined therapies sometimes prove to be more effective than the single drug administration (Kim et al., 2004; Yadav et al., 2005; Gao and Hu, 2006; Panda et al., 2009,Akadiri et al 2013;Patience et al.,2022). However, it may not be true for all the diseases and for all the plant extracts. In fact, in some cases combined therapies have been found to be less effective or toxic (Ahmed and Sharma, 1997; Al-Yahyaa et al.; 2000; Sultana et al., 2008; Sushant Sud,2019).

In recent years some reports have been made on the effects of different herbal extracts in combination for regulating different disorders including diabetes mellitus, thyroid abnormalities and hepatotoxicity (Web et al.,1992; Ozaki et al., 1993; Dhawan and Goel,1994; Frisch et al.,1995; Bhattacharya et al.,1997; Panda and Kar,2000; Tahiliani and Kar, 2003; Yang et al.,2005; Jeong et al,2008; Panda and Kar,2009;Panda et al, 2009; Xiao-Quin Chu et al., 2018) . However, these are primarily based on mixture of multiple herbal extracts of leaf / bark/root/fruit/fruit peels. On vegetable peel extracts no report was available on their combined effects with respect to regulation of diabetes mellitus and thyroid dysfunctions.If any ,it is very less that too reviews are available but research work reports are meager

(Bhardwaj k et al.; 2022) Because of this paucity of literature / information in this specific area of research, an attempt was made to investigate the combined effects of some of the promising test peel extracts which were otherwise found to be effective in our earlier studies , where the peel extracts of *L. siceraria, C. pepo, C. sativus, S. tuberosum, I. batatas* and *D. carota* could potentially control the alloxaninduced diabetes mellitus in mice.

Materials and Methods:

Preparation of peel extracts:

Hundred grams of the dry powder of each peel was subjected to extraction with 400 ml of 50% ethanol (v/v) at room temperature (RT) for 24 h. The extract was filtered through Whatman filter paper No. 1 and was dried at 37°C to get a dry powder, which was dissolved in double-distilled water (DDW) to prepare a dose equivalent to required concentrations (Ghule et. al., 2006a).

Animals

Healthy colony bred Swiss albino male mice (*Mus musculas*) (30 ± 2 g) were maintained in polypropylene cages (43 x 27 x 25 cm with floor area of 165.85 cm^2 / animal). Seven animals were placed in each cage and were maintained under constant temperature (23 ± 2^0C) and photo- schedule (14h light: 10h dark). They were provided with commercial rodent feed comprised of protein, 20-22 %; oil, 3.5 %; crude fiber, 4 %; ash, 6 %; calcium, 1%; phosphorous, 0.5 %; lysine, 1.2 % and methionine, 0.9 % and metabolic energy 3000 K Cal (Gold Mohur feeds Ltd, New Delhi, India) *ad libitum* and had free access to drinking water. Standard ethical guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India and of Departmental Ethical Committee for Handling and Maintenance for Experimental Animals were followed.

Chemicals

Alloxan (2, 4, 5, 6-tetraoxypyrimidine), Tris, tricarboxylic acid (TCA) and thiobarbituric acid (TBA) were obtained from E. Merck, Mumbai, India; Pyrogallol, sodium dodecyl sulphate (SDS) were purchased from Loba Chemicals, Mumbai, India, while radioimmunoassay (RIA) kits for T_3 and T_4 were supplied by Bhabha Atomic Research Centre (BARC), Mumbai, India.

Preparation of diseased models

Induction of diabetes mellitus in male mice was done by exogenous administration of alloxan *intra peritoneal* (*i.p.*) at two doses of 100 mg / kg after prior overnight fasting (Szkudelski, 2001; Raskovic et al., 2004; Mendez and Hernandez Rde, 2005).

Experimental design

Three different experiments were conducted on combined effects of peel extracts in chemically induced diabetic animals.

Effects of *I. batatas* and *D. carota*

In this experiment thirty-five male mice were randomly divided into five groups of seven each. While, group I and II animals receiving vehicle (D.W.) only served as control, animals of groups III and IV were administered with 240 and 200 mg/kg of *I. batatas* and *D. carota* respectively. Group V animals received equivalent doses of both *I. batatas* and *D. carota* extracts. The administration of the peel extracts was continued for 15 consecutive days. On day 11 and 12 alloxan was also administered (i.p.) at the dose of 100 mg /kg/d along with the peel extracts in the animals of groups III, IV,V and VI, while that of group II received only equivalent amount of alloxan and served as diabetic control. On day 16, the experiment was terminated and different biochemical estimations were performed in serum and tissue samples.

Effects of *C. sativus* and *C. pepo.*

The experimental protocol followed here was similar to that of previous experiments except that two different peel extracts were considered. These were *C. sativus* and *C. pepo* and the dose considered was 500 mg / kg for both.

Effects of *L. siceraria* and *S. tuberosum*

Another experiment was conducted considering *L. siceraria* and *S. tuberosum* (100 and 500 mg/kg respectively) following the same protocol. The endparameters considered for all three experiments were serum glucose, insulin, T_3 and T_4 concentrations and hepatic LPO, SOD and CAT activities

Results

Alterations in serum glucose, insulin and thyroid hormones (Figs. 1, 3 & 5).

While addition of alloxan resulted in a significant increase in serum glucose concentration in all three experiments (P<0.001 for all), a decrease was observed in levels of insulin (P<0.01 in experiment 1; P<0.001 in experiment 2 & 3). There was also a decrease in thyroid hormone concentrations (P<0.01 for T_4 in experiment 2 ; P<0.001 for T_3 and T_4 both in experiment 1 & 3). On the other hand, addition of *D. carota* or *I. batatas* peel extracts resulted in reduction of

serum glucose concentrations significantly (*P*<0.01 in both cases).When *D. carota* +*I. batatas* were administered, also a significant reduction in glucose concentration was observed (*P*<0.05). However, when percent changes were calculated, more inhibition in glucose concentration was observed in case of *I. batatas* alone (52.17%, Table 1). Administration of *C. pepo* or *C. sativus* also resulted in a significant decrease in serum glucose concentration (*P*<0.001 in case of *C. pepo* or *C. sativus* while *P*<0.01 in case of *C. pepo* + *C. sativus*). Percent change was more in case of *C. pepo* (42.85 %). *L. siceraria* and *S. tuberosum* administration also reduced the same significantly (*P*<0.001) but % changes was more in case of *S. tuberosum* alone (59.06%).

Serum insulin level was significantly increased by *D. carota* (*P*<0.05) or *I. batatas* (*P*<0.01), while no alteration was observed when *D. carota* and *I. batatas* were administered together. However, increase was maximum in case of IB (181.53%). Level of insulin was also increased in case of *C. pepo* and *C. pepo* + *C. sativus* (*P*<0.001 for both) as well as in *C. sativus* (*P*<0.01). However, it was maximum in case of *C. pepo* + *C. sativus* (372.46%). Administration of LS or ST as well as *L. siceraria* + *S. tuberosum* could also increase insulin level (*P*<0.001), However percent increase was more in case of *L. siceraria* (452.91%).

An increase in the level of T_3 concentration was observed following the treatment of either *D. carota* or *I. batatas* (*P*<0.01) alone, while *D. carota and I. batatas* in combination could not alter the same. Similarly T_4 concentration was increased in case of IB only (*P*<0.05).T_3 concentration was also increased in case of *C. pepo* or *C. pepo* +*C. sativus* (*P*<0.001), but % increase was more in case of *C. pepo* +*C. sativus* treatment (149.21%).Increase inT_4 concentration was maximum in case of *C. pepo* +*C. sativus* (51.91%), (*P*<0.01 in *C. pepo* or *C. pepo* + *C. sativus*). Significant increase inT_4 and T_3 was also seen in case of *L. siceraria* or *S. tuberosum* and *L. siceraria* + *S. tuberosum* (*P*<0.001 for all). However, when percent changes were calculated increase in T_3 concentration was maximum in case of *S. tuberosum* (86.59%), while increase in T_4 was highest in case of *L. siceraria* +*S. tuberosum* (153.52%).

Alterations in hepatic LPO and endogenous antioxidants (Figs. 2, 4 & 6).

Following the alloxan administration , while a significant increase in hepatic LPO was observed (*P*<0.01 in experiment 1; *P*<0.001 in experiment 2 & 3) a decrease was found in SOD and CAT activity (*P*<0.001 for SOD in experiment 1 and 3, while *P*<0.05 in experiment 2 ; *P*<0.01 for CAT in experiment 1 ; *P*<0.001 in experiment 2 and 3). Administration of *I. batatas* or *D. carota* and *I. batatas* + *D. carota* decreased hepatic LPO significantly (*P*<0.01 for all).When percent decrease in LPO was considered it was more in case of *I. batatas* (79.51%). Also *C. pepo* or *C. sativus* and *C. pepo* +*C. sativus* peel extracts significantly decreased hepatic LPO (*P*<0.01; P<0.05; *P*<0.001 respectively). However, percent decrease was more in case of *C. pepo* +*C. sativus* (65.04%). Hepatic LPO was also reduced when *L. siceraria* or *S. tuberosum* and *L. siceraria* + *S. tuberosum* were administered (*P*<0.01 for all). However, percent decrease was maximum by *L. siceraria* + *S. tuberosum* (56.75%, Table 2). Peel extracts of *D. carota* or *I. batatas* and *D. carota* +*I. batatas* increased SOD activity (*P*<0.001 in case of *D. carota* or *I. batatas* & *P*<0.05 in case of *D. carota* +*I. batatas*).When percent changes were considered it was maximum in case of *I. batatas* (140%). Administration of *C. pepo* or *C. sativus* as well as *C. pepo* + *C. sativus* increased SOD activity significantly (*P*<0.001 for *C. pepo* or *C. sativus* ,while *P*<0.01 for *C. pepo* + *C. sativus* , while percent changes showed maximum effect of *C. sativus* (198.02%). Activity of SOD was also significantly increased by *S. tuberosum* and *L. siceraria* +*S. tuberosum* (*P*<0.01). However, percent increase was more in case of *S.tuberosum* (132.23 %).

A significant increase in CAT activity was also observed following the administration of *D. carota* or *I. batatas* and *D. carota* + *I. batatas* (*P*<0.001 for all). However, when relative percent changes were calculated it was more in case of *I. batatas* (93.13 %). Activity of CAT was also enhanced by *C. pepo* or *C. sativus* as well as by *C. pepo* + *C. sativus* (*P*<0.001 for *C. pepo* and *C. pepo* + *C. sativus*, while *P*<0.01 for *C. sativus*). Percent increase was maximum in case of *C. pepo* + *C. sativus* (144.46%). Similarly peel extracts of *L. siceraria* or *S. tuberosum* increased the CAT activity significantly either alone or together (*P*<0.001 for all) which was maximum in case of *S. tuberosum* (110.04%).

Discussion

Results of the present study revealed varied effects of different peel extracts with respect to different indices in alloxan induced hyperglycemic animals. While in some cases individual peel extract appeared to be more potent as compared to the simultaneous administration of two peel extracts, with respect to some other peels combined effects proved to be more pronounced.. On one hand administration of *D. carota* or *I. batatas* extracts decreased serum glucose concentrations in alloxan induced hyperglycemic animals,on the other hand insulin concentration was increased confirming their anti hyperglycemic nature, as observed in the earlier section. Even with respect to serum thyroid hormone concentrations these two peel extracts could reverse the alloxan induced changes at least with respect to one hormone, i.e.T_3. However, when both *D. carota* and *I. batatas* were administered together, alloxan induced alterations were clearly evident with

respect to glucose and insulin concentrations, but not on the status of thyroid hormones. When relative percent inhibition in serum glucose and stimulation in other 3 parameters were studied, *I. batatas* extract was found to bring the maximum ameliorating effects when given alone followed by*D. carota* extract, indicating clearly the better efficacy after single extract administration ofthese peels as compared to their combined therapy with *D. carota*. Nearly similar findings were obtained with respect *to L. siceraria* and *S. tuberosum* peel extracts, where also combined effects were not much better than the individual effects .While for glucose, T_3 and CAT, *S. tuberosum* alone appeared to be more effective, *L. siceraria* exhibited better positive effects with respect to serum insulin and hepatic SOD activity. However, decrease in LPO and increase in T_4 level were best exhibited by their combined effects.

From these observations it is now clear that cumulative effects of the peel extracts usually depend on the individual test peel used for the purpose. Since no study has been made till to

date on the combined effects of vegetable peel extracts, the present observations can be compared to the earlier findings made with fruit peel extracts (Parmar and Kar,2009) or herbal extracts in general (Tahiliani and Kar 2000; Panda et al.,2003), who also reported differential effects depending on the test materials.

Interestingly, with respect to the effects of *C. pepo* and *C. sativus* combined effects were found to be more pronounced than the individual peel extract in most of the indices. While *C. pepo* alone could maximally inhibit the alloxan induced alterations in glucose, *C. sativus* exhibited best positive effect only in SOD activity. However, when both the peels were administered together not only positive changes were observed with respect to all 4 indices, but also percent increases in the concentration of insulin, T_3 andT_4 as well as decreases in hepatic LPO were much higher as compared to the value of *C. pepo* or *C. sativus* alone clearly indicating a synergistic effect of two test plants. Present findings are some what unusual at least with respect to the extract of *I. batatas* which was found to be more effective even compared to its combined effects with *D. carota*. This is contrary to the common belief that plant extracts of similar nature exhibit synergistic effects when used in combination (Williamson, 2001).However, with respect to *C. pepo* and *C. sativus* as well as *S. tuberosum* and *L. siceraria* (with some indices) combined effects were enhanced/synergistic as normally expected. Therefore, it appears that *C. pepo* and *C. sativus* or *L. siceraria* and *S. tuberosum* if administered simultaneously may produce better ameliorating effects in hyperglycemic animals.

With respect to hepatic LPO andantioxidative enzymes (SOD and CAT), some whatsimilar observations were made in which *I. batatas* alone or *C. pepo* + *C sativus* which altered the peroxidative process and antioxidant enzymes markedly. However, unlike in the serum indices, on hepatic LPO, SOD and CAT maximum positive changes were observed with respect to *S. tuberosum* extract alone. Does it mean that from antiperoxidative point of view, S. *tuberosum* aloneis better than its combined effects with *L. siceraria* ?

Although single mechanism of action cannot be postulated for the mode of action of different peel extracts, it is speculated that the binding of some active components in *I. batatas* and *D. carota* might have inhibited the antioxidative enzymes bringing a better inhibition in net pharmacological efficacy of the individual peel extract. However, reverse mechanism may hold true for peel extracts of *C. pepo* and *C. sativus, L. siceraria* and *S. tuberosum*.

Whatever may be the mode of action (s) of each peel extracts, it can be emphasized that 2 peel extracts may not always produce synergistic effects when administered together or may also bring some negative effects ultimately exhibiting less efficacy. Of course, the combined efficacy of peel extract entirely depends on the type of extract used and probably the duration of the extract also. Obviously detailed investigation will be helpful before a formulation is suggested for therapeutic use.

Conflict of interest

The authors declare that there are noconflicts of interest.

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Table: 1

Relative percent of increase (+) or decrease (-) in serum glucose (GLU, mg / dl), insulin (INS,μIU/mlX10^{-1}), triiodothyronine (T_3, ng/mlX10^{-2}) and thyroxine (T_4, ng /ml) concentrations in alloxan induced diabetic animals following the administration of *D. carota* and *I. batatas* alone (Allx + DC or Allx + IB) or in combination (Allx +DC+IB);*C. pepo* and *C. sativus* alone (Allx + CP or Allx + CS) or in combination (Allx +CP + CS); *L. siceraria* or *S. tuberosum* alone (Allx + LS or Allx + ST) or in combination (Allx + LS + ST) in mice. NS; Non significant

PEELS	GlU	INS	T_3	T_4
Allx + DC	NS	+101.49	+51.94	+31.14
Allx + IB		-52.17+181.53	+67.53	+55.13
Allx + DC + IB		-44.46+62.06	NS	+16.95
Allx + CP		-42.85+80.43	+53.93	+47.65
Allx + CS		-31.95NS	NS	NS
Allx +CP +CS		-26.85+372.46	+149.21	+51.91
Allx + LS		-45.65+452.91	+15.46	NS
Allx+ ST		-59.06+324.45	+86.59	+137.42
Allx+ LS+ST		-44.36+342.42	+81.44	+153.52

Table: 2

Relative percent of increase (+) or decrease (-) in hepatic lipid peroxidation (LPO) ,superoxide dismutase (SOD) and catalase (CAT) activity in alloxan induced diabetic animals following the administration of peel extracts of of *D. carota* and *I. batatas* alone (Allx + DC or Allx + IB) or in combination (Allx +DC+IB); *C. pepo* and *C. sativus* alone (Allx + CP or Allx + CS) or in combination (Allx + CP + CS); *L. siceraria* or *S. tuberosum* alone (Allx + LS or Allx + ST) or in combination (Allx + LS + ST) in mice. NS ; Non significant

PEELS	LPO	SOD	CAT
Allx+ DC	-74.23	+117.86	+71.36
Allx + IB	-79.51	+140.00	+93.13
Allx + DC + IB	-77.01	+34.34	+68.63
Allx + CP	-41.89	+84.21	+119.31
Allx + CS	-35.28	+198.02	+141.78
Allx+ CP+CS	-65.04	+48.68	+144.46
Allx + LS	-50.96	NS	+87.38
Allx+ ST	-47.49	+132.23	+110.04
Allx+ LS+ST	-56.75	+106.87	-00.50

Legend to figures:

Fig. 1 Changes in the concentration of serum glucose (Glu ,mg /dl), insulin (Ins,μIU/mlX10^{-1}), triiodothyronine (T_3, ng /ml X 10^{-2}) and thyroxine (T_4, ηg / ml) concentrations in alloxan induced diabetic animals following the administration of *D. carota* and *I. batatas* alone (Allx + DC or Allx + IB) or in combination (Allx +DC+IB) in mice. Each bar represents the mean ± SEM (n=7). ^{x} *P<0.001*; ^{y}, *P<0.01* as compared to the respective control values and ^{b}, *P<0.01*; ^{c},*P<0.05* as compared to the respective values of alloxan induced diabetic mice.

Fig. 2 Changes in the lipid peroxidation (LPO, nM MDA formed / hr / mg of proteinX10^{-2}), superoxide dismutase activity (SOD, units/ mg proteinX10^{-1}), and the catalase activity (CAT, M of H_2O_2 decomposed / min / mg protein) in hepatic tissues in alloxan (Allx) induced diabetes following the administration of *D. carota* or *I. batatas* alone (All +DC or Allx +IB) or in combination (Allx +DC+IB) in mice. Each bar represents the mean ± SEM (n=7), ^{x}, *P<0.001* as compared to the respective control values and ^{a}, *P<0.001* and ^{b}, *P<0.01* as compared to the respective values of alloxan induced diabetic mice.

Fig. 3 Changes in the concentration of serum glucose (Glu ,mg /dl), insulin (Ins,μIU/mlX10^{-1}), triiodothyronine (T_3,ng /ml X 10^{-2}) and thyroxine (T_4, ng / ml) in alloxan induced diabetic animals following the administration of *C. pepo* and *C. sativus* alone (Allx + CP or Allx+ CS) or in combination (Allx + CP + CS) in mice. Each bar represents the mean ± SEM (n=7). [x] *P<0.001*; [y], *P<0.01* as compared to the respective control values and a *P<0.001* and b, *P<0.01* as compared to the respective values of alloxan induced diabetic mice.

Fig. 4 Changes in the lipid peroxidation (LPO, nM MDA formed / hr / mg of protein X10^{-2}), superoxide dismutase activity (SOD, units/mg protein X10^{-1}) and the catalase activity (CAT, □ M of H_2O_2 decomposed / min / mg protein) in hepatic tissues in alloxan (Allx) induced diabetes following the administration of *C. pepo* or *C. sativus* alone (All +CP or Allx +CS) or in combination (Allx +CP + CS) in mice. Each bar represents the mean ± SEM (n=7), x, *P<0.001* as compared to the respective control values and [a], *P*<0.001, [b], *P*<0.01 and [c], *P*<0.05 as compared to the respective values of alloxan induced diabetic mice.

Fig. 5 Changes in the concentration of serum glucose (Glu, mg / dl), insulin (Ins,μIU/mlX10^{-1}), triiodothyronine (T_3, ng /ml X 10^{-2}) and thyroxine (T_4,ng /ml)concentrations in alloxan induced diabetic animals following the administration of *L. siceraria* or *S. tuberosum* alone (Allx + LS or Allx + ST) or in combination (Allx + LS + ST) in mice. Each bar represents the mean ± SEM (n=7). [x] *P<0.001* as compared to the respective control values and [a] *P<0.001* and [b], *P<0.01* as compared to the respective values of alloxan induced diabetic mice.

Fig. 6 Changes in the lipid peroxidation (LPO, nM MDA formed / hr / mg of protein X10^{-2}), superoxide dismutase activity (SOD, units/ mg protein X10^{-1}), and the catalase activity (CAT, □ M of H_2O_2 decomposed / min / mg protein) in hepatic tissues in alloxan (Allx) induced diabetes following the administration of *L. siceraria* or *S. tuberosum* alone (All +LS or Allx + ST) or in combination (Allx +LS + ST) in mice. Each bar represents the mean ± SEM (n=7), x *P<0.001* as compared to the respective control values and a *P<0.001* and b, *P<0.01* as compared to the respective values of alloxan induced diabetic mice.

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Fig.1

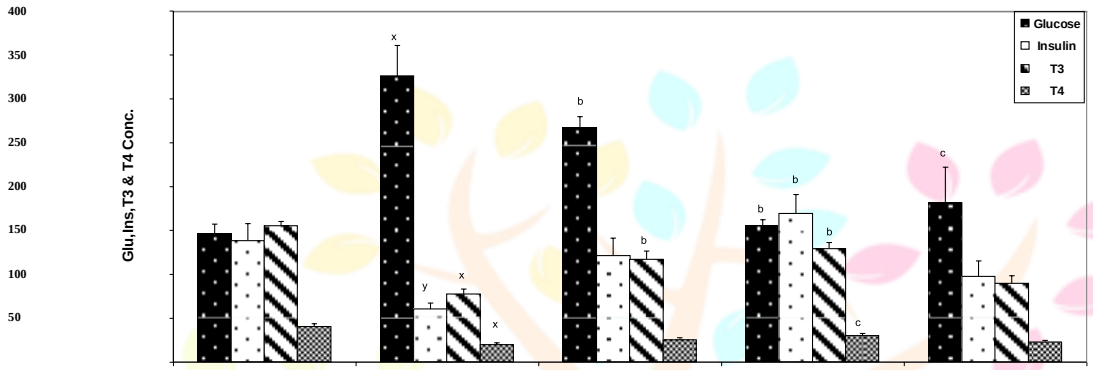

Fig.2

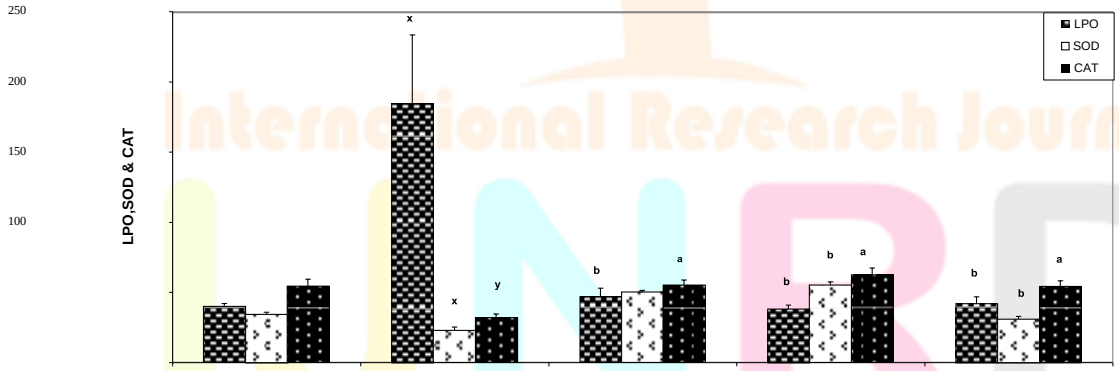

Fig.3

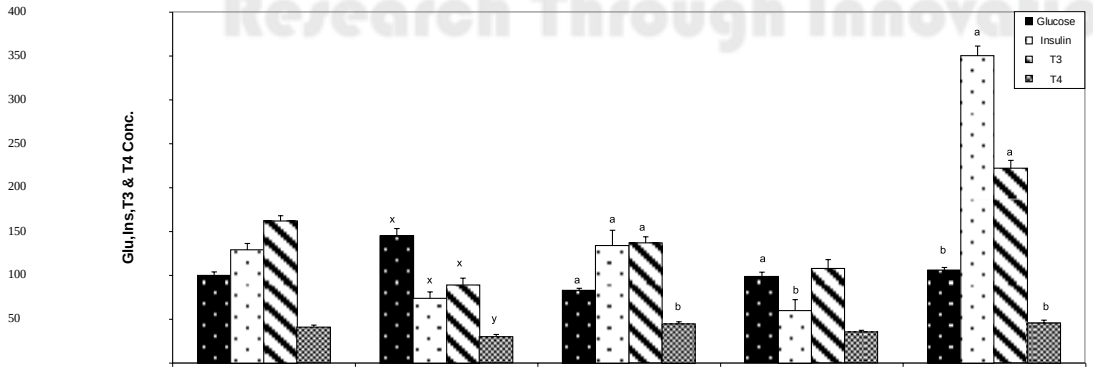

Fig.4

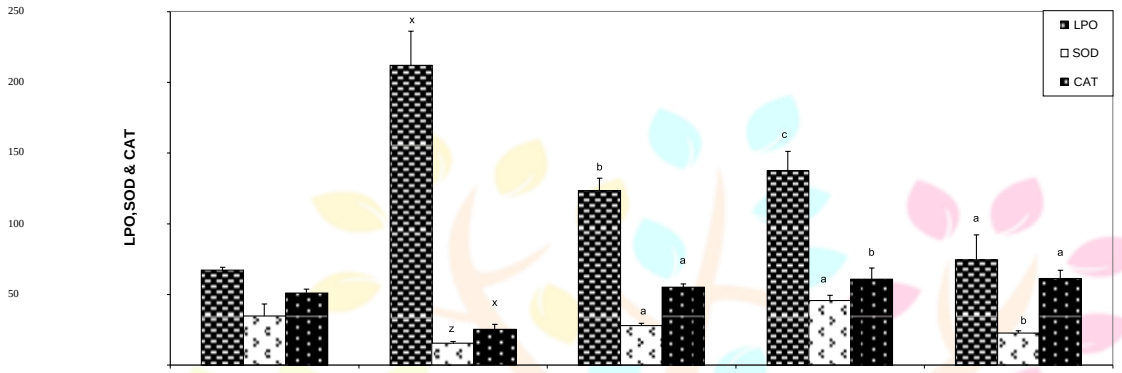

Fig.5

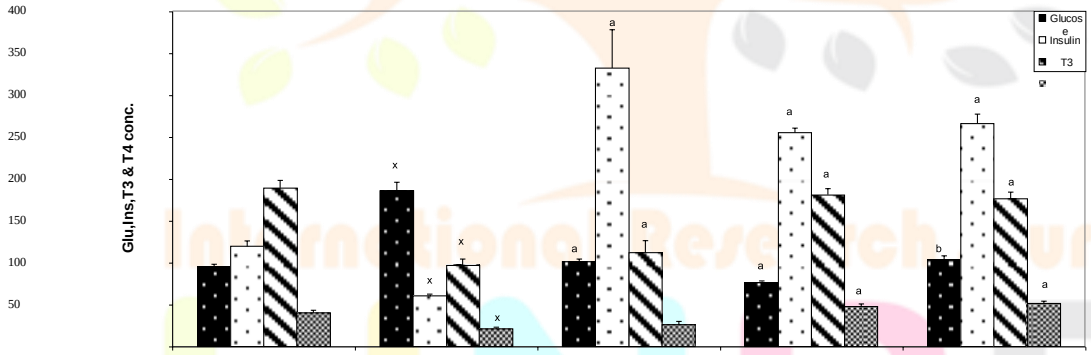

Fig.6