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Protective effect of *Aurelia aurita* against free radicals and streptozotocin-induced diabetes

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Abstract

The present work was carried out to identify the anti-oxidant and anti-diabetic activities of *Aurelia aurita*. The chemical profiling analysis showed that it possess different biologically active secondary metabolites like phenols, alakoids, steroids etc. The methanolic extract showed different free radical scavenging activity as ascorbic acid with IC_{50} values 202, 205, 153 µg on DPPH, hydroxyl and superoxide free radicals. The extract significantly reduced the hyperglycemic conditions with percentage of reduction 18.7 ± 1.3 to 53.5 ±1.5 of streptozotocin-induced animals and the positive result of *in-vitro* aldose reductase enzyme inhibition with IC_{50} value 163 µg suggests that *A. aurita* have potential to cure the diabetic complications.

Introduction

Natural products are the basic source for the development of therapeutics which has been using in treatment of human diseases since ancient times (Paterson and Anderson, 2005). From the last two centuries, there was tremendous progress in the science and technology and is helping in studies of different diseases' pathology and isolation, development of new drug molecules from natural products to treat the diseases (Newman and Cragg, 2007; Harvey, 2000; Henkel et al., 1999). The scientists are currently working on natural products mainly on terrestrial origins. But, there is ample sources are available in marine origins (Malve, 2016; Kong et al., 2010; Mayer et al., 2010; Jha and Zi-rong, 2004).

In our earlier studies, three marine algae *Chaetomorpha antennina*, *Gracilaria corticata* and *Ulva faciata* from Visakhapatnam coast (Battu et al., 2011) and uncommon moss, *Taxithelium napalense* broth from Bhitarkanika Island, India were found to have antibacterial, anti-oxidant and anti-diabetic activities (Tatipamula et al., 2017).

Aurelia aurita is a common jelly fish present all over the world and is a widely studied species. The species is feed on phytoplankton present in oceans, which are made up of different biologically secondary metabolites (Zoccarato et al., 2016). The earlier studies reports that, different phytoplankton possess more biologically active compounds and *A. aurita* also have different chemical compounds and it host for different microbial community in its body which are possess biologically active metabolites (Ahmed et al., 2017; Leone et al., 2013; Wright et al., 2003). So, the present work carried out on anti-diabetic activity of *A. aurita*.

Materials and Methods

Chemicals

Streptozotocin for diabetes induction was purchased from the Sigma-Aldrich, USA. Anti-diabetic drug metformin (Lupin, India) was purchased from the local market. The other chemicals, reagents used in current research were analytical grade.

Collection of jellyfish

The specimens of *A. aurita* were collected from the Rishikonda Beach, Visakhapatnam (17° 68′ latitude and 83° 21′ longitude), Andhra Pradesh, India in July, 2015. The collected specimens were identified based on the standard literature by Prof. E. Babu, Zoology Department, Andhra University, Visakhapatnam, Andhra Pradesh, India.

Preparation of extract

The collected material was preserved in methanol and kept at room temperature and dry place for 3 days. The material soaked in methanol was decant by using Whatman filter paper No. 1 and concentrated under pressure to obtain the crude methanol extract.

Chemical screening

The different qualitative chemical tests were performed to establish the chemical composition profile of *A. aurita* extract with various standard chemical tests (Trease and Evans, 2002; Rao, 2013).

Total phenolic content assessment

The phenolic content of the extract was assessed using standard procedure using Folin-Ciocalteau reagent in gallic acid equivalents as mg/g. The process is on light absorption measurement of the compounds present in the tested extract due to their reaction (color reduction) with tungsten and molybdenum oxides in Folin-Ciocalteau reagent (Rao, 2013; Singleton and Rossi, 1965).

Total alkaloid content assessment

The alkaloid content was assessed using bromocresol green solution as atropine equivalents. The assessment was carried out with the selected extract (1 mg/2N HCl mL) blended with 5 mL of phosphate buffer (0.1 mM), 5 mL of BCG. Then, alkaloid content was extracted with chloroform. The absorbance of color complex in chloroform was measured at 470 nm (Rao, 2013).

Free radical scavenging activity

Free radical scavenging activity was carried out on different free radicals like superoxide, hydroxyl and 2,2 -diphenyl-1-picrylhydrazyl (DPPH) free radicals by comparing with the standard drug ascorbic acid (Rao et al., 2013; Rao et al., 2012). The extract was dissolved in at different concentrations in dimethyl sulfoxide for the study and the experiment was repeated thrice, results showed in mean ± SEM. The percentage inhibition was calculated as $(Ao\text{-}A_1)/A_0 \times 100$.

Where, A_0 is the absorbance of control; A_1 is the absorbance with addition of extract/ascorbic acid

The 50% inhibition concentrations (IC_{50}) were calculated with each concentration of the extract/ascorbic acid was plotted taking concentration on X-axis and percentage inhibition on Y-axis.

Superoxide radical scavenging activity

Superoxide free radical scavenging activity was carried out using standard procedure, which depends on light induced superoxide generation by riboflavin and the corresponding reduction of nitroblue tetrazolium (Mc Cord et al., 1977; Rao et al., 2013; Rao et al., 2012).

Hydroxyl radical scavenging activity

Hydroxyl free radical scavenging activity was assessed by using standard procedure, which is mainly based on measurement of color intensity of tested extracts on reduction in production of hydroxyl radicals through iron-EDTA solution reaction with dimethyl sulfoxide, ascorbic acid by addition of cold trichloroacetic acid and Nash reagent (Klein et al., 1981).

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

The DPPH radical scavenging activity was measured, as color absorbance by tested extract comparing with ascorbic acid. Prior to the measurement, DPPH (0.004%) solution was prepared using ethanol and incubated for overnight in dark place. On next day, 3 mL of DPPH solution mixed vigorously with 100 µL of different concentrations of extract, then incubated for 30 min and then measured the absorbance at 517 nm against control (Braca et al., 2003; Murali et al., 2011).

Selection of animals

Healthy albino rats of single sex weighing between 180-250 g, 60-90 aged days were used for the study from Mahaveer Enterprises, Hyderabad, India. They were maintained on a 12 hours light/dark cycle. They were fed with regular grain chow (Rayans Biotechnologies Pvt. Ltd., India).

Toxicity studies

The albino rat of either sex, were selected into four groups of consisting of 6 animals. They were maintained for one week before the experiment, under room temperature and allowed free access to water and diet. The animals were subjected for acute toxicity study using *A. aurita* extract at doses 5, 50, 300, 2000 mg/kg body weight orally in four groups at regular intervals of time for 7 days. During this time, the animals were under observation to note the different conditions like skin changes, morbidity, aggressiveness, oral secretion, sensitivity to sound and pain, respiratory movement and finally their mortality.

Induction of diabetes induction (Tatipamula et al., 2017)

The animals were induced for diabetes with streptozotocin in normal saline (0.1 mol/L) after the overnight fasting. After three days of streptozotocin adminis-

tration, the blood glucose levels were measured using a glucometer for the blood collected through tail vein puncture (D'Orazio et al., 2005). The animals with blood glucose levels over the 200 mg/dL were considered as diabetic and used for further study.

Glucose response in normal rat to single dose of A. aurita extract

Normal rats were divided three groups (n=6): Group I treated as control (normal); Group II was treated with metformin (500 mg/kg body weight) and Group III was treated with methanolic extract of *A. aurita* (500 mg/kg body weight). After the overnight fasting, the control group fed with 10 mL/kg body weight of 1% carboxymethyl cellulose (vehicle) through orally using force-feeding needle; Group II and III were administrated with extract and drug orally. Blood samples were collected through tail vein puncture at 0 min and after 30 min of post drug and extract administration to measure the glucose levels at 0, 30, 60, 90 and 120 min (Nabi et al., 2013; Gupta et al., 2004).

Glucose tolerance test in normal and streptozotocin-induced diabetic animal

The rats were divided in five groups (n = 6): Group I to IV were normal rats and Group V was diabetic rats. Prior to the experiment, the fasting blood glucose levels were measured to all groups of rats (0 min), then Group II treated with 10 mL/kg body weight of 1% carboxymethyl cellulose (vehicle), Group III treated with metformin (500 mg/kg body weight), Group IV and V were treated with methanolic extract of *A. aurita* (500 mg/kg body weight) orally using force-feeding needle. All the groups were administrated with 2 g/kg body weight sugar orally except Group I (control/ normal) within 30 min of vehicle, metformin and methanolic extract of *A. aurita* administration. Then, the blood was collected through tail vein puncture and the glucose levels were measured at 60, 90 and 120 min time intervals using a glucometer (D'Orazio et al., 2005; Orhan et al., 2006; Pandhare et al., 2011).

Hypoglycemic activity

The rats were divided into five groups (n = 6); Group I was normal rats (control), Group II was diabetic rats (negative control) without any treatment, Group III was normal rats treated with 1 g/kg methanolic extract of *A. aurita*, Group IV was diabetic rats treated with metformin (500 mg/kg body weight) as positive control and Group V was diabetic rates treated with 1 g/kg methanolic extract of *A. aurita* treated daily for 7 days respectively. The fasting blood was collected on 0, 1st, 3rd, 5th and 7th days through tail vein puncture to estimate the blood glucose levels using a glucometer. During these days, the body weight of each group animals were estimated. On 7th day after glucose level estimation, the blood from each group animals was collected through retro-orbital plexus under anesthetic conditions (diethyl ether). The collected blood samples were used for the estimation of plasma total cholesterol, triglycerides, high density lipoprotein and low density lipoproteins, aspartate transaminase, alkaline phosphatase, alanine aminotranferase, creatinine, albumin, total protein levels using Span diagnostic kits on semi-auto analyzer. Finally, the rats were sacrificed. The kidneys and liver were separated and stored at -20°C and used for histopathological studies.

Aldose-reductase activity

Aldose reductase activity was determined for the methanolic extract of *A. aurita* (Patel and Mishra, 2009). Eyes from the normal rats were separated, washed with saline and transparent lenses free from diseases were pooled. The homogenate (10%) was prepared with 0.1M phosphate buffer (Saline, pH 7.4), then homogenate was centrifuged in a refrigerated centrifuge at 5,000 rpm for 10 min and then the supernatant was separated and kept in ice. The supernatant was used for the determination of aldose reductase activity. The process simply, for 0.1 mL lens supernatant was added to 0.7 mL phosphate buffer (0.067M), 0.1 mL NADPH (25×10^{-5} M), 0.1 mL of DL-glyceraldehyde (substrate at 5×10^{-4} M) except reference and then finally the solution was made up to 1 mL. When the substrate was added, the enzymatic reaction started and absorbance was recorded for every 30 sec interval up to 3 min at 340 nm. In the similar way, different concentrations 25, 50, 100, 200 and 400 µg/mL prepared with phosphate buffer saline used for aldose reductase activity. The negative control was prepared with phosphate buffer saline. Percentage inhibition for different concentrations were measured using the formula:

%Inhibition = ΔAbs (Negative control) - ΔAbs (Extract)/ΔAbs (Negative control)

IC_{50} value for the extract was by plotting graph dose concentration versus percentage inhibition

Statistical analysis

The results were expressed in mean ± SEM and compared with control group using two-way ANOVA and followed by Dunnett's test. The p value <0.05 were considered as significant.

Results

Chemical analysis

The chemical analysis of *A. aurita* methanolic extract showed the presence of alkaloids, carboxilic acids, phenols, proteins, amino acids, saponins, steroids, terpenoids and absence of carbohydrates, coumarins, flavonoids, glycosides, quinones, and tannins (Table I). Based on chemical analysis, the total alkaloid and

Table I

Chemical analysis of *Aurelia aurita* methanolic extract

SL. No	Name of chemical tests	Inference
1	Alkaloids	+
2	Carbohydrates	-
3	Carboxylic acids	+
4	Coumarins	-
5	Flavanoids	-
6	Glycosides	-
7	Phenol compounds	+
8	Proteins and amino acids	+
9	Quinones	-
10	Saponins	+
11	Steroids	+
12	Tannins	-
13	Terpenoids	+

(+) = Presence; (-) = Absence

phenolic contents were assayed for the extract. The amount of phenol compounds and alkaloids were 5.8 ± 0.5 mg/g and 4.4 ± 0.7 mg/g respectively.

Free radical scavenging activity

The methanol extract of *A. aurita* showed the concentration-dependent scavenging activity, concentration along with ascorbic acid and the activity was directly proportional (Figure 1). The extract showed more activity at 400/100 µL concentration. The IC_{50} values for methanol extract of *A. aurita* and ascorbic acid on DPPH, hydroxyl and superoxide free radicals were 202, 278, 205, 110, 153 and 130 µg. The extract showed better activity on DPPH and superoxide free radicals.

Toxicity studies

The toxicity studies were carried out on rats at different concentrations of *A. aurita* methanolic extract. There was no abnormalities and the mortality were observed at tested doses even at 2,000 mg/kg. Then, further study was continued on the anti-diabetic activity.

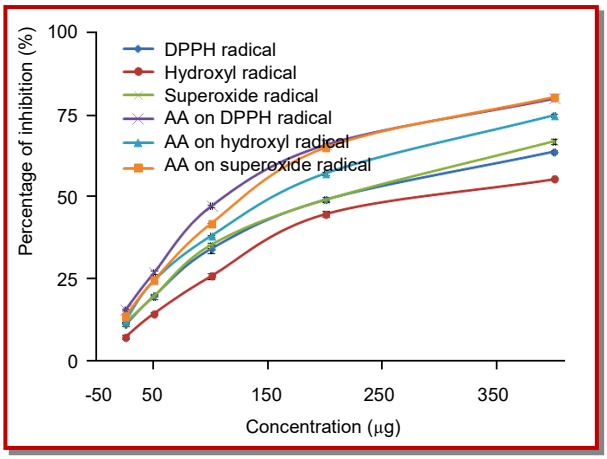

Figure 1: Effect *A. aurita* extract (single dose) on free radical scavenging activity

Glucose response in normal rat to single dose of A. aurita extract

In all groups, blood glucose levels were normal at 0 and 30 min but at 60 min blood glucose levels were increased because of glucose dosage. In the extract- and metformin-treated groups, blood glucose levels were decreased at 90 and 120 min compared to normal rats (Group I).

Glucose tolerance test in normal and STZ-induced diabetic animals

The single dose effect of methanolic extract on normal and diabetic rats were estimated. The blood sugar levels were raised in each group except in diabetic group (Group V), may be because the group animals were already diabetic and there was no significant effect of glucose administration. But, at 90 and 120 min blood

Table II

Effect of methanolic extract of *A. aurita* on blood glucose level in different days of experiment

Day	Control (Group I)	Untreated diabetic (Group II)	Normal rats treated with extract (Group III)	Diabetic rats treated with metformin (Group IV)	Diabetic rats treated with extract (Group V)
0	91.2 ± 1.5	255.0 ± 1.3	89.7 ± 1.6	247.5 ± 3.5	254.5 ± 1.3
1	91.5 ± 1.6	237.7 ± 1.3	90.8 ± 0.8	232.0 ± 1.1	234.2 ± 1.6
3	90.2 ± 1.7	235.0 ± 2.2	89.5 ± 0.4 (61.9 ± 0.4)[a]	182.5 ± 1.8 (22.3 ± 1.2)[a]	190.8 ± 1.3 (18.7 ± 1.3)[a]
5	90.2 ± 1.5	240. 2 ± 3.0	87.3 ± 1.7 (63.6 ± 0.8)[a]	131.0 ± 2.4 (45.5 ± 0.6)[a]	153.0 ± 1.7 (36.2 ± 1.2)[a]
7	89.8 ± 1.9	241.2 ± 2.3	86.0 ± 1.9 (64.3 ± 1.0)[b]	100.3 ± 1.4 (58.4 ± 0.5)[a]	112.0 ± 2.9 (53.5 ± 1.5)[b]

Data were mean ± SEM and [a]p<0.05, [b]p<0.01, [c]p<0.001

Table III

Effect of methanolic extract of *A. aurita* on different plasma parameters

Name of the plasma parameter	Control (Group I)	Untreated diabetic (Group II)	Normal rats treated with extract (Group III)	Diabetic rats treated with metformin (Group IV)	Diabetic rats treated with extract (Group V)
AST (IU/L)	46 ± 0.2	103 ± 0.6	48 ± 1.3	50 ± 0.8	62 ± 0.7
ALT (IU/L)	22 ± 0.0	83 ± 0.1	26 ± 0.5	24 ± 0.4	51 ± 1.3
ALP (IU/L)	60 ± 0.1	185 ± 1.7	66 ± 0.7	57 ± 0.4	72 ± 1.5
Creatinine (mg/dL)	0.6 ± 0.0	1.8 ± 0.0	0.7 ± 0.8	0.6 ± 0.3	0.7 ± 0.3
Albumin (g/dL)	4.2 ± 0.9	2.4 ± 0.7	4 ± 0.2	4 ± 0.3	3.8 ± 0.1
Total protein (g/dL)	6 ± 0.4	3.5 ± 0.3	6 ± 0.3	6.2 ± 0.1	5.4 ± 0.3
Total cholesterol (mg/dL)	60 ± 1.2	150 ± 0.9	73 ± 0.8	70 ± 1.7	85 ± 0.5
Triglycerides (mg/dL)	42 ± 0.9	175 ± 1.3	50 ± 1.4	45 ± 0.6	63 ± 0.3
LDL (mg/dL)	30 ± 0.3	138 ± 0.2	36 ± 0.7	35 ± 1.3	47 ± 0.5
HDL (mg/dL)	64 ± 0.2	35 ± 0.4	58 ± 0.3	60 ± 0.9	56 ± 1.3

Data were mean ± SEM

glucose levels measurement showed the decline in blood glucose levels. Group I (normal rats), Group II (treated with vehicle) showed equal response. Group IV almost showed same response as Group I and Group II at 120 min measurement. The Group V rats showed decline in the blood glucose levels from 0 to 120 min but at 120 min it was little bit higher than the other groups.

Hypoglycemic activity

Anti-diabetic activity of the methanolic extract of *A. aurita* studied through different ways on normal and diabetic rats. Finally, hypoglycemic activity was studied for 7 days on streptozotocin-induced diabetic animals, the variations in blood glucose levels were observed in different groups (Table II). The blood glucose levels in Group II animals were high, in Groups IV and V were very high as Group II animals but during and end of the study blood glucose levels were gradually decreased because Group IV was treated with standard drug metformin and Group V was treated with methanolic extract of *A. aurita*. The percentage of reduction in blood glucose levels of Group III animals were constant, that indicate while normal rats treated with extract didn't show any alteration in blood glucose levels but diabetic animals treated with metformin and methanolic extract of *A. aurita* showed gradual increase in percentage of reduction in blood glucose levels from day 3 to day 7, i.e. 22.3 ± 1.2 to 58.4 ± 0.5 in group IV, 18.7 ± 1.3 to 53.5 ± 1.5 in Group V, at the end almost the blood glucose levels became normal. At the same time the body weights of different groups were recorded. The body weight of normal rats were increased and diabetic rats losses weight because of no treatment, but the animals treated with extract and metformin lost some weight up to day 3, then gradually recovered from loss of weight (data not shown).

The methanolic extract of *A. aurita* was restored the altered different plasma parameters like TC, TG, HDL, LDL, AST, ALP, ALT, creatinine, albumin, total protein (Table III). The plasma parameters were normal conditions in group I and III, but in Group IV and V the parameters were tiny high compared to them, this may indicate if the treatment can prolong parameters can be normal as Group I.

The effect of methanolic extract of *A. aurita* was assessed with aldose reductase enzyme using DL-glyceraldehyde as substrate and quercetin as standard drug (Figure 2). The extract showed dose-dependent inhibitory activity on aldose reductase enzyme. The extract showed the inhibitory activity almost along with quercetin. The IC_{50} values for methanolic extract of *A. aurita* and quercetin were found to be 163 and 212 µg respectively.

The histopathological studies of liver and pancreas showed the differences in structural variations in normal, untreated diabetic and diabetic treated with metformin and methanolic extract of *A. aurita* (Figure 3). There were a surge was observed in size and nuclei of hepatocytes and large vacuoles were also observed in diabetic rats, the reduction of hepatocytes may be due to the oxidation of cell membrane because of free radicals, it leads to reduced cytosol/nuclei ratio. These leads to cellular necrosis and alteration of liver biomarker enzymes. But, these characteristics were less or normal in normal, metformin-treated and *A. aurita* extract treated groups, may be because the extract of *A. aurita* showed potent antioxidant activity on free radicals and successfully restored the altered biomarker enzyme' levels due to diabetes (Figure 3).

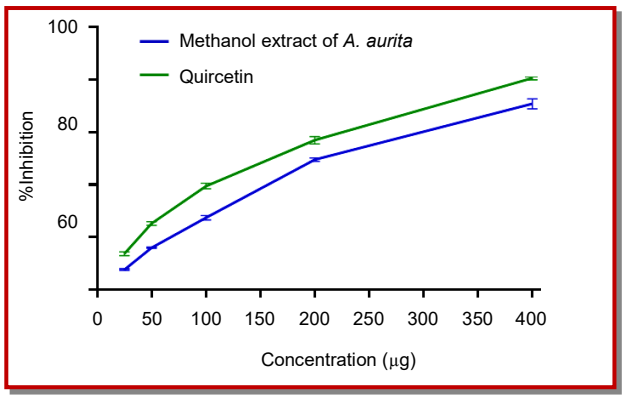

Figure 2: Effect of *A. aurita* extract on percentage inhibition of aldose reductase

Discussion

The present work carried out and identified the presence of different biological active compounds like alkaloids, phenolics, saponins, steroids etc. (Fernando et al., 2016; Farvin and Jacobsen, 2013; Yao et al., 2012; Guven et al., 2010) on chemical profile analysis of methanolic extract of *A. aurita*. Based on chemical profiling, the extract of *A. aurita* was evaluated for its anti-oxidant and anti-diabetic activity. The tested extract showed dose-dependent free radicals scavenging activity and results were comparable with standard drug ascorbic acid. The generation of free radicals will occur through different biological metabolisms. The free radical were unstable ions and like be pair with other atoms, in this process they react with stable atoms and destabilizes it and then again forms a new free radical (Bedwell et al., 1989; Cohen, 1977). The formation of free radical in the body is an chain reaction, then that process they effect the cellular metabolisms and damages to cell membranes (Lipids) and finally leads to diseases (Stadtman and Levine, 2000; Marnett, 2000). The tested extract showed the more activity against superoxide free radical, which is most generate free radical and precursor for different free radicals like hydroperoxyl and hydroxyl radicals (McCord et al., 1977; Bielski and Cabelli, 1996).

The extract treated normal and diabetic animals showed good tolerance against glucose over dose and extract showed good anti-diabetic activity against streptozotocin-induced diabetic rats. Diabetes is a chronic disease, increases the blood glucose levels due to the insufficient production of insulin or decrease in

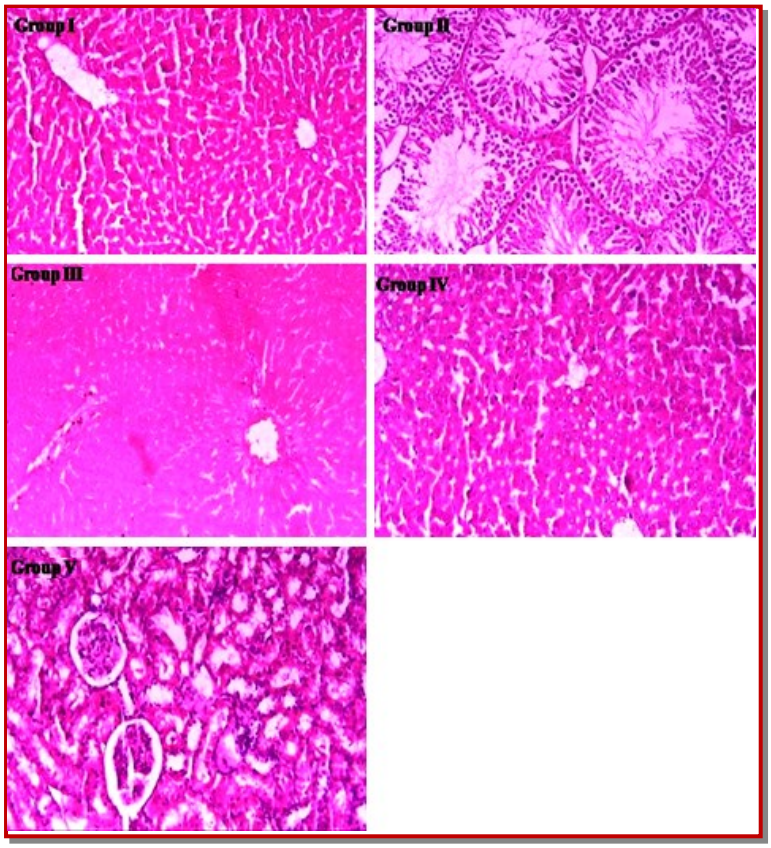

Figure 3: Histopathological changes of different groups' liver tissue in STZ-induced anti-diabetic activity. Group I- Control (Normal rats); Group II-Untreated diabetic; Group III- Normal rats treated with extract; Group IV-Diabetic rats treated with metformin; Group V-Diabetic rats treated with extract

response of body cells to insulin i.e. insulin is main transporter for the digested energy food (glucose) from blood to cells. The glucose is energy source for cells, inadequate and decrease in response of cells to insulin leads to hyperglycemia in blood and on long term conditions leads to different complications (Papatheodorou et al., 2016) to the body and finally leads to death. In the present study, STZ-induced diabetic rats showed the high blood glucose levels, variations in different plasma parameters like AST, ALT, ALP, creatinin, albumin, total protein, total cholesterol, triglycerides, LDL and HDL and the histopathological studies of pancreas and liver showed inflammation and structural variation (Yeom et al., 2016; Zadhoush et al., 2015; Association, 2010). The structural and functional changes in the liver and pancreas may leads to over production of different free radicals and may cause failure of different organs due to oxidative stress and further complications (Talluri et al., 2016; Ajuwon et al., 2014; Schuppan and Kim, 2013; Zamin Jr et al., 2002). But, the metformin and methanolic extract of *A. aurita* treated animals showed good recovery from the raised blood glucose levels, altered plasma parameters and structural restoration of the liver and pancreas. The *in vitro* aldose reductase activity of tested extract showed good inhibition of aldose reductase enzyme, aldose reductase is an enzyme mainly present in eyes, works on formation of fructose under normal glycemic conditions, but at hyperglycemic conditions glucose flux will occur through polyol pathway leads to glaucoma, cataracts, diabetic retinopathy (Cheng and González, 1986). The current study results provide the significant contribution to the recent research and development studies in identification of new biologically active compounds from different sources. In recent times, there were many reports about presence of biologically active compounds from terrestrial medicinal plants (Altemimi et al., 2017; Wilson and Brimble, 2009) and marine sources like algae and others (Malve, 2016; Kong et al., 2010; Jha and Zi-rong, 2004) on different chronic and acute diseases and their complications. The further studies could be worth for bio guided isolation of active metabolites from *A. aurita* and different marine sources.

Conclusion

A. aurita showed the presence of different biological active compounds like alkaloids, phenolics, saponins, steroids etc in it and significantly make well the streptozotocin-induced diabetes rats and showed free radical scavenging activity. The active metabolite in *A. aurita* may be individually or synergistically showed the activities, further research will be needed to know the individual active metabolites or combinational.

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Ethical Issue

The acute toxicity study was conducted for extract of *A. aurita* as per Organization for Economic Co-operation and Development (OECD) guidelines (OECD, 2001) and regulations of the Institutional Animal Ethics Committee.

Conflict of Interest

Authors declare no conflict of interest

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