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ANTIHYPERCHOLESTROLEMIC POTENTIAL OF OMEGA-3-FATTY ACID CONCENTRATE IN ALLOXAN INDUCED DIABETIC RODENT

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ABSTRACT: Exhaustive study of scientific literature provides the initial evidence that omega-3-fatty acids the principal component of fish oil is responsible for exerting important biological effects when administered to population at risk of coronary heart diseases and diabetes mellitus. The main reason behind the study was to evaluate the anti-atherogenic properties of marine lipids in alloxan induced diabetic mice. Furthermore the current analysis endeavours to scrutinize the Hypoglycemic effects of the natural omega-3-fatty acids. Mice were made diabetic by a single intraperitoneal (I.P.) injection of alloxan monohydrate 150 mg/kg. Treatment with appropriate dose of omega-3-fatty acid concentrate started 7days after alloxan injection. At the end of the selected period of study the blood glucose level, and lipid profile was evaluated and the data obtained was compared with normal control and positive control. All the data were subjected to due statistical evaluation. The omega-3-fatty acid treatment led to a significant dose dependent decline in the blood glucose content ($P<0.05$), along with crucial reduction in the lipid profile in alloxan induced diabetic mice. Also an improvement was observed in clotting time in the mice fed on the bioactive extract compared to the control mice.
Preliminary studies suggest that omega-3-fatty acid concentrate demonstrates potential hypoglycaemic and hypolipidemic efficacy in alloxan induced diabetic rodent model.

INTRODUCTION: Epidemiological studies ranks diabetes mellitus (DM) among the leading etiological concerns currently plaguing human Populace. According to WHO reports, more than 176 million patients suffer worldwide from the disease and it is estimated that in 2025, there will be about 300 million patients living with this condition [1]**.** Medical dictionary defines diabetes mellitus (DM) as a chronic medical condition, hallmarked with cardinal symptoms viz hyperglycemias, glucosuria, dehydration, polydipsia and polyphagia.

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Chronic hyperglycemias of DM is associated with long-term damage, dysfunction and organ failure as particularly eyes, kidneys, nerves, heart and blood vessels [2]. Sustained hyperglycemias leads to oxidative stress, alterations in enzyme activity, protein glycosylation and several structural changes [3]. Patients with diabetes are prone to develop infections of the bladder, skin, and vaginal areas. Fluctuations in blood glucose levels can lead to blurred vision also constantly elevated glucose levels can lead to lethargy and coma. Also increased incidence of coronary heart diseases especially atherosclerosis is observed in subjects tormented with DM, a fact widely attributed to lipoprotein abnormality associated with the disease.

Insulin is a potent lipolytic agent. DM renders adipocytes dysfunctional owing to insulin

resistance consequently restricting the release of free fatty acids into the plasma. This results in increased circulating free fatty acid content triggering cascade of events promoting enhanced production of low density lipoprotein moieties with atherogenic potential. Also the dysfunctional adipocytes further release inflammatory cytokines like tissue necrosis factor, interleukin-6 and pro-coagulation PAI-1. Hence chronic inflammation, coagulation abnormalities are associated with and envisage alliance between cardiovascular disorders and diabetes mellitus. Thus from clinical standpoint it has been verified that management of lipid profile causes significant reduction in the occurrence of micro vascular disease and associated mortality in patients agonized with DM [4]. Management of DM with synthetic hypoglycaemic agents is limited owing to the wide array of side effects ranging from untoward weight gain to hepatic and renal insufficiency associated with their use. Popular hypolipidemic, anticoagulants and anti inflammatory agents sloshes through the entire system and still can miss their mark [5]. Therefore the quest for safer and potent hypoglycaemic and hypolipidemic is extensively dwelled upon.

Omega-3 (ω-3) or n-3 fatty acids are class of essential polyunsaturated fatty acids with a C=C double bond at the third carbon atom. Most popular n-fatty acids include eicosapentaenoic acid (EPA, 20 carbons and 5 double bonds), docosahexaenoic acid (DHA, 22 carbons and 6 double bonds) and α-linolenic acid (ALA, 18 carbons and 3 double bonds) [6]. The most widely available dietary source of EPA and DHA is cold water oily fish, such as salmon, herring, mackerel, anchovies, and sardines. Oils from these fish have a profile of around seven times as much n−3 as n−6. Docosapentaenoic acid (DPA) (22:5n-3), a long-chain n-3 PUFA metabolite of EPA, is present in smaller amounts in fish. Alpha-linolenic acid (ALA) (18:3n-3) is the plant derived n-3 fatty acid found in a relatively limited set of seeds, nuts, and their oils [7].

Omega-3-fatty acid concentrate for the on hand venture was extracted from Cod liver oil. Cod or *Gadus morrhua* is an ocean fish known as the "beef of the sea." Cod Liver Oil is the partially de-stearinated fixed oil obtained from fresh livers of *Gadus morrhua* linn and other species of family Gadidae [8].

The research fraternity has unanimously proclaimed the prophylactic efficacy of omega-3-fatty acids against complications associated with diabetes and coronary heart diseases. From the performed literature review it has been elucidated that omega-3 fatty acid supplementation posses preventive role in cardiovascular disease**.** They have mild antihypertensive effects. Evidently, n−3 fatty acids reduce blood triglyceride levels, thereby providing preventive action in atherogenesis while regular intake may reduce the risk of secondary and primary heart attack [9]. Thus the present study is architecture to evaluate the antiatherogenic properties of marine lipids in alloxan induced diabetic mice. The study also aims to monitor the effect of omega-3-fatty acids on the blood glucose level of the treated animals.

MATERIALS AND METHODS:

Procurement of chemicals:

Alloxan was purchased from Loba Chemical Pvt., Ltd., Bangalore, Karnataka, India. Standard drug Glibenclamide was purchased from Orphan Chemicals, Chandigarh, India. Cod liver oil was purchased from Aventis Pharma limited (Sanofi consumer health care division). All other chemical and reagent used were of analytical grade. Lipid profile estimation kit was procured from Transasia Bio Medical Limited Mumbai, Maharashtra, India. The diagnostic kit used in the study was procured from Roche Diagnostic Pvt. Ltd., Mumbai, Maharashtra, India. All other chemicals and reagents used were of analytical grade.

Preparation of ω-3 fatty acid concentrate:

Approximately 100g of cod liver oil was saponified with 200ml of sodium hydroxide solution in ethanol. The mixture was stirred for 30 minutes at 60^{o}C. 25ml of 25 ml hexane was added and the mixture was stirred for 1 h to extract fatty acids. The process yielded formation of two layers. The upper layer contained un-saponified matter was removed. HCl was added to the lower layer and it was stirred until achieving a pH value of 1. Consequently two layers were again formed and the lower layer was removed and the upper layer (hexane layer) was evaporated at 30°C. The fatty

acid extract was then added to the hot urea solution (temperature of 60-65°C) in methanol and agitated at a constant rate and allowed to cool. Urea crystals were formed at 10°C which were separated from the mother liquor by filtration and the ω-3 fatty acids in the filtrate was further extracted with 1 L hexane and 0.5 L concentrated HCl. The mixture was agitated for 1 h. The hexane layer was separated and hexane was evaporated at 30°C to obtain ω-3 fatty acids [10].

Acute oral toxicity study and dose selection

Cod liver oil and ω-3 fatty acid concentrate was weighed about 3000 mg/kg and suspended in 20ml of 0.2% Tween 80. The dose was administered according to the weight of animal. After the administration of doses the animals were observed for three days for any toxicity. 1/10 of the dose was selected for the experiment [11].

Selection of animals and induction of Type 2 diabetes:

Albino mice weighing 25-30g were selected, grouped and housed in polyacrylic cages (38x23x10 cm) with not more than six animals per cage. The animals were allowed to acclimatize to the laboratory conditions for one week prior to the advancement of the experimental protocol, approved by Institutional Animal Ethical Committee (IAEC). Diabetes mellitus was induced in overnight fasted (12hrs) Albino mice by single intraperitoneal injection of freshly prepared solution of alloxain monohydrate (150mg/kg BW) in physiological saline followed by administration of 5% glucose in their drinking water for the first 24 h to counter any initial hypoglycaemia. Fasting blood glucose was estimated at the time of induction of diabetes and postprandial-glucose was checked regularly until stable Hyperglycaemia was achieved. The mice showing fasting blood glucose level up to 250 mg/dl were considered diabetic and selected for the experimentation.

Experimental Design:

The animals were randomly divided into postulated study groups (n = 3 mice per group) as given below:

Group I (Normal control): composed of healthy animal treated with distilled water only.

Group II (Diabetic control): diabetic animals treated with normal saline.

Group III (Diabetic+ Glibenclamide): diabetic animals treated with Glibenclamide.

Group IV (Diabetic+ Oil): the animals were treated with cod liver oil.

Group V (Diabetic+ Concentrate) diabetic animals treated with ω-3 fatty acid concentrate.

Acute and sub acute analysis of anti-hyperglycaemic activity of the ω-3 fatty acid concentrate:

Acute estimation is performed by determining the blood glucose level in the experimental animals at 0hr, 2hr, 4hr, 6hr and 24 hr after administration of the standard drug (Glibenclamide) and the bioactive (ω-3 fatty acid concentrate), while the sub acute studies involved daily administration of the glibenclamide and ω-3 fatty acid concentrate for a period of 28 days and the level of blood glucose was determined on 0^{th}, 7^{th}, 14^{th}, 21^{th}, 28^{th} day respectively [12]. Blood samples for the analysis was collected by puncturing the tail vein of the animals and blood glucose was estimated using an Accu-Check Glucometer. The blood glucose levels were expressed in mg/dl.

Plasma lipid profile analysis:

Determination of blood lipids includes measurement of the concentration of total cholesterol, triglycerides low density and high density lipoproteins respectively. The results are expressed in mg/dl'. The plasma lipid profile of the experimental animals were measured at the end of the study protocol and recorded. For determination of VLDL and LDL cholesterol Friedwald's formula was used according to which VLDL cholesterol = Triglyceride/5 and LDL cholesterol = Total Cholesterol- (VLDL+ HDL cholesterol [13].

Body weight analysis:

The body weight of the experimental animals was measured on the 0^{th}, 7^{th}, 14^{th}, 21^{th}, 28^{th} day of the study and the data obtained were tabulated.

Clotting time analysis: The clotting time is defined as the time required for the formation of

blood clot (Thrombus) in response to bleeding thereby avoiding haemorrhage. Platelet cell activation and thrombosis are important components predisposing hyperglycaemia induced atherosclerosis. Thrombosis is the formation of a blood clot (thrombus) inside a blood vessel, which obstructs blood flow to cause hypoxia, anoxia and infarction [14]. Clotting time is significantly reduced in such condition indicating the precipitation of atherogenic activities in diabetic subjects.

The clotting time of the experimental animals were measured on the 0^{th}, 7^{th}, 14^{th}, 21^{th}, 28^{th} day by collecting blood samples from the retro-ocular plexus of the animal. The samples obtained were subjected to determination of clotting time by routine capillary method.

Statistical analysis of experimental data:

All the data were presented as mean ±SEM. Statistical analysis was performed by one way analysis of variance (ANOVA) test for multiple comparisons followed by Bonferroni's test. The statistical significance was set accordingly.

RESULT AND DISCUSSION:

The acute toxicity studies performed for both cod liver oil and ω-3 fatty acid concentrate administered via oral route revealed no sign of toxicity up to a dose of 2000mg/kg body weight, accordingly $1/10^{th}$ of the safe dose was selected for executing the protocol.

Alloxan is cytotoxic to the pancreatic β- cells and thus it is an effective diabetes-induction agent. It has been widely used to induce diabetes mellitus in experimental animal models allowing investigation of hypoglycaemic agents in the treatment of diabetes. Alloxan induced diabetic mice exhibiting persistent hyperglycemias (blood glucose> 250mg/dl) was further selected for assessing the biological potential of the bioactive concentrate.

Acute and sub acute analysis of anti-hyperglycaemic activity of the ω-3 fatty acid concentrate:

The data in **(Table 1)** describes the blood glucose concentration at the assorted time intervals to detect the acute effect of the prescribed treatment strategies. Comparative analysis of the data showed significant ($p<0.05$) difference in the blood glucose level of all treatment groups compared to that of the diabetic control. The maximum percentage decrease in the blood glucose level was observed in case of Glibenclamide treated group (41.88%) followed by that in the ω-3 fatty acid concentrate treated group (23.45%) while least difference was observed in the cod liver treated group (12.31%).

TABLE 1: ACUTE EFFECT OF ω-3 FATTY ACID CONCENTRATE ON ORAL GLUCOSE TOLERANCE TEST (OGTT) IN ALLOXAN INDUCED DIABETIC MICE

Group no.	Treatment (mg/kg)	Blood glucose (mg/dl)				
		0 h (FBG)	2hr	4hr	6hr	24hr
I	Normal control	87±2.1	93±2.5	98±1.4	96±3.7	92.10±2.9
II	Diabetic control	227 ±5.3	288±3.4	281±1.8	277±3.1	267±2.4
III	Diabetic+ Glibenclamide	234±2.3	186±3.8	155±1.8	130±1.1	136±2.5*
IV	Diabetic+ Oil	240 ± 2.4	236±2.5	239±2.4	238±1.2	210±3.3*
V	Diabetic+ ω-3 Concentrate	243±3.4	234±1.6	229±2.4	212±1.5	186±2.5*

n =3 mice in each group, values are mean ± SEM

p>0.05 compared to negative control group (ANOVA applied by Dunnett's test)

The data in **(Table 2)** describes the blood glucose concentration at the assorted time intervals to detect the sub acute effect of the prescribed treatment strategies. Comparative analysis of the data showed significant ($p<0.05$) difference in the blood glucose level of all treatment groups compared to that of the diabetic control. The maximum percentage decrease in the blood glucose level was observed in case of Glibenclamide treated group (43.58%) followed by that in the ω-3 fatty acid concentrate treated group (27.82%) while least difference was observed in the cod liver treated group (09.58%).

In view of the above obtained data it can be envisaged that ω-3 fatty acid concentrate demonstrates mild but significant ($p<0.05$) anti-hyperglycemic effect, and although the hypoglycemic potential of the bioactive is less than that of the standard drug Glibenclamide, but its effect is observed to be more profound than cod

liver oil administered in an analogous dosage regimen.

TABLE 2: SUB ACUTE EFFECT OF ω-3 FATTY ACID CONCENTRATE ON ORAL GLUCOSE TOLERANCE TEST (OGTT) IN ALLOXAN INDUCED DIABETIC MICE

Group no.	Treatment (mg/kg)	Blood glucose (mg/dl)				
		0 day	7 day	14day	21day	28 day
I	Normal control	87±2.1	93±2.5	98±1.4	96±3.7	92.10±2.9
II	Diabetic control	227 ±5.3	288±3.4	281±1.8	277±3.1	267±2.4
III	Diabetic+ Glibenclamide	234±2.3	186±3.8	155±1.8	138±1.1	132±2.5*
IV	Diabetic+ Oil	240 ± 2.4	226±2.5	230±2.4	236±1.2	217±3.3
V	Diabetic+ ω-3 Concentrate	230±3.4	187±1.6	144±2.4	128±1.5	166±2.5*

n = 3 mice per group
**p<0.05 compared to normal control group
*p<0.05 compared to negative control group (ANOVA applied by Dunnett's test)

Plasma lipid profile analysis:

From the statistics in **(Table 3)** it can be elucidated that the serum lipid profile has been significantly improved (P < 0.05) in the ω-3 fatty acid concentrate. After sub acute treatment with the bioactive concentrate serum plasma cholesterol, LDL and triglyceride level abridged approximately by 59.86%, 63.64%, 24.68% respectively, while the level of serum HDL increased by approximately 74.34%. The cholesterol profile of the animals in the oil treated group also significantly (P < 0.05) improved however the level of improvement was found to be less than that observed in the concentrate treated group. Subsequent to the treatment with cod liver oil the serum cholesterol level, LDL level and triglyceride level reduced approximately by 22.76%, 38.30% and 21.40% respectively while serum HDL level enhanced by 37.65%. No improvement was however observed in the glibenclamide treated group animals.

TABLE 3: SUB ACUTE EFFECT OF BIOACTIVE EXTRACTS ON LIPID PROFILE IN ALLOXAN-INDUCED DIABETIC MICE

Group no.	Treatment (mg/kg)	Cholesterol (mg/dl)		HDL (mg/dl)		LDL (mg/dl)		TG (mg/dl)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
I	Normal control	112.16 ±5.97	112.37 ±2.45	32.35 ±0.21	34.96 ±1.32	47.68 ± 3.5	45.12 ± 2.4	147.62 ±7.26	144.01 ±3.15
II	Diabetic control	172.82 ±2.28	198.58 ±1.07	17.01 ±1.26	13.45 ±0.39	118.74 ±8.26**	138.74 ±2.13**	185.42 ±5.06**	205.31 ±3.12**
III	Diabetic+ Glibenclamide	178.46 ±7.56*	188.53 ±7.56*	18.26 ±1.04*	15.17 ±2.13*	110.68 ±2.18*	123.54 ±0.25*	172.13 ±4.44*	192.06 ±3.21*
IV	Diabetic+ Oil	173.33 ±3.3	133.88 ±1.8	18.35 ±1.4	25.26 ±0.5	115.79 ±1.7	71.21 ±0.46	183.14 ±3.09	143.91 ±3.09
V	Diabetic+ ω-3 Concentrate	174.57 ±3.0	114.71 ±2.1	17.11 ±1.2	29.83 ±0.3	124.47 ±2.0	45.25 ±3.5	186.33 ±3.13	140.34 ±2.07

n = 3 mice per group
**p<0.05 compared to normal control group
*p<0.05 compared to negative control group (ANOVA applied by Dunnett's test)

Body weight analysis: Alloxan-induced mice showed loss in body weight, which was reversed by oral administration of standard drug glibenclamide. The body weight of the normal control mice did not show any significant difference. Also no significant effect on the decrease in the body weight of the experimental animals was observed in the bioactive concentrate and cod liver oil treated group animals **(Table 4)**.

Clotting time analysis: The data in **(Table 5)** portray the clotting time values at the assorted time intervals to detect the sub acute effect of the prescribed treatment strategies on the duration of blood clotting. Comparative analysis of the data showed significant (p<0.05) difference in the blood glucose level of all treatment groups compared to that of the diabetic control. The maximum percentage decrease in the clotting time was observed in case of diabetic control group (35.39%). However in the ω-3 fatty acid concentrate treated group significant percentage increase was observed in the clotting time (28.26%) while mild but significant (p<0.05) difference was observed in the cod liver treated

group(16.81%). On the other hand Glibenclamide, exerted no effect on the decrease in clotting time of the experimental animal when administered in a parallel dosage regimen.

TABLE 4: SUB ACUTE EFFECT OF BIOACTIVE FRACTIONS ON BODY WEIGHT IN ALLOXAN-INDUCED DIABETIC MICE

Group no.	Treatment (mg/kg)	Body weight (g)				
		0 day	7 day	14day	21day	28 day
I	Normal control	26±0.77	28±0.12	30±0.19	31±0.39	30±0.72
II	Diabetic control	38±1.08	34±0.44	40±0.37	36±2.9	33±1.26**
III	Diabetic+ Glibenclamide	39±1.1	39±2.3	38±0.29	36±2.8	38 ±1.1*
IV	Diabetic+ Oil	39±0.78	40±0.33	42±0.25	41±0.56	41 ±0.12*
V	Diabetic+ ω-3 Concentrate	36±0.13	38±0.27	39±0.29	40±0.18	38 ±1.5*

n = 3 mice per group
**p<0.05 compared to normal control group
*p<0.05 compared to diabetic control group
(ANOVA applied by Dunnett's test)

TABLE 5: SUB ACUTE EFFECT OF BIOACTIVE FRACTIONS ON CLOTTING TIME IN ALLOXAN-INDUCED DIABETIC MICE

Group no.	Treatment (mg/kg)	Clotting Time (sec)				
		0 day	7 day	14day	21day	28 day
I	Normal control	300±16.20	300±14.30	300±13.23	300±15.42	300±14.30
II	Diabetic control	226±14.26*	204±16.20	190±15.12	176±17.36	146±14.30*
III	Diabetic+ Glibenclamide	235±14.30**	217±15.25	202±17.32	196±13.36	158±15.42**
IV	Diabetic+ Oil	230±12.44***	244±13.27	256±11.40	264±19.36	295±16.66***
V	Diabetic+ ω-3 Concentrate	226±15.44***	234±11.21	240±15.44	257±12.22	264±13.22

n = 3 mice per group
**p<0.05 compared to normal control group
*p<0.05 compared to negative control group (ANOVA applied by Dunnett's test)

CONCLUSION: The current study unveils the anti-atherogenic and antidiabetic potential of the ω-3 fatty acid concentrate obtained from the cod liver oil. The bioactive at a dose of 300 mg/kg exhibited mild anti-hyperglycaemic and significant anti-hypolipidemic activities in alloxan induced diabetic mice model. The activity of ω-3 fatty acid concentrate is justified by its potential of lowering the fasting blood glucose level, improved lipid profile and clotting time values in the experimental model.

Thus from this project it can be concluded that omega-3-fatty acid concentrate can be used as an efficiently in the clinical management of diabetes induced hypercholesterolemia and consequent atherosclerosis as it effectively address all the pathological aspects of the disease.

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