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Anti-diabetic and anti-oxidant activities of *Devdarvadyarishta* in streptozotocin induced diabetic rats

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Devdarvadyarishta is a honey based medicated alcoholic formulation that has been documented to elicit hypoglycemic activity in Ayurvedic lexicon. The aim of this present study was to evaluate the anti-diabetic and anti-oxidant effect of *Devdarvadyarishta* in STZ induced type II diabetic rats. 24 Wistar albino rats were distributed into four groups with six animals in each group *viz*., Group I (Normal Control Group), Group II (Diabetic control group), group III (Standard drug Glibenclamide at 10 mg/kg of body weight), group IV (*Devdarvadyarishta* at 2000 mg/kg of body weight). Diabetes was induced by intraperitoneal injection of STZ at dose level of 35 mg/kg. The whole study was conducted for 30 days. Changes in parameters like body weight, blood glucose, blood urea, serum cholesterol, triglycerides, creatinine, insulin, alkaline phosphatase, oral glucose tolerance test and liver anti-oxidant parameters *viz.*, superoxide dismutase and reduced glutathione were recorded. Histopathology of liver and pancreas was also done. Result showed significant improvement in parameters like body weight, lipid profile, blood glucose, serum creatinine, insulin and alkaline phosphatase which were almost analogous to potent antidiabetic drug glibenclamide. Histopathological studies reinforce the healing of pancreas by increase in pancreatic islet numbers and size, amelioration in atrophy, well-rejuvenated normal cellular arrangement and reduced necrosis with normal blood vessels in liver by test drug as a possible mechanism of its antidiabetic and anti-oxidant activity our study suggests that *Devdarvadyarishta* suppresses the symptoms of diabetes and diabetes related oxidative stress in animal study.

Keywords: Anti-oxidant, *Devdarvadyarishta*, Diabetes, Hypoglycaemic, Streptozotocin, Toxicity

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Diabetes Mellitus is known to be the biggest silent killer globally. According to IDF (International Diabetes Federation), in 2030 approximately 643 million people will have diabetes in the world and by 2045 this will rise to 783 million[1]. Also, a study by the American Diabetes Association reports that India will see the greatest increase in people diagnosed with diabetes by 2030[ref. 2]. Currently oral hypoglycemics and insulin are employed for the treatment of diabetes, but none of them are without side effects viz., prolonged use of insulin may lead to insulin resistance, atrophy of brain, anorexia etc. Intricate etiology of diabetes has led to shifting pattern of treatment from monotherapy to combination therapy.

Asava–Arishta, self-generated medicated alcoholic formulations have found extensive therapeutic uses from pediatrics to geriatrics in present scenario, but questions regarding their application in Diabetes considering their higher percentage of sugar still needs to be addressed. Use of honey in Diabetes has been validated by Biomedical Science which was a well-established fact as per Ayurveda[3-6]. Also the complications caused due to oxidative stress in diabetes are the major cause for deterioration of health that needs to be overcome by interventions possessing both therapeutic and nutritive effect. Albeit, sugar craving is not a symptom of DM, but almost all diabetics face it as lots of dietary restrictions are imposed on them. Asava–Arishta formulations may offer the best possible answer to all these questions and *Devdarvadyarishta* is the outcome of the search for an effective, sweet, delectable formulation quoted in Bhaishajya Ratnavali[7]. It is a polyherbal formulation that contains

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phytoconstituents like glycosides, alkaloids, terpenoids, flavonoids, tannins, saponins and is proven to be effective in this clinical condition[8-13]. Hence, the purpose of this research was to experimentally assess the anti-hyperglycaemic and anti-oxidant effect of *Devdarvadyarishta* in Streptozotocin (STZ) induced diabetic rats and compare it with glibenclamide as a reference standard. In addition to this, liver and kidney profile, effect of exogenous glucose uptake through oral glucose tolerance test and histopathology was performed to check the effect of treatment on pancreas.

Materials and Methods

Chemicals

Glibenclamide, batch no. P010745463, Mfg date: 02/2014, manufactured by Hetero Labs Ltd., and Streptozotocin, batch No.091k1635, Mfg date: 04/2014, manufacturer: SIGMA Aldrich Inc. USA were purchased from Bilwal Pharmaceuticals, Jaipur Rajasthan.

Procurement of drugs and formulation preparation

The herbs used in *Devdarvadyarishta* preparation were procured from local market in Haridwar after authentication by subject experts. *Devdarvadyarishta* was prepared as per the reference of Bhaishajya Ratnavali[7] in the Department of Rasa Shastra & Bhaishajya Kalpana, Rishikul Campus, Haridwar, Uttarakhand Ayurveda University. Decoction was prepared after overnight soaking of drugs viz., *Cedrus deodara* (Roxb. Ex D. Don) G. Don, *Adhatoda vasica* Nees, *Rubia cordifolia* L., *Holarrhena antidysenterica* (Roth) Wall. Ex. A. DC., *Baliospermum montanum* (Willd.) Mull.Arg., *Valeriana wallichii* DC., *Curcuma longa* L., *Berberis aristata* DC., *Plucheal anceolata* (DC.) C. B. Clarke, *Embelia ribes* Burm. f., *Cyperus rotundus* L., *Albizzia lebbeck*, *Acacia catechu* (L. f.) Willd., *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn., *Trachyspermum ammi* (L.) Sprague, *Holarrhenaanti dysenterica* (Roth) Wall. Ex. A. DC., *Santalum album* L., *Tinospora cordifolia* (Willd.) Miers, *Picrorrhiza kurroa* and *Plumbago zeylanica* L. in water which was further filtered with muslin cloth. Afterwards honey, Prakshepdravyas viz., *Zingiber officinale* Roscoe, *Piper nigrum* L., *Piper longum* L., *Cinnamomum zeylanicum*, *Elettaria cardamomum* (L.) Maton, *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm., *Mesua ferrea* L., *Callicarpa macrophylla* Vahl (after powdering and sieving), *Woodfordia fruticosa* (L.) Kurz flowers were added and stirred properly. The mixture was kept in porcelain jar, sealed and kept for fermentation.

Experimental animals and ethics committee approval

30 Wistar strain albino rats (24 rats for anti-diabetic and 6 rats for acute oral toxicity study) of either sex weighing between 120±20 g were used for the present study. The animals were housed in suitable cages and acclimatized for about one week. All the rats were freely allowed to eat Gulmohar brand animal feed manufactured by Lipton India Ltd. and water *ad libitum* during the study period. The study was carried out after obtaining permission from Institutional Animal Ethics Committee with approval number- IBIR/IAEC/ 2014-07 and the guidelines of CPCSEA (Committee for the purpose of control and supervision of experiments on animals), Govt. of India, were strictly followed during the study.

Acute oral toxicity study

It was carried out according to OECD guideline 423, ANNEX 2c and as per the protocol of Institute of Biomedical and Industrial research it was mandatory to carry out the toxicity study of every formulation even if it is already used clinically. Three animals each at two dose levels were selected. The dose level to be used as the starting dose is selected from one of two fixed levels 300 and 2000 mg/kg body weight Group 1 having 3 rats received 300 mg/kg test sample and Group 2 having 3 rats received 2000 mg/kg test sample by gavage using an oral feeding needle. Animals were observed individually after dosing, once during first 30 min, periodically during the first 24 h, with special attention given during the first 4 h and daily thereafter, for a total of 14 days. All observations were systematically recorded for each animal *viz.*, changes in skin and fur, eyes, mucous membranes, salivation, lethargy, sleep, coma, convulsions, tremors, diarrhoea, morbidity, mortality and haematological parameters. Histopathology of kidney, heart, liver, spleen and brain was also carried out to find any noticeable change in cyto-architecture of these organs.

Experimental design

Twenty four animals were randomly allocated in to four groups with six animals in each group namely group I (Normal Control), group II (Diabetic Induced Control), group III (Standard drug Glibenclamide 1 mg/kg of body weight), group IV (*Devdarvadyarishta* 2000 mg/kg of body weight). Considering adult dose of *Sandhana Kalpana* with reference to various *Asava-arishta* mentioned in AFI, 10-20 mL of human adult dose of *Devdarvadyarishta* was converted into

animal dose based on the body surface area ratio using the table of Paget and Barnes 1969 (Human adult dose × Body surface area ratio convertible factor i.e., 0.018) and human dose of glibenclamide is given as 10 mg OD and the suitable dose for rats was calculated by referring to table of Paget and Barnes.

Test drug dose calculation

According to result obtained from acute toxicity study at dose 2000 mg /kg found that it is safe. So we use 2000 mg /kg as therapeutic dose.

The rats were kept on fasting overnight prior to STZ administration day. STZ solution was injected to rats of group II, group III and group IV at a dose of 35 mg/kg through insulin syringes as it has been depicted through various researches that STZ at a lower dose is known to resemble Type II diabeticmodel and does not kill pancreatic β cells[14]. The STZ solution was freshly prepared by dissolving it in 50 mg of sodium citrate buffer (*p*H 4.5) to prepare a final concentration of 1 mg/mL, just prior to itsintraperitoneal administration in rats for the induction of Diabetes Mellitus. On affirmation of hyperglycaemia after 72 h, rats of group III were treated with standard antidiabetic drug Glibenclamide at a dose of 1 mg/kg of body weight and rats of group IV were administered with *Devdarvadyarishta* at a dose of 2000 mg/kg of body weight which is equivalent to 20 mL human dose of *arishta kalpana* (as per drug dose calculation) respectively. While the rats of group II were not given any treatment. The medicaments were administered orally with the help of intragastric tube for a time period of 30 days. Animals were assessed for various biochemical parameters *viz.*, blood glucose, serum cholestrol, blood urea, alkaline phosphatise activity, serum creatinine, serum Insulin, serum triglycerides and anti-oxidant parameters *viz.*, reduced glutathione and SOD estimation before induction, on 6th day and on completion of the study. Rats were also subjected to GTT at the end of study by administering glucose solution 2 g/kg by oral route and the plasma glucose level was estimated using glucometer. Finally, the animals were sacrificed under anaesthesia for routine histopathological examination.

Statistical analysis

The results were expressed as mean ±SE by using statistical software SPSS version 16.0. All statistical comparisons between the groups were made by means of One Way ANOVA (Analysis of Variance) with Dunnet's multiple comparison test. Within the group comparison was done by paired't' test. The p value <0.05 was regarded as statistically significant and < 0.01, <0.001 were taken as statistically highly significant. Oral GTT analysis has been done by two way ANOVA followed by Bonferroni post test.

Results

Acute toxicity

Results revealed the test drug to be safe at a highest dose of 2000 mg/kg body weight as no signs of toxicity appeared over a period of 14 days. All the haematological parameters were found to be within normal limits and histopathology of kidney, liver, spleen, heart and brain in all sections revealed normal cytoarchitecture of these organs.

Anti diabetic activity

Group 1 shows statistically significant ($p<0.0001$ body weight gain that may be attributable to the normal physiological mechanism of body, whereas no significant change was observed in other biochemical parameters during the whole duration of study as it was normal control group in which no diabetes induction was done. In Group 2 no significant change, either increase or decrease was noticed in any of the parameters after completion of study as no intervention was given in this group. Reduction in body weight of rats, although non-significant was noticed till end that might be the result of protein wasting due to unavailability of carbohydrate for utilization as an energy source. No changes in blood sugar level were noticed in both Group 1 and Group 2 after completion of study. Group 3 showed statistically significant increase in the body weight as well as serum insulin levels and decrease in all other biochemical parameters with p-value being <0.0001as a result of treatment with standard anti-diabetic drug. Group 4 shows statistically significant increase in body weight ($p<0.0001$) and serum insulin level ($p=0.001$) whereas decrease in all other biochemical parameters with ($p< 0.0001$) in blood glucose, ($p<0.0001$) in serum triglyceride, ($p<0.0001$) in blood urea, ($p<0.0001$) in serum creatinine and ($p<0.0001$) in alkaline phosphatase and in serum cholesterol ($p=0.001$) was observed as a result of treatment with the test drug as given in Table 1.

Inter group comparison was done by Dunnett's multiple comparison test whereby all the groups *viz.*, normal control, standard drug and test drug were compared with group 2 i.e., diabetic control group. As per the data pertaining to table 2, statistically significant change either increase or decrease in all the parameters was observed between all the groups.

Table 1 — Intra group comparison using Student Paired t test

Bio- Chemical Paramters	GROUP-1						GROUP-2						GROUP-3						GROUP-4					
	Before TT		After TT		T Value	P value	Before TT		After TT		T Value	P value	Before TT		After TT		T Value	P value	Before		After		T Value	P value
	Mean	SEM	Mean	SEM			Mean	SEM	Mean	SEM			Mean	SEM	Mean	SEM			Mean	SEM	Mean	SEM		
Weight (gm)	130	8.16	137.6	8.29	0.032	<0.0001	123.9	4.6	117.5	5.25	0.196	0.004	120.2	4.96	128.3	4.86	0.068	<0.0001	127.4	4.98	137.5	4.45	0.081	<0.0001
Blood Glucose(mg/dl)	81.58	0.28	82.36	0.49	0.741	0.235	248.5	6.18	254.1	4.71	0.442	0.073	254.1	8.51	103	3.41	0.059	<0.0001	251	6.3	121.1	5.5	0.067	<0.0001
Sr. Cholesterol (mg/dl)	147.1	5.03	146.7	4.71	1.07	0.392	255.7	3.52	255.2	5.39	6.416	0.882	244.4	4.53	124.6	2.3	0.044	<0.0001	252.5	9.01	175.3	4.84	0.133	0.001
Sr. Triglyceride (mg/dl)	85.27	3.38	84.8	2.96	1.27	0.466	196.9	4.06	196.9	3.94	42.9	0.982	199.4	5.93	106.5	3.51	0.074	<0.0001	192.6	4.19	145	3.87	0.122	<0.0001
Blood Urea (mg/dl)	21.39	0.36	21.4	0.25	25.16	0.969	77.28	1.09	78.05	1.07	0.278	0.015	77.39	0.6	30.93	1	0.023	<0.0001	77.1	0.95	40.99	0.69	0.03	<0.0001
Sr. creatinine (mg/dl)	0.58	0.03	0.57	0.03	3.26	0.771	1.77	0.05	1.78	0.06	2.082	0.651	1.83	0.03	0.67	0.04	0.031	<0.0001	1.8	0.06	0.92	0.01	0.071	<0.0001
Alkaline Phosphatase	113.7	2.18	114	2.24	1.74	0.591	334.3	6.95	334.4	6.85	6.133	0.877	330.2	5.55	113.8	2.72	0.017	<0.0001	330.4	6.56	150.8	4.74	0.058	<0.0001
Serum insulin (ng/ml)	1.65	0.07	1.65	0.07	0.68	0.203	0.74	0.03	0.75	0.03	1.693	0.58	0.76	0.02	1.27	0.02	0.024	<0.0001	0.7	0.05	1.04	0.01	0.149	0.001

Table 2 ─ Inter Group Comparison by Dunnett's Multiple Comparison Test

Inter Group Comparison	Group 1		Group 2		Group 3		Group 4		p value
	Diff	SEM	Diff	SEM	Diff	SEM	Diff	SEM	
Weight (g)	7.56	0.25	6.42	1.26	8.10	0.55	10.05	0.81	<0.0001
Blood Glucose (mg/dL)	0.78	0.57	0.77	0.57	151.15	8.84	129.95	8.67	<0.0001
Sr. Cholesterol (mg/dL)	0.32	0.34	0.44	2.81	119.78	5.28	77.20	10.29	<0.0001
Sr. Triglyceride (mg/dL)	0.47	0.60	0.01	0.57	92.99	6.85	47.63	5.83	<0.0001
Blood Urea (mg/dL)	0.012	0.29	0.77	0.21	46.46	1.06	36.11	1.08	<0.0001
Sr. creatinine (mg/dL)	0.002	0.005	0.01	0.02	1.16	0.04	0.88	0.06	<0.0001
Alkaline Phosphatase (U/L)	0.30	0.53	0.10	0.59	216.37	3.71	179.60	10.43	<0.0001
Serum insulin (ng/mL)	0.005	0.003	0.01	0.01	0.51	0.01	0.34	0.05	0.0001

Table 3 — Oral Glucose tolerance test

Group	0 min		30 min		60 min		90 min		120 min	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	88.78	1.79	129.99	1.87	138.7	3.05	112.02	3.29	89.07	2.16
2	261.96	3.83	327.41	5.44	344.06	7.89	300.81	5.66	274.28	3.74
3	107.82	1.62	163.01	4.28	205.09	4.25	168.93	7.88	96.44	3.43
4	128.71	4.44	242.13	5.83	354.22	5.25	267.39	4.78	196.58	3.7
Post hoc test										
Group 2 vs. Group 1	P<0.001		P<0.001		P<0.001		P<0.001		P<0.001	
Group 2 vs. Group 3	P<0.001		P<0.001		P<0.001		P<0.001		P<0.001	
Group 2 vs. Group 4	P<0.001		P<0.001		P<0.001		P<0.001		P<0.001	

Significant weight gain was noticed in each group as compared to diabetic control, but remarkable increase occurred in test drug group certainly due to the nutritional benefits offered by *Devdarvadyarishta*, it being a Sandhana Kalpana product which is very well known for its nutritional value since ages. No significant mean difference was noticed in any of the biochemical parameter between normal and diabetic control group due to non-intervention in these groups. The mean difference in various biochemical parameters between group 2 vs group 3, group 2 vs group 4 was statistically significant. Results shows that effect of standard drug are better in serum cholesterol, serum triglyceride and blood urea aspects as compared to test drug. Comparable results of both test drug and standard drug has been found for blood glucose, serum creatinine, alkaline phosphatase activity and serum insulin level.

Oral glucose tolerance test

Data pertaining to this parameter can be seen Table 3. Rapid increase in blood glucose level was observed up to 60 min after glucose administration, the peak of blood glucose level in all groups increases rapidly from fasting value and then subsequently decreased. Bonferroni post test shows statistically significant change ($p< 0.001$) in the difference between the blood glucose values of different groups at different time intervals.

Anti-oxidant effect

It has been suggested that oxidative stress can play an important role in tissue damage associated with diabetic complications coexisting with a reduction in anti-oxidative parameters such as superoxide dismutase (SOD) and reduced glutathione (GSH)[15]. A significant decrease in both the parameters were observed in diabetic control group, which indicates hyperglycemia decreases anti-oxidant capacity attributed to the accumulation of superoxide anion radicals and hydrogen peroxide. Data shown in Table 4 shows that the level of Superoxide dismutase and glutathione in group 3 and group 4 is on higher side as compared to diabetic control group but does not reaches the value of normal control group which indicates that both the test and standard drug can help in relieving oxidative stress in diabetes to some extent by reduction of hydrogen peroxides and protect the tissues from highly reactive hydroxyl radicals.

Histopathology of pancreas

Group 1 exhibited the normal structure of exocrine region and islets of Langerhans, with scattered β cells and red blood cells visible in the vicinity. With the treatment of STZ, decrease in pancreatic islet numbers and size, atrophy and vacuolation, and invasion of connective tissues in the parenchyma was evident in Group 2. These features were well corrected in terms of development in pancreatic islet numbers and size; with improvement in atrophy and vacuolation in both standard drug treated Group 3 and DVA treated Group 4 though the improvement was little less in the Group 4, (Group 1-4).

Histopathology of liver

Group 1 showed normal histology with sinusoidal cords of hepatocytes with central vein and portal tracts. On induction of diabetes, hepatocyte showed distortion in the arrangement of cells around the central vein, enlargement, thickening of the walls of

Table 4 — Anti-oxidant parameters

Anti oxidant parameters	Group 1		Group 2		Group 3		Group 4		p value
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	
SOD (U/mL)	9.24	0.353	4.06	0.48	6.99	0.52	6.24	0.28	0.0013
GSH (mg/100 g of tissue)	50.83	2.199	26.6	0.57	40.09	1.01	34.86	2.29	0.0228

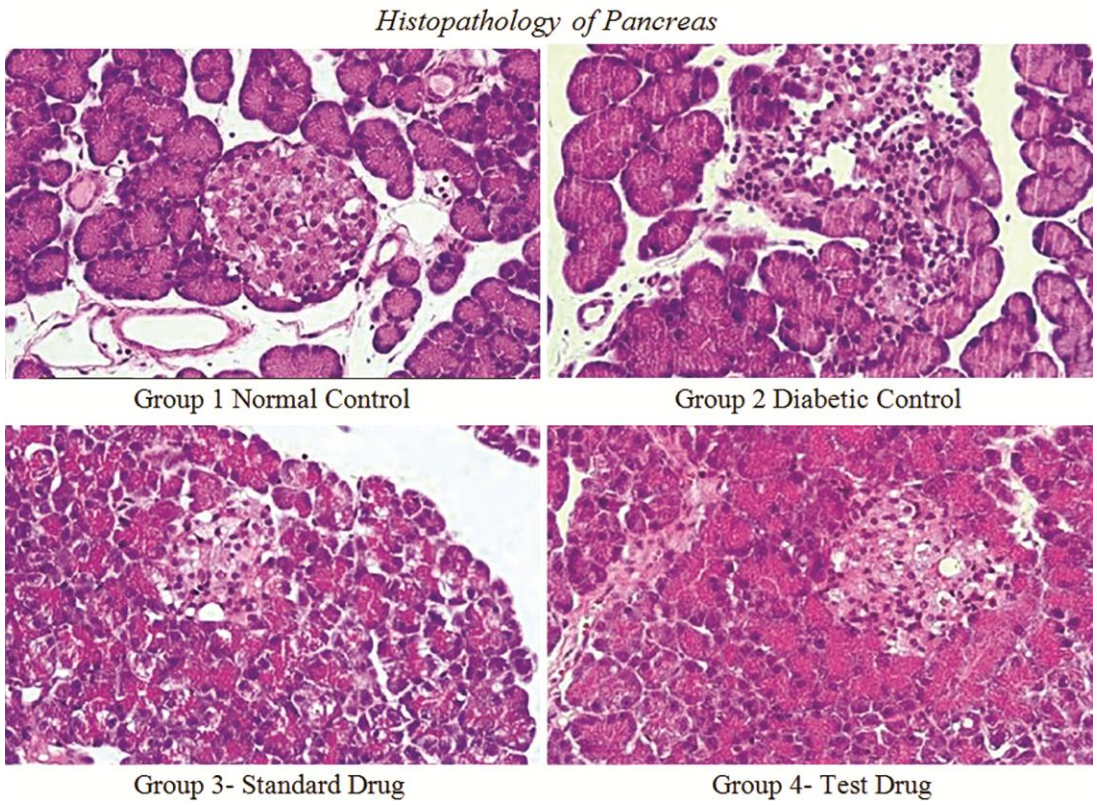

Fig. 1 (Group 1-4) — Group 1 Normal Control; Group 2 Diabetic Control; Group 3 Standard Drug; Group 4 Test Drug

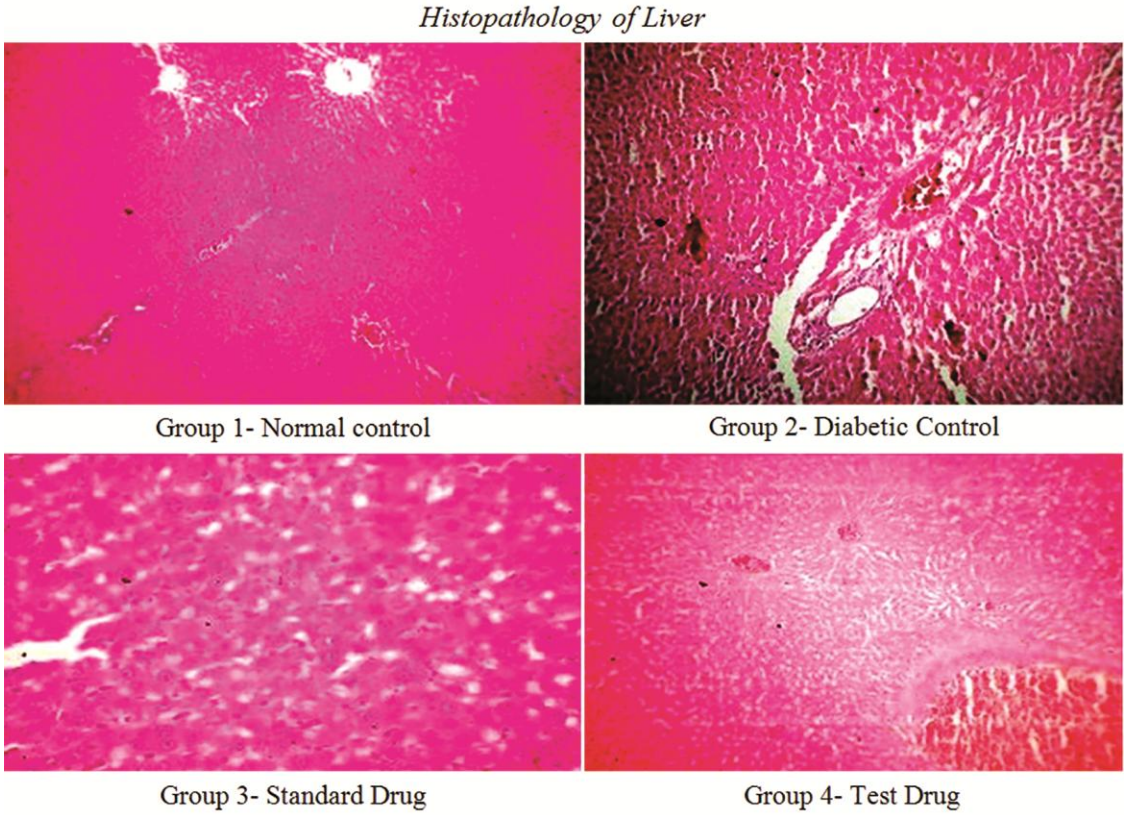

Fig. 2 (Group 1-4) — Group 1 Normal control; Group 2 Diabetic Control; Group 3 Standard Drug; Group 4 Test Drug

veins and capillaries, development of fibrosis and necrosis with slight congestion as well as peri-portal fatty infiltration (Group 2). Treatment with standard drug (Group 3) showed normal cellular arrangement around the central vein and reduced necrosis with mild to moderate intrahepatic haemorrhage and few erythrocytes in central vein. Similarly Group 4 showed well-rejuvenated normal cellular arrangement around the central vein and reduced necrosis and normal blood vessels (Group 1-4).

Discussion

Animal models of diabetes are constructive and indispensable research tools to perceive the molecular basis, pathogenesis of complications, and the utility of therapeutic agents in diabetes. The most prominent diabetogenic chemical is Streptozotocin (STZ) that is toxic to the insulin producing β cells of pancreatic islets[14]. In the present study, it was observed that *Devdarvadyarishta* can reverse the metabolic derangements occurring in Streptozotocin induced diabetes in rats as indicated by parameters like body weight & lipid profile along with serum creatinine, serum urea and serum alkaline phosphatase activity. The therapeutic effectiveness of DVA can be attributed to its individual ingredients. *Cedrus deodara*[16], *Adhatoda vasica*[17], *Rubia cordifolia*[18], *Curcuma longa*[19], *Berberis aristata*[20], *Embelia ribes*[21], *Acacia catechu*[22], *Terminalia arjuna*[23], *Tinospora cordifolia*[24], *Picrorrhiza kurroa*[25], *Piper longum*[26], *Holarrhena antidysenterica*[27], *Cyperus rotundus*[28], *Albizzia lebbeck*[29], *Holarrhena antidysenterica*, [30] *Santalum album*[31], *Plumbago zeylanica*[32], *Zingiber officinale*[33], *Piper nigrum*[34], *Cinnamomum tamala*[35], *Callicarpa macrophylla*[36] and honey[5-6] are known to possess anti-diabetic property as per both Ayurveda and chemical profile by virtue of their *Rasa Panchaka* and chemical composition respectively. Ancient seers have clearly mentioned anti diabetic property of honey[3-4] which has been very well documented by biomedical science also[5-6]. In the past, people with diabetes were advised to avoid “simple sugars” including honey as it was thought that consuming simple sugars would cause a rapid elevation in blood glucose levels and an overwhelming insulin demand. In fact, research has shown that some complex carbohydrates raise blood glucose levels more significantly than certain simple sugars (present in

honey) and honey has been shown to produce a lower glucose response[37]. Also it has been observed that impact of honey on blood sugar levels was far less than other sugars in both Type 1 and Type 2 Diabetes mellitus[38-39].

It has been reported that plants which contain the active principles like glycosides, alkaloids, terpenoids, flavonoids, tannins etc, have antioxidant activity and are claimed to possess antidiabetic effects[8]. Tannins and flavonoids are reported to have glucose-lowering[9], lipid-lowering activities[10-11], and anti-oxidant properties[12]. Plant polyphenolics and saponin inhibit glucose transport across the intestine by inhibiting sodium glucose co-transporter-1 (S-GLUT-1)[40]. Saponins are also known to posses hypolipidaemic activity[13]. All these functional groups are present in ingredients of *Devdarvadyarishta*, so it can be said that due to synergistic action of a number of phytoconstituents with their specified mechanism of actions makes DVA a more effective antidiabetic agent in comparison to individual drug material. The results of test drug have also been found to be analogous to those of glibenclamide. Treatment with test drug showed much protective effect on pancreas and liver by significantly decreasing the intensity of diabetes induced degenerative changes. Asavaarishta are generally not prescribed in Diabetes due to higher concentration of sugar in them, but by virtue of anti-diabetic property of various ingredients including honey, *Devdarvadyarishta* can be used as a supportive intervention in diabetic people, it being a highly stable formulation having shelf life of 371.657 months (30.97 years) as per the accelerated study conducted on it according to ICH guideline QA1 (R2)[41]. Also *Devdarvadyarishta* was found to possess good nutritional value i.e., 86.82 kcal energy that can prove useful to overcome the deteriorated health caused due to oxidative stress in diabetics[42].

Conclusion

From the above mentioned results, it can be concluded that oral administration of *Devdarvadyarishta* in STZ induced diabetic rats showed good anti-diabetic as well anti-oxidant property, so it may be employed as an intervention in Diabetic people to attenuate various bio-chemical parameters and to reduce diabetes related oxidative stress.

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Conflict of Interest

Author declare that they do not have any conflict of interest

Author's Contribution

CG- Conceptualisation, Manuscript preparation, Collection of data, Data Interpretation and analysis, Editing, Correction, KCS- Conceptualisation and Editing, NJ- Conceptualisation, Data Interpretation and analysis.

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