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CARDIOPROTECTIVE EFFECT OF SANDAL WOOD (*SANTALUM ALBUM* LINN.): AN EXPERIMENTAL TRAIL

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ABSTRACT: Background: In the Unani System of Medicine, *Sandal safed* (Sandalwood) is used in many cardiac problems as it possesses *Mufarreh* (exhilarant) and *Muqawwi Qalb* (cardiotonic) activities. The present study was designed to evaluate the cardioprotective effect of *Sandal safed* in Isoproterenol-induced Myocardial Infarction. **Methods:** Male Wistar rats, weighing 150-200gm, divided into five groups of ten in each. Group I and III rats were given 5% gum acacia (vehicle) and Sandalwood powder in the dose of 800 mg/kg body weight, orally once daily for seven days, followed by subcutaneous administration of normal saline on the 8th and 9th day. Group II, IV & V were administered 5% gum acacia, test drug in the dose of 600 & 800mg/kg body weight, orally once daily for seven days, respectively, followed by isoproterenol hydrochloride (50 mg/ kg body weight) subcutaneously, twice at an interval of 24 h on 8th and 9th day. On 10th day, animals were sacrificed, heart and adrenal glands were weighed, and serum cardiac enzymes and lipid profile were analysed. Histopathological study of apex of the heart was carried out. **Results:** In group- II rats, serum cardiac enzymes, serum cholesterol, TG, LDL, VLDL, and weight of the heart and adrenal gland were found to be increased significantly ($P< 0.001$), and HDL, cardiac glycogen and adrenal ascorbic acid were decreased significantly along with gross pathological changes in heart tissues, but in group IV & V rats, the above parameters were normal. **Conclusion:** Sandal safed revealed cardioprotective effect in dose dependent manner without any side effects.

INTRODUCTION: Myocardial infarction (MI), is an acute condition of myocardial necrosis caused due to imbalance between coronary blood supply and myocardial demand, regularly followed by several biochemical changes leading to qualitative and quantitative alterations of myocardium [1]. Atherosclerosis in the coronary artery is a key factor in developing MI [2].

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Pain is the cardinal symptom of MI, and breathlessness, vomiting, and collapse or syncope are the common features [3]. The MI is managed by lifestyle modifications, pharmacological therapy, and revascularization techniques [4]. The prevalence, incidence and death due to myocardial infarction indicate that the contemporary drugs are not enough to fulfill the therapeutic requirements.

Therefore, there has been growing interest in alternative medicines and the therapeutic use of natural products in recent years, especially those derived from plants [5]. Unani physicians paid great attention to treating this vital organ, the heart (*Uzue Rais*), responsible for the existence of life [6].

Unani savants like *Buqrat, Jalinoos, Ibn Sina, Ibn-e- Nafees, Jurjani, Razi etc*., have vividly discussed about cardiovascular disorders and their management in their writings. The cardiovascular problems in Unani System are being treated mainly with the drugs having *Mufarreh* (Exhilarant) and *Muqawwi Qalb* (cardiotonic) activities [7].

There are several single and compound *Mufarreh wa Muqawwie Qalb* drugs in Unani medicine, and *Sandal safed* (*Santalum album* Linn.) is one of them. It possesses *Mufarreh*, *Muqawie Qalb*, *mohallile warm* (anti-inflammatory) [8, 9, 10, 11, 12], *Muqawie Dimagh* (brain tonic) [12, 13]. *Muqawwie Hararate Gareezi* (strengthen the innate heat), *Muqawie Kabid* (liver tonic) [14, 15] *Tiryaq* (Antidote) and *Mujaffife Qurooh* (desiccant) etc. activities [9, 15, 16].

Many scientific studies have proven that sandalwood possesses, Anti-oxidant, Analgesic and Anti-inflammatory, Anti-anginal (in formulation), Antihyperlipidemic, Anti-oxidant, and Antihyperglycemic activities [17, 18] because of its phytochemicals but the protective effect of *Sandal safed* in cardiovascular diseases has not been investigated scientifically. Therefore, the present study is conducted to evaluate the cardioprotective effect of sandalwood in isoproterenol-induced MI.

METHODS:

Animals: Healthy male albino Wistar rats weighing 150-200gm were procured from an authentic breeder (Biogen, Bangalore). The animals were housed in standard environmental condition at room temperature 25±2°C, humidity 45-55%, with 12hrs light & dark cycle and were provided with standard diet and water *ad libitum*.

Rats were acclimatized for a week in accordance with CPCSEA norms, and before beginning the experiment, ethical clearance was taken (Reg. No: IAEC/X/01/IA) from Institutional Animal Ethics Committee (IAEC), National Institute of Unani Medicine, Bangalore.

Plant Material: The fine powder of wood of *Sandal safed* (*Santalum album* Linn.) was procured from Cauvery Emporium (Receipt No. 13746), Bangalore, Karnataka. For future reference, a voucher specimen of the test drug was deposited in the Dept. of Ilmul Advia, NIUM, Bangalore.

Phytochemical Studies of Sandalwood: The Phytochemical studies of sandalwood have identified over 100 constituents in its oil. The major constituent is alpha-santalol, which is the chief constituent of oil and responsible for most of the biological activities of Sandalwood essential oil [19].

The constituents of sandalwood oil have been reported in the categories of tannins, terpenes, resins, and waxes such as hydrocarbons- santene, nortricyclo- ekasantalene, α- and β- santalenes; alcohols-santenol, teresantalol; aldehydes- nor-tricyclo-kasantalal, α-and β- santalic acids and teresantalic acids, cyclosantalal, isocyclo-santalal, Tricyclosantalal, α-santalene, trans-β- bergamo-tene, β-santalene (S & E), α-curcumine, α- santalol, beta-santalol (S&E), nuciferol, α-santalal and β-santalal. The chief constituents of the oil are santalol (90% or more) a mixture of two primary sesquiterpene alcohols *viz,* α-santalol and β-santalol in which α– form predominate [20, 21].

Acute Oral Toxicity (LD_{50}) of Sandalwood: The calculated dose of Sandalwood powder considered to be safest, as it has a long history of oral use without any reported adverse effects. Moreover, the acute oral toxicity (LD50) of sandalwood oil in rats has been reported as 5.58 g/kg of body weight [19].

Dose Fixation and Test Drug Preparation: In this study, lower and higher doses of 5 and 7gm were selected, as mentioned in Unani classical literature [22]. The dose of the drug for Wistar rate was calculated by multiplying the human therapeutic dose by a conversion factor of 7 (Freirich *et al.* 1968) [23] and was found to be around 600 & 800 mg/kg body weight, respectively. The fine powder of the test drug was suspended in 5% gum acacia and administered orally with the help of feeding canula. Each time the dose was freshly prepared at the time of administration to animals.

Drugs and Chemicals: Isoproterenol hydrochloride (Product I6504) was obtained from Sigma Aldrich. Other chemical kits like Creatine kinase (CK), Creatine Kinase MB (CK-MB), Lactate Dehydrogenase (LDH), and Lipid profile were purchased from Spinreact, S.A; AST, ALT from Prism diagnostic, Pvt. Ltd. Thane, Mumbai and HDL cholesterol kit was purchased from

Beijing Leadman Biochemistry Co., Ltd. Ch. All chemicals used in this research were of the analytical score.

Induction of Myocardial Infarction: Isoproterenol hydrochloride was dissolved in 0.9% saline at a concentration of 50 mg/ml as recommended by the company and injected subcutaneously between two shoulder blades, in the dose of 50mg/kg body weight, for two consecutive days (8^{th} & 9^{th} day) with an interval of 24 h for induction of MI [24, 25].

Experimental Study Design: 50 male albino Wistar rats weighing 150-200gm were taken and divided into five groups of ten in each.

Group I (Plain Control): Rats of this group were given 1ml of 5% gum acacia (p. o) once daily for seven days, followed by subcutaneous administration of 1 ml of 0.9% normal saline between two shoulder blades, on two consecutive days on 8^{th} and 9^{th} day, with an interval of 24 h.

Group II (Negative Control): Rats of this group were given 1ml of 5% gum acacia (p. o) once daily for seven days followed by isoproterenol hydrochloride in a dose of 50 mg/ kg body weight dissolved in 0.9% normal saline, subcutaneously between two shoulder blades, twice at an interval of 24 h on 8^{th} and 9^{th} day to induce myocardial infarction.

Group III (Test Drug Control): Rats of this group were administered a test drug suspended in 5% gum acacia, in the dose of 800mg/kg body weight (p. o) once daily for 7 days, followed by subcutaneous administration of 1 ml of 0.9% normal saline on two consecutive days, with an interval of 24 h on 8^{th} and 9^{th} day.

Group IV & **V- (Pre-treated Test Groups in Lower & Higher doses):** the rats of these groups were administered test drug suspended in 5% gum acacia in the dose of 600 & 800mg/kg body weight (p. o), respectively, once daily, for 7 days followed by isoproterenol hydrochloride, dissolved in 0.9% normal saline, in the dose 50 mg/kg BW, subcutaneously, twice at an interval of 24 h on 8^{th} and 9^{th} day for the induction of myocardial ischemia. On 10^{th} day of the experiment, the animals of each group were given thiopentone sodium (50 mg/kg B. W) intraperitoneal, the abdominal cavity and thorax was opened, blood was drawn directly by cardiac puncture, and fresh serum was obtained by centrifugation at 4000 rpm for 10 minutes for the estimation of serum cardiac enzymes (CK, CK-MB, LDH, AST, and ALT) and lipid profile. The heart and adrenal glands of the animals were dissected out, separated carefully from adjacent structures, and weighed individually by using digital electronic weighing balance. The apex of the hearts was preserved in 10% formalin and sent for histopathological study. A portion of cardiac muscles from the same heart and adrenal gland site of all the animals were removed for estimation of cardiac glycogen and adrenal gland ascorbic acid.

Marker Enzymes Assay in Serum: The marker enzymes of myocardial infarction such as Alanine transaminase (ALT), Aspartate transaminase (AST), Lactate dehydrogenase (LDH), and creatine kinase-MB (CK-MB) were determined by using a commercially available diagnostic kit.

Measurement of Serum Lipid Profile: Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) were measured by using a commercially available diagnostic kit. Low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) were measured by using the Friedewald formula. [26]

$$\text{VLDL cholesterol (mg/dl)} = TG / 5$$

$$\text{LDL cholesterol (mg/dl)} = TC - HDL - VLDL$$

Estimation of Cardiac Glycogen: Estimation of cardiac glycogen was carried out by David Mortanai *et al.* [27] The cardiac tissue, 0.1gm was dissolved in 0.5 ml of 30% potassium hydro oxide (KOH) in a vial and heated at 100 °C for 10 minutes. After adding 1.5ml of absolute ethanol, the sample was centrifuged at 4500 rpm for 15 minutes. The supernatant was discarded, and the residue was re-suspended in 0.5 ml of water and 1 ml 0.2% anthrone reagent (0.2 g in 100 ml of 98% H_2SO_4) and then again heated at 100 °C for 10 min. The solution was assayed by using a UV-Visible Spectrophotometer at a wavelength of 620 nm.

Estimation of Adrenal Gland Ascorbic Acid: Estimation of adrenal gland ascorbic acid was

carried out by the method of Sudhanshu *et al.* [28] to estimate the ascorbic acid content, the adrenal gland was homogenized in 2ml of distilled water by tissue homogenizer. In this homogenate, 6 ml of 6% Trichloroacetic acid (TCA) was added and centrifuged at 4500 rpm for 15 min.

The supernatant was taken and coupled with 1 ml of 2, 4, N-dinitrophenyl hydrazine (DNPH) in the presence of 1 drop of thiourea as a mild reducing agent. To this solution, 2ml of 85% cold H_2SO_4 was added drop by drop, which converts DNPH into a red compound, which was assayed by a UV-Visible spectrophotometer at 520nm.

Histopathological Examination: On 10th day of the experiment, rats were sacrificed, and the heart was excised, washed, and then apexes of the hearts were preserved in 10% formalin solution and sent to Prakash Diagnostic Laboratory, Rajaji Nagar, Bangalore, for histopathological study.

Statistical Analysis: Data presented as mean ± SEM, analyzed for statistical significance using one-way variance analysis (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. *P* <0.05 was considered significant.

RESULTS

Effect on Weight of the Heart: There was no significant difference found in the mean weight of the hearts of Group-I and Group-III rats, whereas the heart weight was found to be increased significantly (*P*< 0.001) in Group-II. The mean heart weight of Group-IV and V was found to be decreased significantly at *P*< 0.01& *P*< 0.05, respectively, compared to Group-II and was almost the same as Group-I **Table 1, Fig. 1.**

TABLE 1: EFFECT OF *SANDAL SAFED* ON HEART & ADRENAL GLAND WEIGHT IN CONTROL AND EXPERIMENTAL GROUPS

Groups	Heart weight (gm)	Adrenal gland weight (gm)
Group-I (Plain Control)	0.6512 ± 0.009724	0.01682 ± 0.0003589
Group-II (Positive Control)	0.8007 ± 0.01593^{a***}	0.02069 ± 0.0003573^{a***}
Group-III (Test drug control)	0.6837 ± 0.01520^{b***}	0.01368 ± 0.0003596$^{a***, b***}$
Group-IV (Pre-treated LD)	0.7178 ± 0.01652$^{a*, b**}$	0.01803 ± 0.0002520^{b***}
Group-V (Pre-treated HD)	0.7338 ± 0.007313$^{a**, b*}$	0.01785 ± 0.0002078^{b***}

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001.

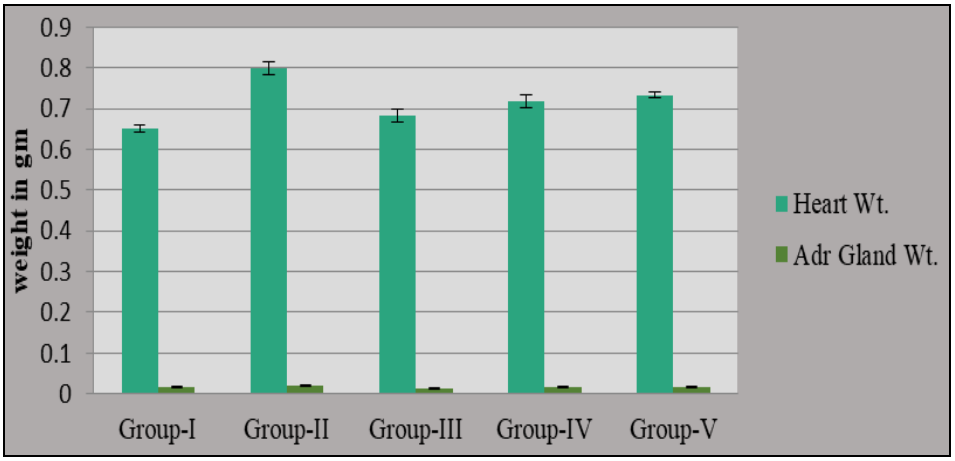

FIG. 1: EFFECT OF *SANDAL SAFED* ON HEART & ADRENAL GLAND WEIGHT IN CONTROL AND EXPERIMENTAL GROUP

Effect on Weight of the Adrenal Gland: The mean weight of adrenal gland of Group-II rats was found to be increased significantly (P< 0.001), on the contrary it was significantly (*P*< 0.001) decreased in Group-III rats as compare to Group-I. When the weight of adrenal glands of group-II was compared with Group-IV and V (pre-treated test groups in lower & higher doses), a significant decrease at *P*< 0.001, *P*< 0.001, respectively, was found in Group-IV and V animals. No significant difference was found between group-IV and Group-V **Table 1, Fig. 1.**

Effect on Serum Marker Enzymes:

Creatine Kinase (CK): The mean CK value of Group-II was significantly (*P*< 0.001) increased as compared to plan control (Group-I). When compared with Group-II, a significant decreased was observed in CK values of Group-III and V at *P*< 0.001, *P*< 0.001, respectively, A significant (*P*< 0.05) difference was also observed between Group-IV and V. There was no significant difference between Group-I and Group-III **Table 2, Fig. 2.**

TABLE 2: EFFECT OF *SANDAL SAFED* ON SERUM CK & CK-MB IN CONTROL AND EXPERIMENTAL GROUPS

Groups	CK (IU/L)	CK-MB (IU/L)
Group-I (Plain Control)	550.8 ± 40.79	436.7 ± 53.47
Group-II (Positive Control)	1173 ± 91.61^{a***}	1169 ± 57.39^{a***}
Group-III (Test drug control)	548.2 ± 43.42^{b***}	480.4 ± 40.95^{b***}
Group-IV (Pre-treated LD)	962.8 ± 32.62^{a***,c***}	804.6 ± 25.56^{a***,b***,c***}
Group-V (Pre-treated HD)	669.1 ± 33.78^{b***,d*}	742.2 ± 37.78^{a**,b***,c**}

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Test drug treated group (c) compared with other groups. ** P< 0.01, *** P< 0.001. Group-IV (d) compared with group V. *P< 0.05, ** P< 0.01, *** P< 0.001.

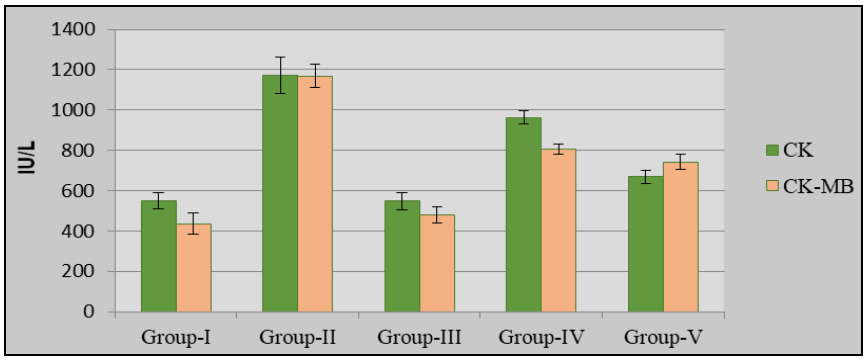

FIG. 2: EFFECT OF *SANDAL SAFED* ON SERUM CK & CK-MB IN CONTROL AND EXPERIMENTAL GROUPS

Serum CK-MB: In Group-II rats, serum CK-MB was significantly increased at *P*< 0.001, when compared to Group-I, whereas Group-IV and V showed a significant (*P*< 0.001, *P*< 0.001) decrease in the mean serum CK-MB levels as compare to Group-II. The value of Group III was not found to be significant as compared to Group-I **Table 2, Fig. 2.**

Serum LDH: The mean serum LDH value was increased significantly (*P*<0.001) in Group-II when compared with Group-I. Whereas, the value of serum LDH enzyme in Group-IV and V decreased significantly at P<0.001 compared with Group-II. The mean enzyme value was found to be statistically the same in Group-I and Group-III **Table 3, Fig. 4**.

Serum AST/SGOT: The level of serum SGOT in Group-II rats was significantly (*P*<0.001) increased when compared with Group-I and III. The value of SGOT was found to be the same in Group-I and III. Though the value was decreased slightly in Group IV and V compared to Group II, statistically, it was not significant **Table 3, Fig. 4.**

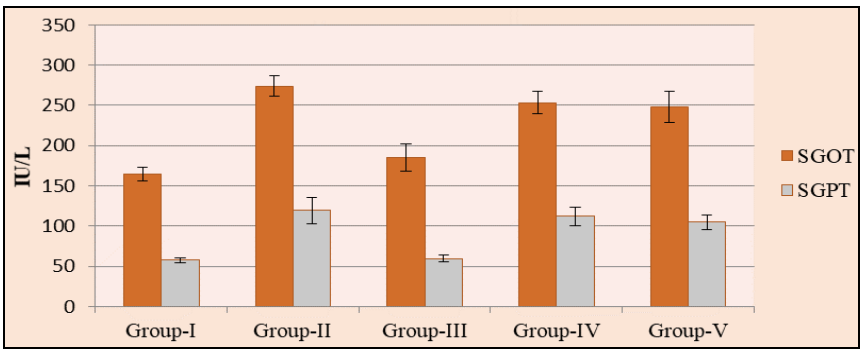

FIG. 3: EFFECT OF *SANDAL SAFED* ON SERUM SGOT & SGPT IN CONTROL AND EXPERIMENTAL GROUPS

Serum ALT/SGPT: The value of serum SGPT in Group-II rats was increased significantly at *P*<0.001, compared with Group-I and III, whereas the level of SGPT was found to decrease in Group-IV and Group-V when compared to Group-II, but statistically it was not significant. There was no statistical difference found between the value of SGPT in Group-I & III **Table 3, Fig. 4.**

TABLE 3: EFFECT OF *SANDAL SAFED* ON SERUM LDH, SGOT & SGPT IN CONTROL AND EXPERIMENTAL GROUPS

Groups	LDH(IU/L)	SGOT (IU/L)	SGPT (IU/L)
Group-I (Plain Control)	1160 ± 102.2	165.0 ± 8.719	57.69 ± 3.035
Group-II (Positive Control)	2811 ± 153.8 ^{a***}	274.1 ± 12.96 ^{a***}	119.4 ± 16.36 ^{a***}
Group-III(Test drug control)	1162 ± 81.67 ^{b***}	185.4 ± 16.57 ^{b***}	59.90 ± 4.024 ^{b***}
Group-IV(Pre-treated LD)	2204 ± 175.1 ^{a***,b*,c***}	253.4 ± 14.24 ^{a***,c*}	112.0 ± 11.27 a ^{**,c**}
Group-V(Pre-treated HD)	1821 ± 84.09 ^{a*,b***,c*}	248.4 ± 19.24 ^{a**,c*}	104.9 ± 9.440 ^{a*,c*}

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001.

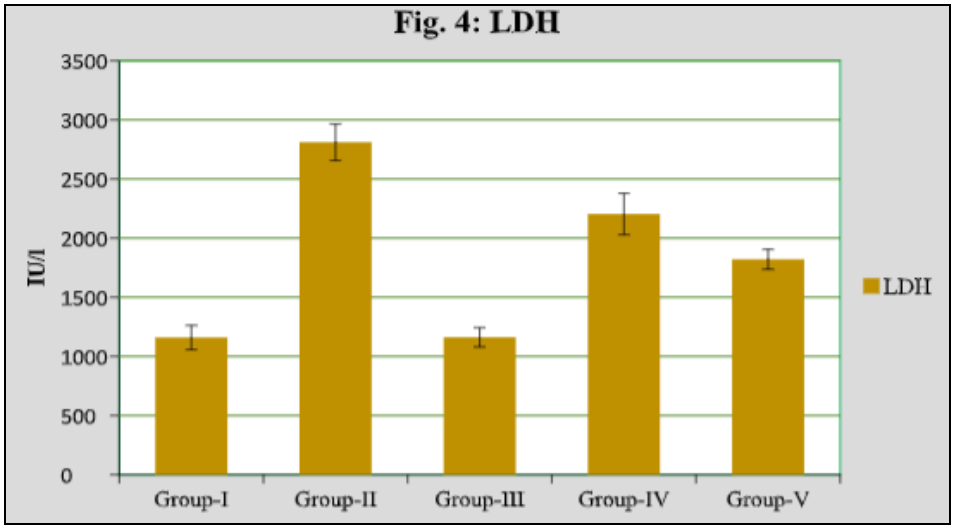

FIG. 4: EFFECT OF *SANDAL SAFED* ON SERUM LDH IN CONTROL AND EXPERIMENTAL GROUPS

Effect on Serum Lipid Profile:

Serum Total Cholesterol: The mean value of total cholesterol in Group-I and Group-III rats was found to be the same, but the value was increased significantly (P<0.001) in Group-II compared to Group-I and III. The values were found to be significantly decreased in Group-IV and Group-V at *P*<0.001, *P*<0.05, respectively when compared with Group-II. When the values were compared between Group IV and V, a significant decrease in total cholesterol level was observed in Group IV **Table 4, Fig. 5.**

TABLE 4: EFFECT OF SANDAL SAFED ON SERUM T. CHO, TG & AMP; HDL IN CONTROL AND EXPERIMENTAL GROUPS

Groups	T. Cho (mg/dl)	TG (mg/dl)	HDL (mg/dl)
Group-I (Plain Control)	60.51 ± 2.199	60.43 ± 1.941	36.50 ± 1.643
Group-II (Positive Control)	85.63 ± 2.352 a***	90.06 ± 2.372 a***	26.32 ± 1.509a**
Group-III(Test drug control)	60.75 ± 1.673 b***	66.29 ± 3.502 b***	41.44 ± 1.884 b***
Group-IV(Pre-treated LD)	76.42 ± 1.407 a***,b*,c***	64.75 ± 2.730 b***	32.88 ± 1.333 c*
Group-V(Pre-treated HD)	64.01 ± 2.290 b***,d**	54.93 ± 2.433 b***	39.79 ± 3.242 b***

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Test drug treated group (c) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Group-IV (d) compared with group V. *P< 0.05, ** P< 0.01, *** P< 0.001.

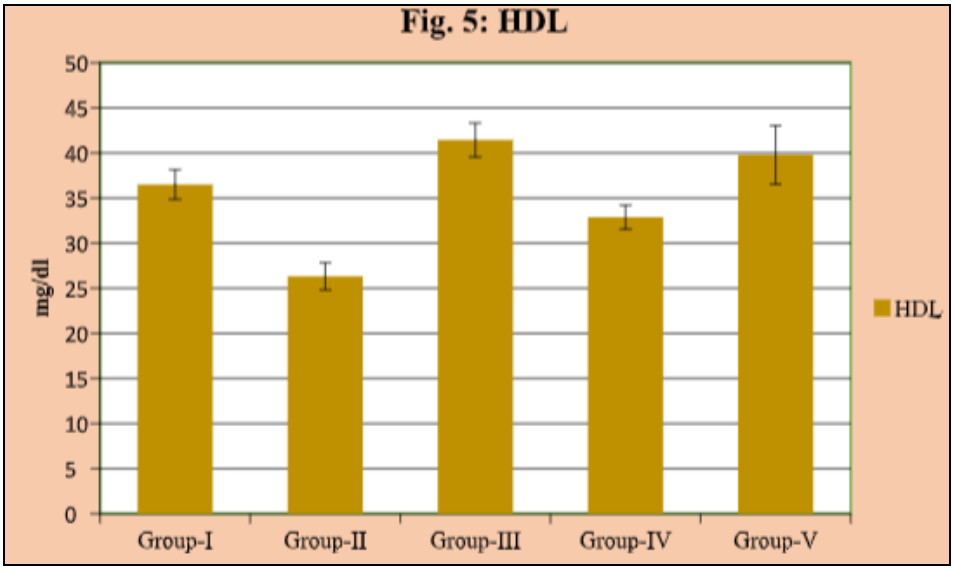

FIG. 5: EFFECT OF *SANDAL SAFED* ON SERUM HDL IN CONTROL AND EXPERIMENTAL GROUPS

Serum Triglyceride (TGL): The mean value of serum TGL was found to be the same in Group-I and Group-III, but the value was significantly increased (*P*<0.001) in Group-II as compared to Group-I and III.

The value was found to decrease significantly in Group-IV and V at P<0.001 and *P*<0.001, respectively, when compared with Group-II. No significant difference was observed between Group-IV & V **Fig. 6.**

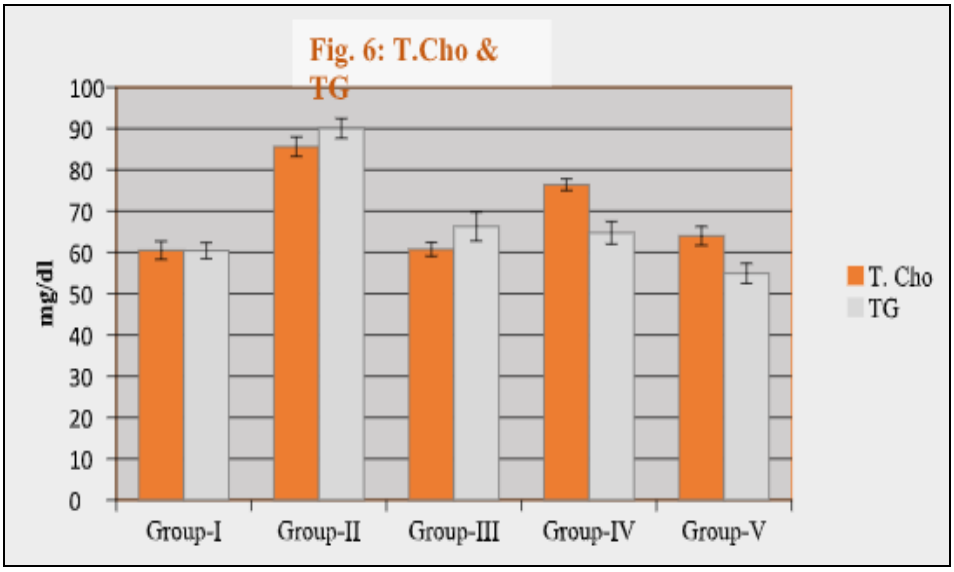

FIG. 6: EFFECT OF *SANDAL SAFED* ON SERUM T. CHO & TG IN CONTROL AND EXPERIMENTAL GROUPS

Serum HDL-C: When the mean value of serum HDL-C was compared in different groups, the values of Group-I and Group-III were found to be the same.

Group II showed a significant decrease level of serum HDL-C at *P*<0.01 and *P*<0.001 when compared to Group-I and III, respectively, when Group II was compared with Group IV and Group V, a significant (*P*<0.001) increase in the level of mean serum HDL-C was observed in Group-V **Fig.**

7. Serum LDL: The mean value of serum LDL of Group-I and Group-III was found to be the same, but the value was significantly (P<0.001) increased in Group-II compared with Group-I and III. When Group-II was compared with Group IV and Group-V, no significant difference was observed in Group-IV. Still, the level of serum LDL decreased significantly (*P*<0.001) in Group V.

The level also decreased significantly (*P*<0.01) in Group V compared to Group IV **Table 5, Fig. 7.**

TABLE 5: EFFECT OF SANDAL SAFED ON SERUM LDL & VLDL IN CONTROL AND EXPERIMENTAL GROUPS

Groups	LDL (mg/dl)	VLDL (mg/dl)
Group-I (Plain Control)	11.83 ± 3.727	12.08 ± 0.3885
Group-II (Positive Control)	41.29 ± 2.580 a***	18.01 ± 0.4744 a***
Group-III (Test drug control)	6.710 ± 1.328 b ***	13.26 ± 0.7005 b***
Group-IV (Pre-treated LD)	30.62 ± 2.530 a***,c***	12.95 ± 0.5460 b***
Group-V (Pre-treated HD)	13.24 ± 2.258 b***,d**	10.99 ± 0.4866 b***

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Test drug treated group (c) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Group-IV (d) compared with group V. *P< 0.05, ** P< 0.01, *** P< 0.001.

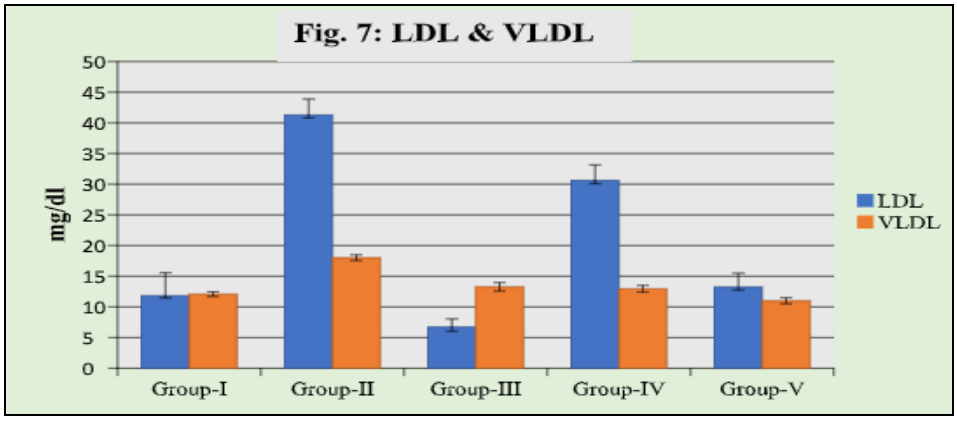

FIG. 7: EFFECT OF *SANDAL SAFED* ON SERUM LDL & VLDL IN CONTROL AND EXPERIMENTAL GROUPS

Serum VLDL: The mean value of serum VLDL of Group-I and Group-III was the same, but the value was significantly increased in Group-II at P<0.001 compared with Group-I and III. The value was significantly decreased at *P*<0.001 in Group-IV and V compared with Group-II. No significant difference was observed between Group IV and V **Table 6, Fig. 8.**

TABLE 6: EFFECT OF SANDAL SAFED ON CARDIAC GLYCOGEN & AMP; ADRENAL GLAND ASCORBIC ACID IN CONTROL AND EXPERIMENTAL GROUPS

Groups	Cardiac glycogen (620 nm)	Adrenal gland ascorbic acid (540 nm)
Group-I (Plain Control)	1.014 ± 0.1032	0.0930 ± 0.003037
Group-II (Positive Control)	0.5365 ± 0.05575	0.0863 ± 0.002840
Group-III (Test drug control)	1.593 ± 0.2350 b***	0.1246 ± 0.007942 a*, b**
Group-IV (Pre-treated LD)	1.046 ± 0.1612	0.0975 ± 0.005106
Group-V (Pre-treated HD)	1.277 ± 0.1715 b*	0.1112 ± 0.01765

All values are expressed as mean ± SEM using one-way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test. Plain control (a) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001. Positive Control (b) compared with other groups. *P< 0.05, ** P< 0.01, *** P< 0.001

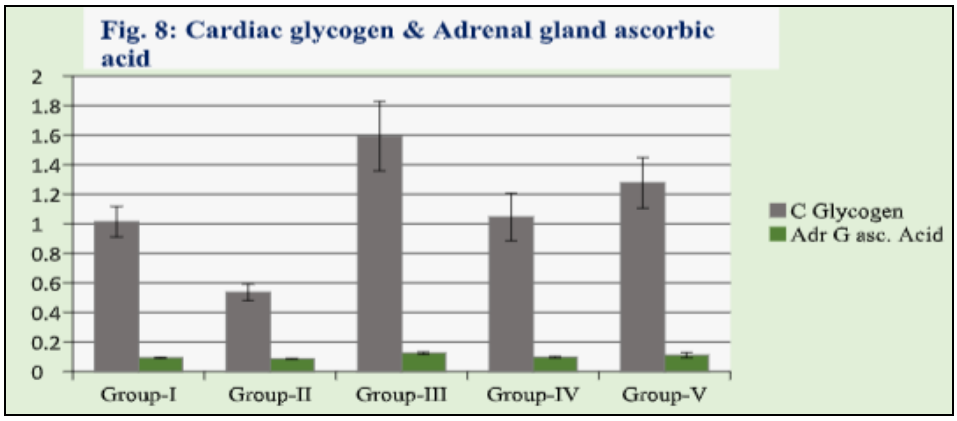

FIG. 8: EFFECT OF SANDAL SAFED ON CARDIAC GLYCOGEN & AMP; ADRENAL GLAND ASCORBIC ACID IN CONTROL AND EXPERIMENTAL GROUPS

Effect on Heart Tissue Glycogen: The absorbance of Cardiac glycogen in Group II was found to be significantly less at $P<0.001$ when compared to Group-III and at $P<0.05$ with group V. There was no significant difference found in Group-I, III, IV & V, as the absorbance was almost the same in these groups **Fig. 8.**

Effect on Adrenal Gland Ascorbic Acid: The absorbance of adrenal gland ascorbic acid was decreased in Group-II compared with all the groups, though it was not statistically significant. A significant increase in the absorbance at $P<0.001$ was observed in Group III compared to Group II **Fig. 8.**

Histopathological Examination: The section study of the myocardium of Group-I and Group-III animals showed an intact arrangement of the cardiac muscle fibers with intact cell membrane integrity. The myofibrillar structure showed striations and continuity with adjacent myofibrils. The interstitial space and vascular spaces appeared unremarkable **Fig. 1-13.** The section study of Group-II animals showed predominantly damaged cardiac muscle fibers along with coagulative necrosis comprising of loss of integrity of myocardial cell membrane, myofibrillar structure with loss of striations, and lack of continuity with adjacent myofibrils. The interstitial spaces appear to be increased in many areas containing severe edema with aggregates of inflammatory cells. Some of the vascular spaces amidst necrosis and cardiac fibers appear disrupted **Fig. 9.**

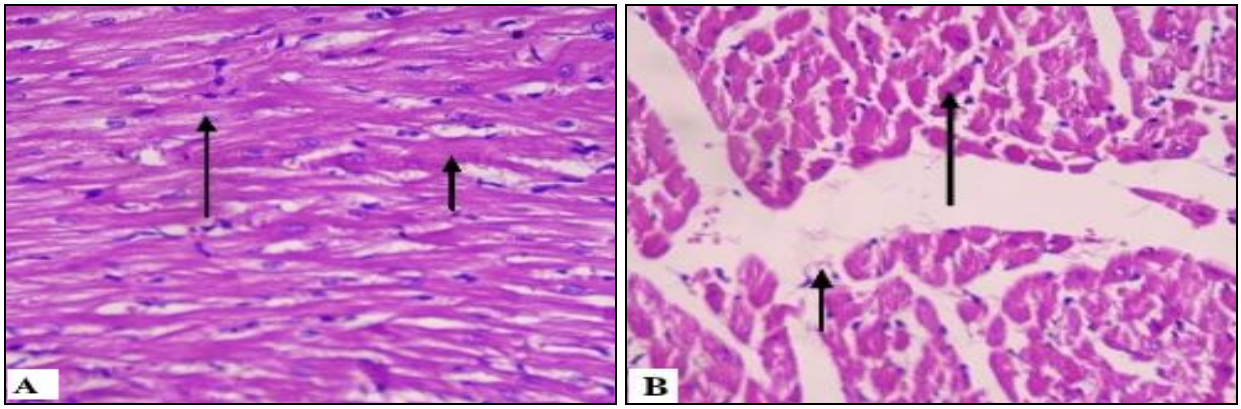

FIG. 9: GROUP-I (PLAIN CONTROL): SHOWS NORMAL MYOFIBRILLAR STRUCTURE WITH STRIATIONS [X400

Group-IV animals showed a partially intact arrangement of the cardiac muscle fibers with loss of integrity of myocardial cell membrane at some places, myofibrillar structure with lack of striations, and loss of continuity with adjacent myofibrils. The interstitial space in some areas appears to be increased with mild edema and inflammatory cell infiltrations. The vascular spaces appeared unremarkable **Fig. 10**.

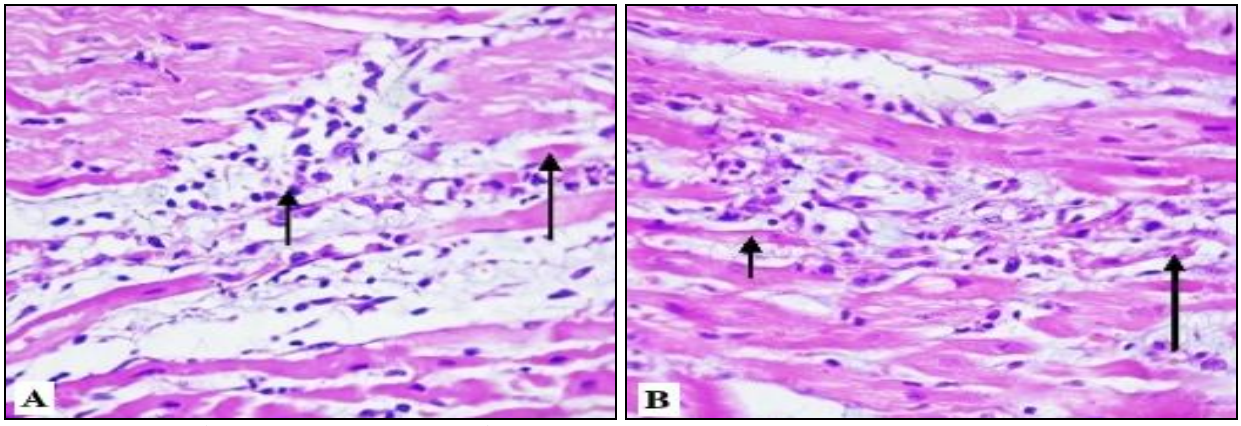

FIG. 10: GROUP-II (POSITIVE CONTROL): SHOWS PREDOMINANTLY DAMAGED CARDIAC MUSCLE FIBRES WITH COAGULATIVE NECROSIS, INCREASED INTERSTITIAL SPACE AT MANY AREAS CONTAINING SEVERE EDEMA WITH AGGREGATES OF INFLAMMATORY CELLS [X400]

The myocardium of Group-V animals showed an intact arrangement of the cardiac muscle fibers. Few of these cardiac muscle fibers showed loss of intact integrity of myocardial cell membrane, myofibrillar structure with lack of striations and loss of continuity with adjacent myofibrils. The interstitial spaces at focal areas appear to be increased with mild edema. The vascular spaces and cardiac muscle fibers appeared unremarkable **Fig. 11.**

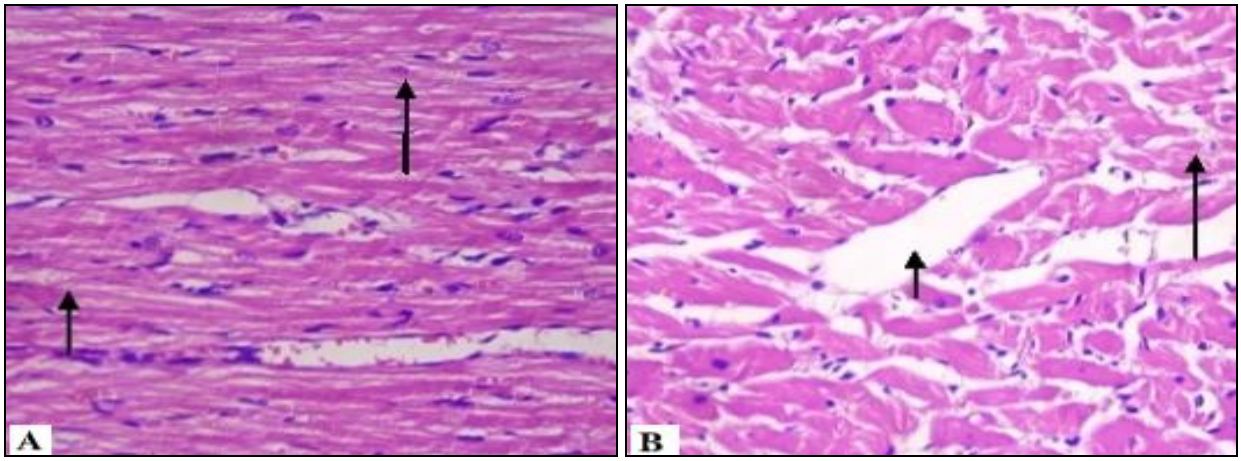

FIG. 11: GROUP-III (TEST DRUG TREATED): SHOWS NORMAL MYOFIBRILLAR STRUCTURE WITH STRIATIONS [X400]

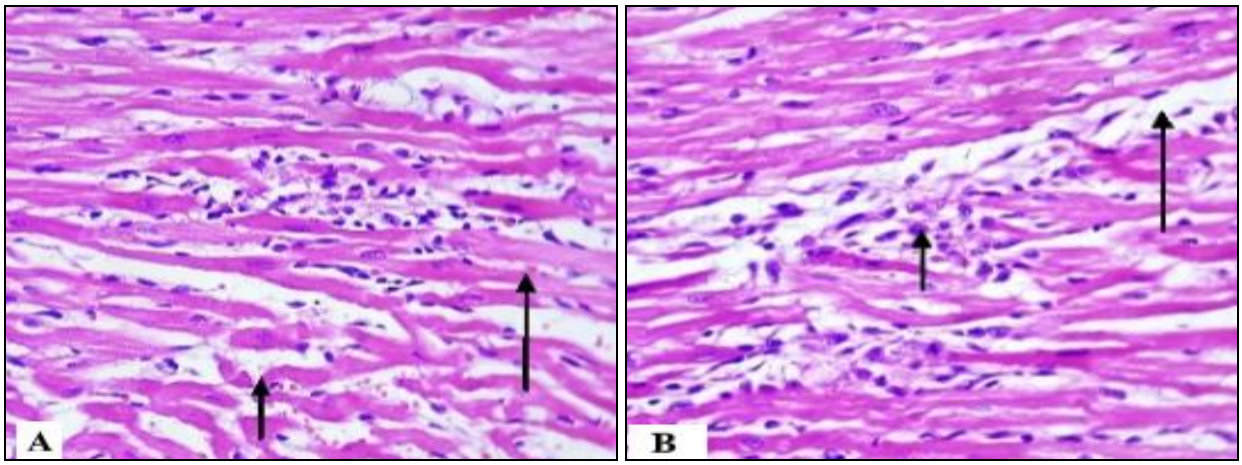

FIG. 12: GROUP-IV (PRE-TREATED WITH LD): SHOWS PARTIALLY INTACT ARRANGEMENT OF CARDIAC MUSCLE FIBRES WITH NECROSIS, INCREASED INTERSTITIAL SPACE AT MANY AREAS CONTAINING MILD EDEMA WITH FEW OF INFLAMMATORY CELLS [X400]

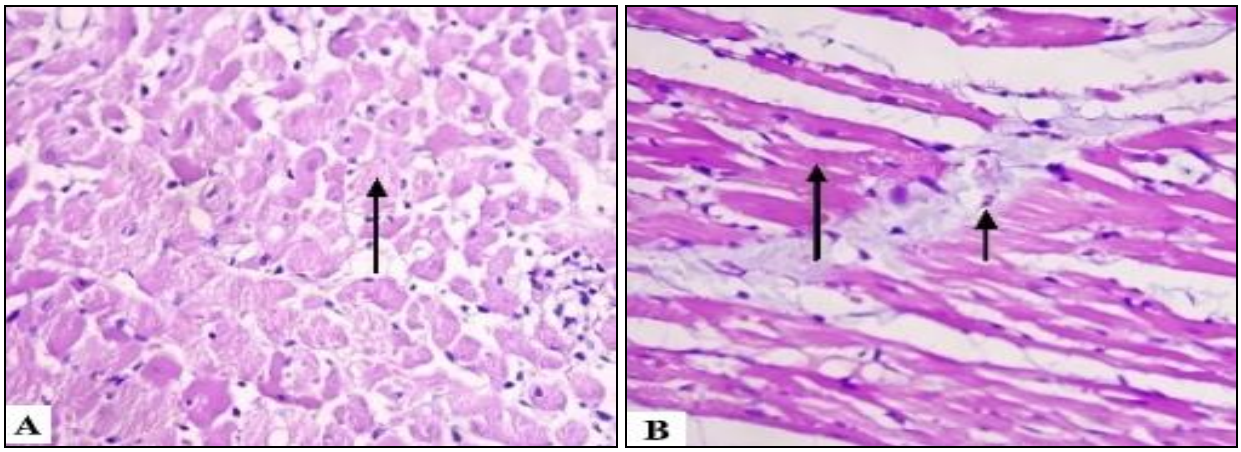

FIG. 13: GROUP-V (PRE-TREATED WITH HD): SHOWS MILD DAMAGED CARDIAC MUSCLE FIBRES WITH MILD NECROSIS, MILD EDEMA WITH FEW INFLAMMATORY CELLS [X400]

DISCUSSION: In Unani Medicine, *Sandal safed* (Sandalwood) has been described to possess cardioprotective effects and has been used to manage cardiac diseases. *Ibne Sina* has also included *Sandal safed* in his book, "*Al-Adviya-al-Qalbiya* [8, 9, 10, 11]. Many scientific studies have been carried out to evaluate its other therapeutic effects, but the protective effect of *Sandal safed* in cardiovascular diseases has not been investigated. Therefore, the present study was envisaged to evaluate and explore the protective effect of *Sandal safed* in ISO-induced MI in male Wistar rats. Isoproterenol (ISO) is a synthetic, potent, β-adrenergic agonist that causes oxidative stress mainly via the β-1 adrenergic receptor stimulation [29] in large doses in the heart muscle, leading to myocardial infarction necrosis in animals [30].

Serum enzymes are used conveniently as a marker to detect cellular damage, which ultimately helps in the diagnosis of the disease. The results and observations of this study showed a significant increase in the level of enzymes such as CK, CK-MB, LDH, AST and ALT in Group-II (negative control) at $P<0.001$ as compared to Group-I and III, which might be due to enhanced susceptibility of the myocardial cell membrane to the isoproterenol mediated peroxidative damage [31]. The increased level of these enzymes indicates severe necrotic damage to myocardial membrane. The value of cardiac enzymes in serum is proportional to the number of necrotic cells [32].

The level of CK, CK-MB and LDH were significantly decreased at $P<0.001$ in Group-IV and V (pre-treated test groups in lower & higher doses), but the level of AST and ALT was not decreased at a significant level. When the values of CK, CK-MB, LDH, SGOT, and SGPT of Group-V were compared with Group-II and IV, it showed highly significant results, indicating its cardioprotective property in a dose-dependent manner. When the Group-III, test drug control, was compared with Group-I, plain control, there was no significant difference in the values of CK, CK-MB, LDH, AST, and ALT enzymes, which proves that *Sandal safed* has no remarkable side effects on the normal heart. The results indicate that *Sandal safed* reduced the extent of myocardial damage and thereby restricted the secretion of these enzymes from myocardium because of its *Mufarreh* and *Muqawwie Qalb* activities, which protect the heart by preventing it from accepting harmful effects and nurturing the *Rooh* (pneuma) to produce *Farhat* (exhilaration) without producing any kinds of adverse effect. According to *Ibn Sina* "*Mufarreh Qalb Advia*" are the drugs that bring strength to *Quwwate Tabiya* (natural faculties) and *Takhalkhul* (fluffiness & ethereality) in *Rooh,* defuse the abnormal and suppressive conditions, and produce a relative degree of *Lazzat* (ecstasy) and *Farhat* by supplying abundant amount of *Jauhare Rooh* (vitality of pneuma) to the heart. At the same time, *Muqawwie Qalb* drugs produce strength to the heart and bring about the balance in consistency and constitution of the heart and render it impervious to obnoxious forces.

These drugs act either through their specific property or by dint of a balance in their temperament [7]. The negative control group (Group-II) rats showed a highly significant increase in the mean values of cholesterol, TG, LDL and VLDL in serum at $P<0.001$, whereas the HDL level was significantly decreased. This may be because of ISO-mediated lipolysis and lipid Peroxidation [33]. The values of cholesterol, TG, LDL, and VLDL of Group-IV and V were significantly decreased at $P<0.001$ compared with the values of Group-II in a dose-dependent manner. The HDL levels in Group IV and V were highly increased when compared with Group II.

There was no significant difference observed in the lipid profile of Group-III and I animals. The improvement in hyperlipidemia by *Sandal safed* could be possibly due to its notable antioxidant, anti-lipid peroxidative [16] and antihyperlipidemic properties [17]. The weight of the heart was significantly increased at $P<0.001$ in Group-II rats as compared to other groups, which identify the hypertrophy of the heart as a compensatory response to necrosis of the heart muscle, which is caused by the severe stress of the heart induced by administration of ISO [34, 35]. The heart weight of Group-IV and V animals was significantly decreased at $P< 0.01$& $P< 0.05$ respectively when compared to Group-II and were almost similar to the heart weight of plain control and test drug control groups. Thus, these findings also indicate that the *Sandal safed* has protected the heart cells against stress caused by ISO.

Rapid anaerobic glycogenolysis results from anoxia of the myocardium, whether due to strenuous exercise, hemorrhagic shock, ventricular tachycardia, fibrillation, or temporary interruption of the coronary blood flow. A histochemical study showed that stainable glycogen disappears from ischemic myocardium within a brief period after coronary artery ligation [36]. Catecholamine also increases the glycogen breakdown making more carbohydrates available for glycolytic energy [37].

Thus, in myocardial necrosis, the level of cardiac glycogen gets depleted. In the present study, Group-II rats have shown a decreased level of cardiac glycogen at $P<0.001$ compared to Group-III and I. The level of Cardiac glycogen was found to be significantly increased at $P<0.05$ in Group-V compared with Group-II, and the Group-III rats showed a high increase level of glycogen content at $P<0.001$ compared with all the groups. The test drug in minimum dose (Group-IV) was found to give the same cardiac glycogen values as in the plain control (Group-I). Thus, the finding suggests that the test drug *Sandal safed* helps in preserving the depletion of cardiac glycogen by inhibiting ISO cardiotoxicity and restoring the myocardial damage. The increased glycogen values in test drug control (Group-III) reveal the preventive and prophylactic potency of *Sandal safed*. While working with rats, Sayers and Sayers demonstrated that adrenal ascorbic acid and adrenal cholesterol decreased when the animals were stressed or when their adrenal cortices were stimulated with corticotrophin (ACTH). Since then, there has been a general acceptance of ascorbic acid requirements in the states of "damage" or stress [38].

Acute myocardial infarction produces severe stress, which causes enhanced adrenocortical activity and depletion of adrenal gland ascorbic acid [39]. In the present study, Adrenal gland weight was increased significantly in Group II when compared with all other groups. Adrenal gland weight was decreased significantly in Group III when compared with Group-I, II, IV, and V. The gland weight was found to be similar in Group-I, IV, V. When ascorbic acid content was compared among the groups, it was found that the content of ascorbic acid was more in Group-III. The ascorbic acid content of Group-I plain control and maximum dose of test drug group V were more than when compared with Group-II. This finding again supports the protective effect of *Sandal safed* against damage and stress produced by ISO, which may be due to its potent antioxidant properties [40]. Moreover, the *Mufarreh* and *Muqawwi Qalb, Muqawwie hararate gareezi, Muhllile warm, Mujaffife Qurooh, and Tiryaq* (antidote) *etc*. properties [8, 9, 10, 11, 12, 13, 14, 15, 21, 41, 42] mentioned in Unani literature are in accordance with many research studies, which revealed that *Sandal safed* possesses anti-inflammatory, antibacterial and antioxidant activities [43].

The anti-oxidant activity of aqueous extract of *Sandal safed* was proven by most common radical scavenging assay of FRAP (Ferric reducing antioxidant power and DPPH (1,1- diphenyl-2-picryl hydrazyl). Antibacterial and antioxidant activities may be responsible for its antitumor, anti-carcinogenic activities, as mentioned in Unani literature [44, 45]. α-Santalol, an active component of sandalwood oil, has shown chemopreventive effects on skin cancer in different murine models [46]. Many studies support anti-cancer activities of sandalwood, *sandal safed* (*Santalum album*) [47]. The histopathological examination of heart tissue of Group-I and III rats showed normal myocardial fibers and muscle bundles with normal architecture. Group-II rats showed predominantly damaged cardiac muscle fibers along with coagulative necrosis comprising of loss of integrity of myocardial cell membrane, increased interstitial spaces containing severe edema with aggregates of inflammatory cells.

Some of the vascular spaces amidst necrosed and cardiac fibers appear disrupted, these changes have confirmed the myocardial damage with ISO treatment **Fig. 10**. The histopathological report of the heart tissues of Group-IV and V animals showed a maximum cardioprotective effect of the test drug by markedly reducing the histopathological changes caused by ISO, in a dose dependent manner as compared to Group-II rats **Fig. 12**. The test drug in Group-IV and V also reduced or prevented severe edema due to myocardial necrosis in Group-II by showing the interstitial and vascular spaces unremarkable in the section study. Test drug has been found to prevent the loss of integrity of myocardial cell membrane and myofibrillar structure, which is evident by the section study of Group-IV & V showing almost

normal striation and continuity with adjacent myofibrils **Fig. 13**. These groups also showed to prevent cardiac muscle fibers from coagulative necrosis and showed an intact arrangement of cardiac muscle fibers. The effect of the test drug may be ascribed due to its chemical constituents that are able to normalize the calcium influx following induction of infarction, which may not only reduce the infarct size but also prevent DNA damage due to necrosis and may also prevent excessive NO production, which may injure the myocardium [48].

CONCLUSION: In the light of the above results and discussion of the study, it can be concluded that the administration of powder of *Sandal safed* has prevented biochemical and histo-morphological alteration induced by ISO. The protective effect of *Sandal safed* could be attributed to its main *Mufarreh* (exhilarant) *Muqawwi Qalb* (cardiotonic), *Muqawwie Hararate Gareezi* (strengthen the innate heat) and *mohallile warm* (anti-inflammatory) properties which protect the heart by preventing it from accepting harmful effects and nurturing the *Rooh* (pneuma), to produce *Farhat (exhilaration)* and thus provides strength to the heart and due to its phytochemicals which are proved to be antioxidant and anti-inflammatory activities, which significantly lowers the oxidative threat and lead to normal physiological and structural functions.

The findings of the study support the use of *Sandal safed* as a cardioprotective and antioxidant drug. Since, the test drug possesses a dose-dependent effect without any observable side effects, it can be used in different (acute, sub-acute & chronic) cardiovascular disorders.

Further, work should be embarked upon to elucidate the exact possible mechanisms of action of the test drug. The present study results can form the initial impetus for future researchers to investigate the potential discovery of naturally occurring bioactive compounds from sandalwood for its cardioprotective effect.

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