

Protective Effect of Peanut (*Arachis Hypogaea* L.) and Its Combination with Propranolol in Cardiotoxic Rats

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Abstract

Background: Cardiotoxicity (CT) can be developed due to prolonged use of higher doses of some drugs, exposure to some chemicals, toxins or infectious agents and also by some disease conditions. Natural plant foods such as peanut (*Arachis hypogaea* L.) may have free radical scavenging activity, thereby can be used for the prevention and management of heart disease. **Objective:** To observe the protective effect of peanut (*Arachis hypogaea* L.) and its combined action with propranolol on histological changes in isoproterenol induced cardiotoxic rats. **Method:** This experimental study was carried out in the Department of Physiology, Sir Salimullah Medical College, Dhaka in 2012. For this purpose, 20 Wistar albino rats, age 85- 100 days, weighing 120 to 150g (initial body weight) were included in the peanut treated group. They were sub-divided into CT-ISO-P (Cardiotoxic group with isoproterenol after peanut treatment) and CT-ISO-C (Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol). Age and weight matched 30 Wistar albino rats without any peanut supplementation were taken and sub-divided into three sub-groups, BC (Baseline control), CT-ISO (Cardiotoxic group with isoproterenol) and CT-ISO-PRO (Cardiotoxic group with isoproterenol after propranolol treatment). Each sub-group consisted of 10 rats. After taking final body weight all the rats were sacrificed on 22nd day. The heart was removed and preserved in 10% formalin for histological processing. To find out the histopathological changes of heart tissue, histological slides were prepared and were observed under microscope in the Department of Pathology, SSMC. Histological findings were categorized by scoring as mild, moderate and severe histological changes. The statistical analysis was done by one way ANOVA and Bonferroni test as applicable. **Result:** In this study, percent change from initial body weight to final body weight was significantly ($p < 0.01$) lower both in CT-ISO-P and CT-ISO-C as compared to that of BC. Again, histological score was significantly ($p < 0.01$) higher in CT-ISO in comparison to that of BC. Moreover, these scores were significantly lower in CT-ISO-PRO ($p < 0.01$), CT-ISO-P ($p < 0.05$) and CT-ISO-C ($p < 0.05$) in comparison to that of CT-ISO. Similarly, this score was significantly ($p < 0.01$) lower in CT-ISO-C when compared to that of CT-ISO-P. **Conclusion:** The present study revealed that peanut can preserve almost normal histological architecture of heart tissue in isoproterenol induced cardiotoxic rats. However, the combined therapy of peanut with propranolol showed synergistic effect on preventing histological changes in heart tissue.

Key words: Peanut, Propranolol, Isoproterenol, Histology

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Introduction

Cardiotoxicity (CT) is the electrophysiological dysfunction of heart and myocardial damage¹. It may be caused

by chemotherapy treatment with cytotoxic drugs such as doxorubicin, epirubicin, cisplatin etc, adverse effects of heavy metals intake like lead, cadmium etc, and an incorrectly administered

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drug such as high dose of isoproterenol and also by some cardiotoxins².

Isoproterenol (ISO) is a sympathomimetic non-selective β -adrenergic receptor agonist used to produce myocardial injury in experimental animals for evaluation of various cardioprotective agents³. High dose of isoproterenol causes severe oxidative stress in the myocardium resulting in infarction, it also generate free radicals and stimulate lipid peroxidation⁴.

Isoproterenol induced cardiotoxicity leads to severe histological changes in the myocardium due to free radical injury³. Histopathological examination of heart tissue showed disorganization of normal histological architecture of myocardium⁵. Loss of myocardial integrity, widespread necrosis with diffuse inflammation were observed by some investigators after using high dose of isoproterenol in their study⁶.

However, propranolol (PRO) is a non-selective β -blocker used in patients with hypertension, ischemic heart disease, cardiac arrhythmias and other cardiovascular diseases⁷. But long term use of propranolol may produce dyslipidemia, bradycardia, insomnia, light-headedness etc⁸.

Arachis hypogaea L. known as peanut belongs to the family of fabaceae have been valued for their high nutritional content throughout the world for many years⁹. Peanuts are energy dense foods that are particularly rich in fat, mostly unsaturated fatty acids and this unsaturated fatty acid of nuts through its lipid lowering effect may be responsible for their protective effects against ischemic heart disease¹⁰. Peanuts are also a rich source of vitamin-B, vitamin-E, magnesium, copper, phosphorus, plant protein, arginine, dietary fiber and numerous bioactive substances like flavonoids, resveratrol and plant sterols¹¹. Peanut consumption is relatively safe but approximately 1% in the general population showed nut allergy¹².

Some researchers observed that consuming about an ounce of peanuts every day can reduce the risk of heart diseases by up to half¹³. Moreover, some other researchers found that consumption of peanut 5 times per week (about 155g of nuts/week) reduced the risk of death from coronary heart diseases by 35%¹⁴. Recently in an experimental study some researchers observed significant improvement in the histological structure in rats treated with conventional cardioprotective drug propranolol (β -blocker) along with *Semecarpus anacardium* (a species of nut closely related to cashew) nut extract in isoproterenol treated cardiotoxic rats¹⁵.

Therefore, the present study has been designed to observe the effect of peanut (*Arachis hypogaea* L.) and its combination with propranolol on the histological changes in heart tissue in isoproterenol induced cardiotoxic rats.

Methods

This experimental study was conducted in the Department of Physiology, Sir Salimullah Medical College (SSMC), Mitford, Dhaka from January to December 2012. The protocol of this study was approved by Institutional Ethics Committee (IEC) of SSMC. Twenty Wistar albino rats, age 85-100 days, weighing 120 to 150g (initial body weight) were included in the experimental group (with peanut). They were sub-divided into CT-ISO-P (Cardiotoxic group with isoproterenol after peanut treatment) and CT-ISO-C (Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol). Age and weight matched 30 Wistar albino rats without any peanut supplementation was taken as control and sub-divided into three sub-group, BC (baseline control), CT-ISO (Cardiotoxic group with isoproterenol) and CT-ISO-PRO (Cardiotoxic group with isoproterenol after propranolol treatment). Each subgroup consisted of 10 Wistar albino rats. Before grouping all the animals were acclimatized for 14 days under 12 hour dark and light cycle. During this study they had free access

to food and water *ad libitum*. Each group consisted of 10 rats and was given basal diet for 21 consecutive days. In addition to this, animals of CT-ISO-PRO were given propranolol (10mg/kg body weight; orally) for last seven (from 15th to 21st day of study period) consecutive days, animals of CT-ISO-P were given peanut extract (500mg/kg body weight; orally) for 21 consecutive days (started from 1st day of study period), animals of CT-ISO-C were given both peanut extract (500mg/kg body weight; orally) for 21 consecutive days (started from 1st day of study period) and propranolol (10mg/kg body weight; orally) for last seven (from 15th to 21st day of study period) consecutive days. All the groups of animals except baseline control group were given isoproterenol subcutaneously (150mg/kg body weight/day) for last two (at 20th & 21st day of study period) consecutive days. After acclimatization and before giving any supplementation, body weights of all the rats were measured (initial bw). After giving isoproterenol, propranolol and peanut all the animals including the baseline control rats, were anaesthetized with the help of chloroform (30%) and sacrificed on 22nd day. Before anaesthetized the rats on 22nd day again body weights of rats (final bw) were taken. The heart samples were collected after sacrificing the rats. The heart was washed in ice cold saline and weighed by electric balance analyzer. The heart samples were preserved in 10% formalin for histological processing. To find out the histopathological changes of heart tissue, histological slides were prepared and were observed under microscope in the Department of Pathology, SSMC. Histological findings were categorized by mild, moderate and severe histological changes¹⁷. Statistical analysis were done by one way ANOVA and Bonferroni test by using SPSS windows, version 16.

Preparation of heart for histological examination:¹⁶ Heart tissue was taken in 10% formalin for overnight. Dehydration was carried out by

keeping the tissue in ethanol (ranging from 70-100%). After dehydration the heart sections was cleared in xylene and was kept in a paraffin bath and treated with melted paraffin at 70°C for one hour. Then the tissue was embedded in metallic moulds and was allowed to harden at room temperature to form paraffin blocks, cut into pieces to get tissue blocks, sectioned at 5µm thickness with a rotator microtome. Ribbons of section was placed in a hot water bath at 45-50°C and allowed to float and was taken on glass slides previously treated with adhesive and was dried.

Scoring:^{15,17}

The histological changes of heart tissue in experimental animals determined by scoring method depending on the severity where score 0 = no change, score 1 = mild change (small multifocal degeneration with slight degree of inflammation, scanty inflammatory cell infiltration, absence of hyalinization of muscle fiber, reduced interstitial space), score 2 = moderate change (extensive myofibrillar degeneration, mild necrosis with inflammation, mild hyalinization of muscle fiber, mild inflammatory cell infiltration), score 3 = marked change (widespread myocardial disorganization, hyalinization of muscle fiber, degeneration of myofibrils, infiltration of lymphocyte and macrophage, loss of integrity of myocardial cell membrane, necrosis with diffuse inflammation, increased interstitial space).

Results

The percent change of body weight from final to initial was significantly ($p < 0.01$) lower both in CT-ISO-P and in CT-ISO-C as compared to that of baseline control (Table I).

Again, the histological scores were significantly ($p < 0.01$) higher in CT-ISO in comparison to that of baseline control group. Moreover, these scores were significantly ($p < 0.05$) lower in CT-ISO-P and CT-ISO-C when compared to that of isoproterenol treated control group. Again, the scores were significantly ($p < 0.01$) lower in CT-ISO-C in comparison to that of CT-ISO-P (Table III).

Table I: Body weight in different groups of rats (n=50)

Parameters	Without peanut		With peanut		Combined CT-ISO-C
	BC	CT- ISO	CT- ISO-PRO	CT- ISO-P	
Initial body wt (g)(Day 1)	128.89±6.01	132.78±10.93	134.33±10.03	135.73±5.35	134.44±8.08
Final body wt (g)(Day 22)	137.11±6.43	147.83±11.06***	152.02±10.33**	142.63±5.45**	135.78±7.63 ^{++o}
% of change from final (F) to initial (I) body wt[(F-I)/Ix100]	6.39±1.67	6.73±1.08	6.06±0.93	-1.64±1.07 [—]	-3.24±4.46 ^{^^}

Values are means ±SD. Statistical analysis was done by ANOVA test and then Bonferroni test. For final body wt (***p<0.01, **p<0.01 & *p<0.05 BC vs CT-ISO, CT-ISO-PRO & CT-ISO-P) (*p<0.01 CT-ISO vs CT-ISO-C) (+p<0.05 & ++p<0.01 CT-ISO-PRO vs CT-ISO-P & CT-ISO-C) (°p<0.01 CT-ISO-P vs CT-ISO-C). For % change of body wt (^p<0.01 & ^^p<0.01 BC vs CT-ISO-P & CT-ISO-C) (°p<0.01 CT-ISO vs CT-ISO-C) (°p<0.01 & °p<0.01 CT-ISO-PRO vs CT-ISO-P & CT-ISO-C). BC = Baseline control CT-ISO = Cardiotoxic group with isoproterenol CT-ISO-PRO = Cardiotoxic group with isoproterenol after propranolol treatment CT-ISO-P = Cardiotoxic group with isoproterenol after peanut treatment CT-ISO-C = Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol.

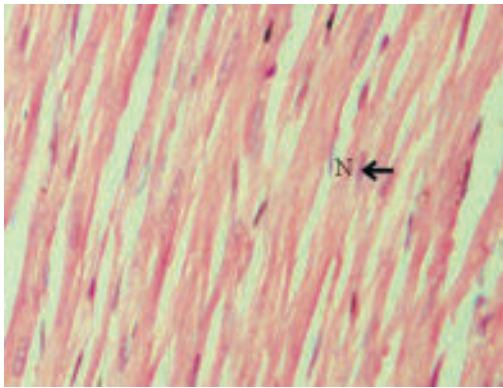
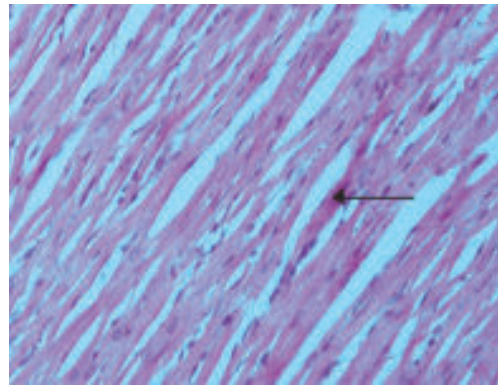
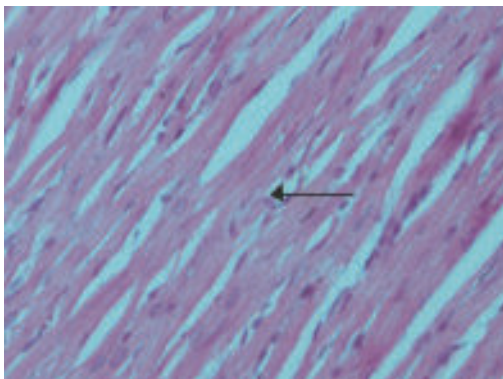
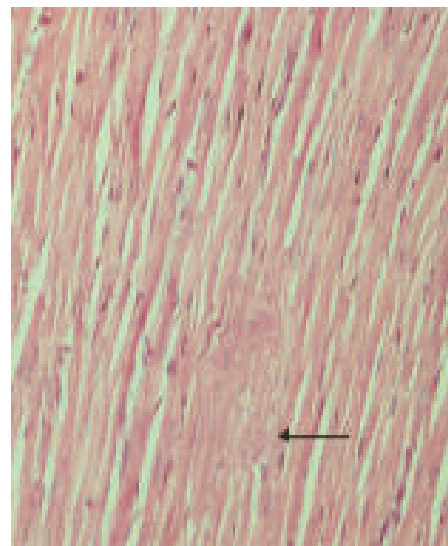
Table II: Histological observation of heart in different groups of rats (n=50)

Group	Observation	findings	Score
BC (n=10) (Baseline control group)	Architecture of • Myocardium • Endocardium • Pericardium Orientation of • Myocardial cell membrane • Nucleus • Intercalated disc	Normal histological findings	'0' (normal)
CT-ISO (n=10) (Cardiotoxic group with isoproterenol)	• Widespread myocardial disorganization • Hyalinization of muscle fibers • Degeneration of myofibrils • Infiltration of lymphocytes • Loss of integrity of myocardial cell membrane • Presence of necrosis with diffuse inflammation	Marked histological changes	'3' (marked)
CT-ISO-PRO (n=10) (Cardiotoxic group with isoproterenol after propranolol treatment)	• Recovery from necrosis with mild inflammation • Absence of hyalinization of muscle fibers • Mild multifocal degeneration • Scanty lymphocyte infiltration • Reduced interstitial space Less histological changes in myocardium	Normal histological findings in 5 rats and mild histological changes in 4 rats	'0' (normal) in 5 rats '1' (mild) in 4 rats
CT-ISO-P (n=10) (Cardiotoxic group with isoproterenol after peanut treatment)	• Recovery from necrosis with mild inflammation • Mild multifocal degeneration • Scanty lymphocyte infiltration • Reduced interstitial space Less histological changes in myocardium	Normal histological findings in 6 rats, mild histological changes in 2 rats	'0' (normal) in 6 rats '1' (mild) in 2 rats
CT-ISO-C (n=10) (Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol)	• Small multifocal degeneration • Absence of necrosis with slight area of inflammation • Scanty inflammatory cell infiltration • Fall in interstitial space • Absence of hyalinization of muscle fibers. Restoration of normal architecture of myocardium	Normal histological findings in 8 rats, mild histological changes in 1 rat	'0' (normal) in 8 rats '1' (mild) in 1 rat

Table III : Distribution of rats by histological changes in heart (n=50)

Histological scores	Without peanut			With peanut	Combined
	BC	CT-ISO	CT-ISO-PRO	CT-ISO-P	CT-ISO-C
Score '0' (%)	10(100.0)	0(0)	5(55.56)	6(75.00) ^{••}	8(88.89) ^{•+}
Score '1' (%)	0(0)	0(0)	4(44.44) ^{•••}	2(25.00)	1(11.11)
Score '2' (%)	0(0)	0(0)	0(0)	0(0)	0(0)
Score '3' (%)	0(0)	9(100.00) ^{•••}	0(0)	0(0)	0(0)

Statistical analysis was done by Fisher's exact test. Figures in parentheses indicate percentage. For histological scores (**p<0.01 BC vs CT-ISO) (•••p<0.01, ••p<0.05 & •p<0.05 CT-ISO vs CT-ISO-PRO, CT-ISO-P & CT-ISO-C) (†p<0.01 CT-ISO-P vs CT-ISO-C). BC = Baseline control CT-ISO = Cardiotoxic group with isoproterenol CT-ISO-PRO = Cardiotoxic group with isoproterenol after propranolol treatment CT-ISO-P = Cardiotoxic group with isoproterenol after peanut treatment CT-ISO-C = Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol.

**Figure 1:** Normal histological architecture of heart tissue**Figure 2:** Mild multifocal degeneration of heart tissue**Figure 3:** Scanty lymphocyte infiltration of myocardium**Figure 4:** Widespread myocardial disorganization

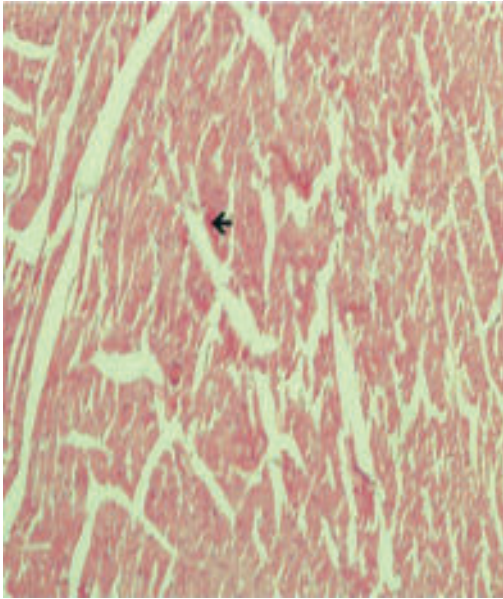


Figure 5: Degeneration of muscle fibers of heart

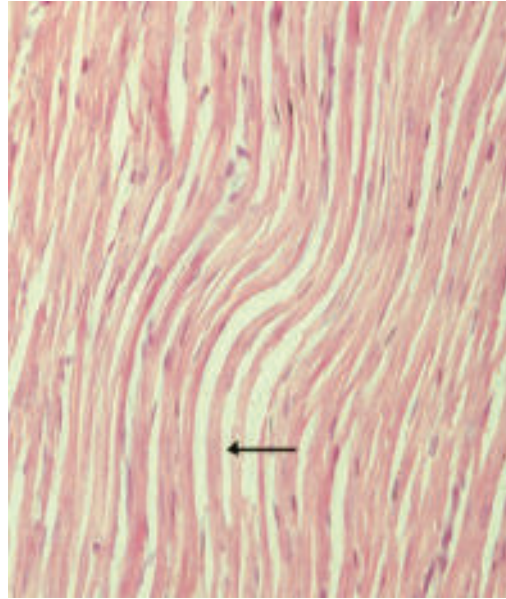


Figure 6: Hyalinization of muscle fibers of heart

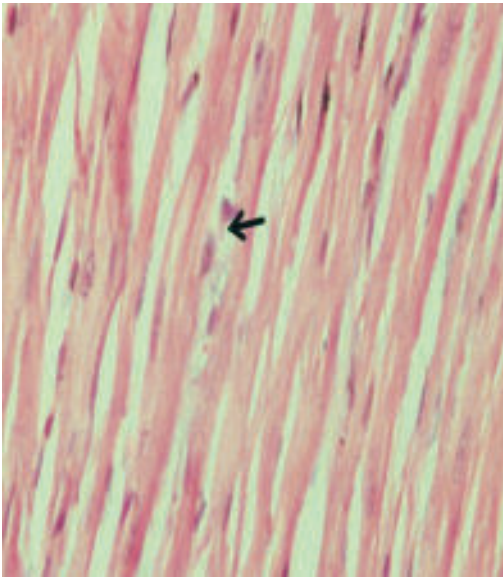


Figure 7: Lymphocyte infiltration of myocardium

Discussion

In the present study, the percent changes of body weight were almost similar to the findings reported by the various investigators from different countries¹⁵

Again, in this study marked histological changes such as widespread myocardial disorganization

(photomicrograph 4), degeneration of myofibrils (photomicrograph 5), hyalinization of muscle fibers (photomicrograph 6) and marked lymphocyte infiltration (photomicrograph 7) were observed in 100% of the rats in CT-ISO (Cardiotoxic group with isoproterenol). Similar type of observation was also made by some other researchers^{15, 17}. However, 55.56% of rats in CT-ISO-PRO (Cardiotoxic group with isoproterenol after propranolol treatment), 75% of rats in CT-ISO-P (Cardiotoxic group with isoproterenol after peanut treatment) and 88.89% of rats in CT-ISO-C (Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol) showed almost normal histological architecture of heart (photomicrograph 1). Whereas, mild histological changes such as mild multifocal degeneration (photomicrograph 2), scanty lymphocyte infiltration (photomicrograph 3) was observed in rest of the rats. Different researchers of other countries observed almost similar type of findings by using different nuts and herbal plant^{7, 15}. On the contrary, some researchers observed that low dose of *Tylophora indica* herbal plant leaves failed to show any

improvement in histological architecture of isoproterenol induced cardiotoxic rats¹⁸.

It has been postulated that, administration of high dose of isoproterenol subcutaneously induced diffuse myocardial necrosis and finally resulted in progressive cardiac enlargement¹⁹. However, rats that received isoproterenol at the dose of 150mg/kg body weight showed marked inflammatory changes in the myocardium and visible ischemic lesion leads to cardiac hypertrophy and thereby increases weight of the heart¹⁵.

Again, high dose of isoproterenol causes lipid peroxidation of myocardial membrane through production of cytotoxic free radicals²⁰. Isoproterenol also enhanced lipid biosynthesis in the myocardium by cardiac cAMP formation, which in turn leads to myocardial necrosis²¹. Some investigators reported that isoproterenol produces a number of biochemical and electrophysiological disturbances which ultimately causes disorganization of normal histological structure of the heart tissue²². Again, high dose of isoproterenol causes degeneration and necrosis of myocardial fibers, accumulation of inflammatory cells, hyalinization of muscle fibers etc due to increased production of free radicals^{17,18}. Moreover, damage to cardiac musculature was also demonstrated and confirmed by histological scores¹⁵.

Again, some investigator suggested that propranolol causes dephosphorylation of myosin light chain kinase thereby decreases generation of oxygen free radicals¹⁸. Thus decreases lipid peroxidation of myocardial membrane, maintain myocardial integrity and preserve myocardial histological architecture^{7,15}.

Furthermore, some other investigators observed that resveratrol, a poly-phenol phytoalexin present in peanut provide protection to myocardium via antioxidant activity²³. Again, some investigators observed that peanut consumption significantly improve the

antioxidant-oxidant status by increasing glutathione peroxidase (GSH) and decreasing thiobarbituric acid reactive substance (TBARS) levels²⁴. High level of L-arginin and vitamine E content of peanut also have antioxidant activity and scavenge oxygen free radicals thereby preserve normal histological architecture of heart²⁵.

In the present study, cardiotoxicity was observed in rats treated with isoproterenol as evidenced by widespread myocardial disorganization, degeneration of myofibrils, hyalinization of muscle fibers, lymphocyte infiltration and necrosis with diffuse inflammation of myocardium.

Again, fewer changes in histological architecture of heart such as recovery from necrosis with mild inflammation, absence of hyalinization of muscle fibers, mild multifocal degeneration and scanty lymphocyte infiltration in CT-ISO-P (Cardiotoxic group with isoproterenol after peanut treatment) and CT-ISO-C (Cardiotoxic group with isoproterenol after combined treatment of peanut and propranolol) of the present study suggested the cardioprotective role of peanut against isoproterenol induced cardiotoxicity. Moreover, in this study combined therapy of peanut and propranolol showed synergistic cardioprotective effect than when they were used alone. These effects are most likely due to anti-oxidant and free radical scavenging activity of peanut and propranolol. However, the exact mechanism involved in the cardioprotective activity of peanut against isoproterenol induced cardiotoxicity in rats cannot be found out from this type of study.

Conclusion

From this study, it can be concluded that peanut can prevent alterations of myocardial histological architecture due to its inhibition of generating and free radicals scavenging activity. However, combined therapy of peanut with propranolol showed synergistic effect on preventing cardiotoxicity by reducing free radical induced

myocardial damage. It is also expected that the result of this study would make peanut acceptable among the people as a rich source of nutrients with medicinal value for the prevention of coronary heart diseases.

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