Jundishapur Journal of Physiology (JJP). **2018 Oct; 1(1); 17-21**

Published online 2018 Oct 20. **Original Paper**

Ameliorative effect of Artichoke (*Cynara scolymus*) on chemically induced arrhythmias in Rats

Negin Amini[1], Mahin Dianat[2*]

1. Student Research Committee, Science and Religion Work Group, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. Department of Physiology, Persian Gulf Physiology Research Center, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

*Corresponding Author: Mahin Dianat, Department of Physiology, Persian Gulf Physiology Research Center, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Cell phone*:* +989163110437, Fax: +986133337370
Email: dianat@ajums.ac.ir; dianatmah@yahoo.com

Received: Feb 27, 2018; Revised: Jun 22, 2018; Accepted: Sep 19, 2018

Introduction: Antioxidant factors play an important role in cardiovascular diseases. Medicinal plants are considered as suitable replacement for chemical drugs. Hydro-alcoholic extract of *Cynara scolymus* L. (artichoke) was effective in the treatment of different diseases due to its strong antioxidant properties. This study was designed to examine the ameliorative effect of hydro-alcoholic extract of artichoke against $CaCl_2$ induced arrhythmia in rats.

Materials and methods: Male Sprague-Dawley rats (200-250 g) were divided into 5 groups: Control (saline 1 ml/kg, gavage, 21 days), Extract (100, 200, 400 mg/kg, gavage, 21 days) and Amiodarone (10 mg/kg, i.v). The rats were anesthetized and the antidysrhythmic effects induced by $CaCl_2$ (140 mg/kg) injection was evaluated. Lead II was recorded at the first and the last days of the experimental period. Heart rate (HR), incidence rate of premature ventricular beats (PVB), ventricular fibrillation (VF) and ventricular tachycardia (VT) were calculated and the data obtained from extract groups were compared to those from the amiodarone group. Results were analyzed using one-way ANOVA and FISHER exact test. Level of statistical significance was set at $P<0.05$.

Results: Significant decreases in VPB, VF and VT were observed with artichoke extract, at doses 100, 200, 400 mg/kg compared to the control group. The highest activity of the extract was at the dose of 200 mg/kg. Also, a dramatic decline was observed in the heart rate of the extract treatment groups.

Conclusion: This study illustrated the antiarrhythmic properties of hydro-alcoholic extract of artichoke. According to the results, this substance is recommended as an antiarrhythmic agent that could be used in the treatment of heart diseases.

Keyword: Cynara scolymus, Arrhythmias, Amiodarone, Rat

Introduction

The most common reason for sudden cardiac death is cardiac arrhythmia, and the ventricular tachycardia and fibrillation have been reported as the most important cardiac arrhythmias (John et al., 2012). Any rhythm other than normal sinus rhythm of the heart is known as cardiac arrhythmia and divided into two categories: bradycardia and tachycardia (Jeong et al., 2012).

Arrhythmias could be due to several factors (Rubart and Zipes, 2005) including myocardial ischemia (Dhalla et al., 2009), left ventricular hypertrophy (Burchfield et al., 2013), and disturbance of autonomic activation of the heart (Zipes, 2008). In addition, cardiac arrhythmia related to oxidative stress is caused by reactive oxygen species (ROS) (Jeong et al., 2012).

Oxygen free radicals and derivatives of oxygen free radicals together are known as reactive oxygen species. Free oxygen radicals include hydroxyl radical, superoxide anion, hydrogen peroxide and single oxygen (Pitocco et al., 2010). Other studies also demonstrated that ROS could disturb cardiac Na^+ channels, calcium ion balance and mitochondrial function, which is known as arrhythmia mechanisms (Jeong et al., 2012; Nass et al., 2008). $CaCl_2$ induces ventricular arrhythmia through the activation of sympathetic nervous system (Maliinow et al., 1953).

Antioxidants can prevent cellular damage by eliminating free radicals through enzymatic and non-enzymatic systems (Deaton and Marlin, 2003). In normal or standard conditions, reactive oxygen species and antioxidants are

balanced and the impaired balance conditions lead to increased ROS and oxidative stress (Deaton and Marlin, 2003).

The role of herbs in improving various diseases has already been shown (Gill and Tuteja, 2010). Flavonoids are compounds with radical scavenging properties, which are abundant in fruits, vegetables and accumulate in bark, seeds, leaves, and flowers of plants (Prochazkova et al., 2011).

Cynara scolymus (artichoke) is a rich source of natural antioxidant such as flavones, hydroxycinnamic acids and vitamin C (Jimenez-Escrig et al., 2003) and the main phenolic components of artichoke are cynarine, chlorogenic acid, caffeic acid and flavonoids (Wittemer et al., 2005). It has been shown that extract of artichoke is obtained from different parts of the plant such as leaves, fruits, roots, and is used in the treatment of cardiovascular diseases (Rondanelli et al., 2013).

Moreover, *in vivo* and *in vitro* studies have proven that the extract of artichoke has protective effects on liver (Mehmetcik et al., 2008; Miccadei S, 2008). In another study, it has been demonstrated that artichoke leaf extract reduces cholesterol level due to its antioxidant properties (Wider et al., 2013). In traditional medicine, *Gundelia tournefortii* L. Properties are similar to artichoke and consumed for lowering cholesterol (Saenz Rodriguez et al., 2002).

It has been shown that amiodarone leads to inhibition of potassium channel and inward sodium and calcium current. While amiodarone has antiarrhythmic effects, it has been demostrated that oral and intravenous consumption of amiodarone is associated with different side effects on heart and other tissues including torsade de pointes, pulmonary fibrosis and gastrointestinal (Van Herendael & Dorian, 2010).

The aim of this study was to compare the effects of hydro-alcoholic extracts of artichoke and amiodarone on $CaCl_2$ induced cardiac arrhythmias in rats.

Materials and Methods

Plant

The purchased leaf parts of artichoke were authenticated by a faculty member of Ahvaz Jundishapur University of Medical Sciences. The samples were carefully washed under running water to remove adhering dirt and other external particles from the surface. Then they were dried, powdered and stored in a refrigerator until extraction. The leaves' powder was mixed with 70% ethanol and the solution was kept at room air for 3 days, during which it was stirred several times daily. After 72 hours, the mixture was passed through a filter paper. The extract solution was spread on a glass surface until solvents were evaporated at room temperature. The obtained powder was maintained at 4 °C temperature.

Animals

In this study, 40 male Sprague Dawley rats (200-250 g) were housed in the polycarbonate cages maintained at 23±2 °C. Water and standard food were provided. Rats were exposed to a 12 h light: 12 h dark cycle and 50% humidity. All the procedures were carried out following animal Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Grant No. ajums. 93S29).

Experimental design

The extract of artichoke was dissolved in saline, and three different doses of the extract were used. The animals were randomly divided into 5 groups:

Group I: control rats were gavaged by saline 1 ml/kg for 21days,

Group II, III, IV: animals were gavaged by hydro-alcoholic extract of artichoke at the dose of 100, 200 and 400 mg/kg, respectively for 21days (Heidarian et al., 2011),

Group V: rats were intravenously injected with amiodarone at dose of 10 mg/kg, before induction of arrhythmias (Dianat et al., 2013).

Surgical procedure

In this study, $CaCl_2$ (140 mg/kg, i.v) was used to induce chemical arrhythmia (Somova et al., 2004). In all groups, rats were anesthetized by ketamine (50 mg/kg) and xylazine (10 mg/kg) (Dianat et al., 2013). 15 minutes after anesthesia, standard bipolar limb lead II was recorded by Bio-Amp and monitored by a Power Lab system (AD Instruments, Australia) to evaluate the chronotropic effect and incidence rate of ventricular premature beats (PVB), ventricular fibrillation (VF) and ventricular tachycardia (VT).

For skin disinfection, alcohol 70% was applied. After disinfection, a longitudinal slot in the groin was created, and the femoral vein was exposed and cannulated with a polyethylene catheter. After intravenous injection of $CaCl_2$ in each group, heart rate, incidence rate of ventricular premature beats (VPB), ventricular fibrillation (VF) and ventricular tachycardia (VT) were computed for three minutes (Somova et al., 2004).

Statistical analysis

The data were shown as mean ± SEM. The data obtained from heart rate were analyzed by one-way ANOVA followed by LSD. Fisher`s exact test was used to evaluate the arrhythmias data. A p-value less than 0.05 was considered significant.

Results

The effect of artichoke extract on heart rate

The rats receiving hydro-alcoholic extract of artichoke at different doses showed a significant decrease ($p<0.05$) in their heart rate, which showed negative chronotropic properties (Fig.1). The group receiving amiodarone (10 mg/kg) showed a significant decrease in heart rate ($P<0.05$).

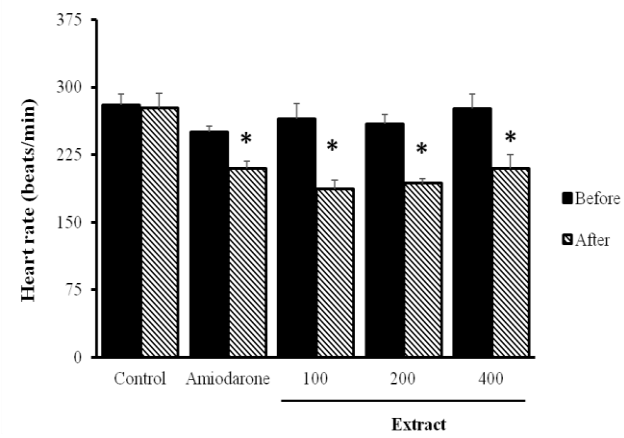

Figure 1. Comparison of heart rate in different groups. [Control (saline), amiodarone (10 mg/kg), extract (100, 200, 400 mg/kg)]. *P<0.05 Significant differences before and after treatment and significant differences with control group (n=8, Mean±SEM, Paired t-Test or One-way ANOVA followed by LSD).

Effect of artichoke extract on ventricular arrhythmia induced by $CaCl_2$

The percentages of incidence rate of arrhythmias (VPB, VF and VT) in all experimental groups are shown in figures 2, 3 and 4. Control rats showed increased premature ventricular beats, ventricular fibrillation and ventricular tachycardia.Rats received hydro-alcoholic extract of artichoke at the dose of 100 mg/kg by gavage showed a significant decrease in VPB (P<0.05), VF (P<0.01) and VT (P<0.05). Rats received artichoke extract at the dose of 200 mg/kg, by gavage showed a significant decrease in VPB (P<0.01), VF (P<0.01) and VT (p<0.01).Also, rats gavaged with hydro-alcoholic extract of artichoke at the dose of 400 mg/kg showed a significant decrease in VPB (P<0.05), VF (P<0.01) and VT (p<0.01). Rats injected with amiodarone at dose of 10 mg/kg showed a significant decrease in VPB (P<0.05), VF (P<0.001) and VT (P<0.05).

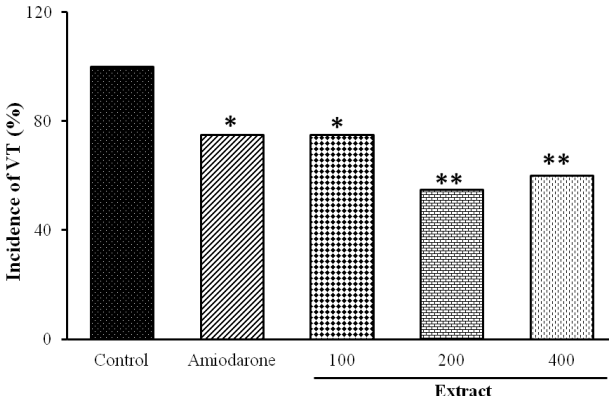

Figure 2. Evaluation of ventricular tachycardia after intravenously $CaCl_2$ (140 mg/kg) injection in different groups. [Control (saline), amiodarone (10 mg/kg), extract (100, 200, 400 mg/kg)]. *P<0.05, **P<0.01 vs control group (n=8, Fisher`s exact test).

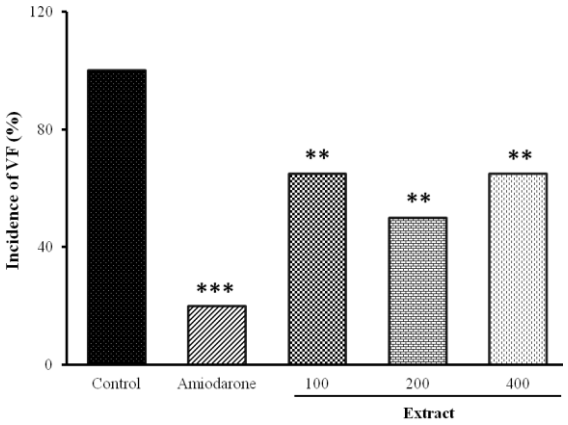

Figure 3. Evaluation of ventricular fibrillation after intravenously $CaCl_2$ (140 mg/kg) injection in different groups. [Control (saline), amiodarone (10 mg/kg), extract (100, 200, 400 mg/kg)]. ***P<0.01, **P<0.01 vs control group (n=8, Fisher`s exact test).

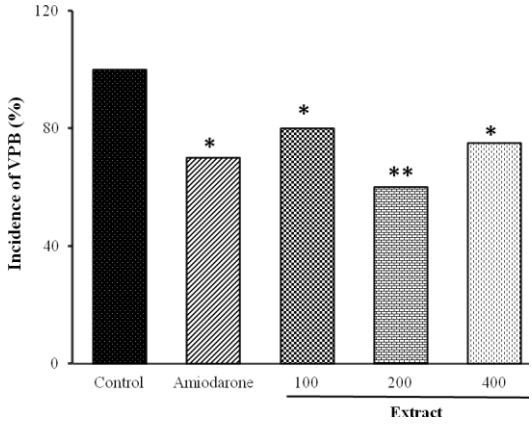

Figure 4. Evaluation of ventricular premature beats after intravenously $CaCl_2$ (140 mg/kg) injection in different groups. [Control (saline), amiodarone (10m g/kg), extract (100, 200, 400 mg/kg)]. *P<0.05, **P<0.01 vs control group (n=8, Fisher`s exact test).

Discussion

In electrocardiogram of rats that received *Cynara scolymus (*artichoke*)* extract, after 21 days gavage, decreased incidence rate of ventricular premature beats (PVB), ventricular fibrillation (VF) and ventricular tachycardia (VT) compared to those of the control rats were observed. Also, in this study, heart rate significantly decreased (p<0.05) in extract groups with different doses. Another study, by the same authors showed that antioxidant compound reduces heart rate, which suggests a negative chronotopic property (Dianat et al., 2013).

Also, the effect of extract of artichoke was shown to be similar to amiodarone in reducing arrhythmia and heart

rate. The extract effect appeared to be dose-dependent, and extract at dose of 200 mg/kg demonstrated the best effects. *In vitro* and *in vivo* studies of artichoke confirm antioxidant effect of artichoke (Mehmetcik et al., 2008; Miccadei et al., 2008). It was proven that polyphenol compound consumption in rats receiving isoproterenol was associated with increased activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase (Kannan and Quine, 2011).

This result was similar to the findings in the current study in that the decreased incidence rate of arrhythmia is probably due to destroyed free radicals following enhanced antioxidant enzymes. Kunzendorf and his colleagues' study on hypertensive rats showed that flavonoid consumption reduced systolic and diastolic blood pressure that could be due to antioxidant activity of this substance (Kunzendorf et al., 2010). Artichoke leaf extract causes a significant reduction in serum cholesterol, triglyceride levels and increases in glutathione peroxidase activity in hypercholesterolemia rats (Kucukgergin et al., 2010).

Artichoke plant has also been used in the treatment of atherosclerosis due to its effect on LDL oxidization (Zapolska-Downar et al., 2002) and is associated with a reducing risk of developing cardiovascular disease (Huikuri et al., 2001). Gebhardt has reported that aqueous extract of artichoke inhibits the activity of HMG CoA reductase (rate limiting enzyme in cholesterol biosynthesis), therefore; it may inhibit cholesterol biosynthesis (Gebhardt, 1998). Another *in vivo* study, showed polyphenols by inhibiting HMG CoA reductase enzyme have antiarrhythmic properties (Kannan and Quine, 2013).

In the present study, it seems that artichoke extract plays an anti-arrhythmic role by inhibiting the activity of HMG CoA reductase enzyme.

In the present study, through intravenous injection of calcium chloride ($CaCl_2$), a chemical model of arrhythmias was induced through sympathetic nervous system of activation (Maliinow et al., 1953). In a previous study, it was shown that injection of $CaCl_2$ induces sympathetic nervous system (Maliinow et al., 1953).

Different components of artichoke have been identified to be involved in these actions including caffeoylquinic acids as important phenolic compounds and luteolin-7-O glycoside as the major flavonoid (Jimenez-Escrig et al., 2003; Wittemer et al., 2005). The results showed that consumption of artichoke extract can protect the heart against arrhythmias such as PVB, VT, VF. The present study provides experimental evidence that the extract of artichoke (100, 200, 400 mg/kg) has cardio protective effects.

Amiodarone is considered as one of the most important antiarrhythmia drug that reduces the incidence of arrhythmias by blocking potassium channels and inhibiting sodium current or calcium current (Van Herendael and Dorian, 2010).

The aim of this study was to compare the effectiveness of the extract and amiodarone. The extract with a similar mechanism to amiodarone could probably be effective in preventing cardiovascular diseases. Therefore, this study shows that the extract of artichoke reduces arrhythmias but the mechanism of its action is not known yet, hence; additional studies are required to elucidate the mechanism of antidysrhythmic effect of the extract.

Conclusion

In summary, the result of this *in vivo* study showed an antiarrhythmic property of hydro-alcoholic extract of artichoke.

Acknowledgments

This study was done in the Physiology Research Center at Ahvaz Jundishapur University of Medical Sciences in Ahvaz, Iran. The authors gratefully acknowledge the help and financial support of the Student Research Committee, Ahvaz Jundishapur University of Medical Sciences (grant No. 93S29).

Conflict of Interest

There is no conflict of interest to be declared.

References

1.Burchfield JS, Xie M, Hill JA (2013). Pathological ventricular remodeling: mechanisms: part 1 of 2. Circulation. 128:388-400. Deaton CM, Marlin DJ (2003). Exercise - Associated oxidative stress. Clinical Techniqes in equine practice. 2:278 - 291.

2.Dhalla AK, Wang WQ, Dow J, Shryock JC, Belardinelli L, Bhandari A, Kloner RA (2009). Ranolazine, an antianginal agent, markedly reduces ventricular arrhythmias induced by ischemia and ischemia-reperfusion. American Journal of Physiology-Heart and Circulatory Physiology. 297: H1923-H1929.

3.Dianat M, Akbari GH, Badavi M (2013). Antidysrhythmic Effects of Gallic acid on $cacl_2$-induced arrhythmia in rat. Int J Res Dev Pharm L Sc. 2: 686-689.

4.Gebhardt R (1998). Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke (Cynara scolymus L.) extracts. J Pharmacol Exp Ther. 286: 1122-1128.

5.Gill SS, Tuteja N (2010). Reactive oxygen species and antioxidant machinery in abiotic stress tolerance in crop plants. Plant Physiol Biochem. 48: 909-930.

6.Heidarian E, Soofiniya Y, Hajihosseini R (2011). The effect of aerial part of Cynara scolymus extract on the hyperlipidemia, plasma antioxidant capacity, and superoxide dismutase activity in diabetic rats. JSKUMS. 13:1-10.

7.Huikuri HV, Castellanos A, Myerburg RJ (2001). Sudden death due to cardiac arrhythmias. N Engl J Med. 345: 1473-1482.

8.Jeong EM, Liu M, Sturdy M, Gao G, Varghese ST, Sovari AA, Dudley Jr SC (2012). Metabolic stress, reactive oxygen species, and arrhythmia. Journal of Molecular and Cellular Cardiology. 52:454-463.

9.Jimenez-Escrig A DL, Daneshvar B v, Saura-Calixto F (2003). In vitro antioxidant activities of edible artichoke (Cynara scolymus L.) and effect on

biomarkers of antioxidants in rats. J Agric Food Chem. 51: 5540-5545.
10.John RM, Tedrow UB, Koplan BA, Albert CM, Epstein LM, Sweeney MO, Miller AL, Michaud GF, Stevenson WG (2012). Ventricular arrhythmias and sudden cardiac death. Lancet 380:1520-1529.
11.Kannan MM, Quine SD (2013). Ellagic acid inhibits cardiac arrhythmias, hypertrophy and hyperlipidaemia during myocardial infarction in rats. Metabolism.62: 52-61.
12.Kannan MM, Quine SD (2011). Ellagic acid ameliorates isoproterenol induced oxidative stress: Evidence from electrocardiological, biochemical and histological study. Eur J Pharmacol. 659: 45-52.
13.Kucukgergin C, Aydin AF, Ozdemirler-Erata G, Mehmetcik G, Kocak-Toker N, Uysal M (2010). Effect of artichoke leaf extract on hepatic and cardiac oxidative stress in rats fed on high cholesterol diet. Biol Trace Elem Res.135: 264-274.
14.Kunzendorf U, Haase M, Rolver L, Haase-Fielitz A (2010). Novel aspects of pharmacological therapies for acute renal failure. Drugs. 70: 1099-1114.
15.Malinow MR, Batlle FF, Malamud B (1953). Nervous mechanisms in ventricular arrhythmias induced by calcium chloride in rats. Circ Res. 1: 554-560.
16.Mehmetcik G, Ozdemirler G, Kocak-Toker N, Cevikbas U, Uysal M (2008). Effect of pretreatment with artichoke extract on carbon tetrachloride-induced liver injury and oxidative stress. Exp Toxicol Pathol. 60: 475-480.
17. Miccadei S, Cardinali A, Romano F, Durazzo A, Foddai MS, Fraioli R, Mobarhan S, Maiani G (2008). Antioxidative and apoptotic properties of polyphenolic extracts from edible part of artichoke (Cynara scolymus L.) on cultured rat hepatocytes and on human hepatoma cells. Nutr Cancer. 60:276-283.
18.Nass RD, Aiba T, Tomaselli GF, Akar FG (2008). Mechanisms of disease: ion channel remodeling in the failing ventricle. Nat Clin Pract Cardiovasc Med. 5: 196-207.
19.Pitocco D, Zaccardi F, Di Stasio E, Romitelli F, Santini SA, Zuppi C, Ghirlanda G (2010). Oxidative stress, nitric oxide, and diabetes. Rev Diabet Stud.7: 15-25.
20.Prochazkova D, Bousova I, Wilhelmova N (2011). Antioxidant and prooxidant properties of flavonoids. Fitoterapia. 82: 513-523.
21.Saenz Rodriguez T, Garcia Gimenez D, de la Puerta Vazquez R. Choleretic activity and biliary elimination of lipids and bile acids induced by an artichoke leaf extract in rats. Phytomedicine. 2002 Dec;9(8):687-93.
22.Rondanelli M, Monteferrario F, Perna S, Faliva MA, Opizzi A (2013). Health-promoting properties of artichoke in preventing cardiovascular disease by its lipidic and glycemic-reducing action. Monaldi Arch Chest Dis. 80:17-26.
23.Rubart M, Zipes DP (2005). Mechanisms of sudden cardiac death. J Clin Invest. 115:2305-2315.
24.Somova LI, Shode FO, Mipando M (2004). Cardiotonic and antidysrhythmic effects of oleanolic and ursolic acids, methyl maslinate and uvaol. Phytomedicine. 11: 121-129.
25.Van Herendael H, Dorian P (2010). Amiodarone for the treatment and prevention of ventricular fibrillation and ventricular tachycardia. Vasc Health Risk Manag. 6: 6:465-72.
26.Wider B, Pittler MH, Thompson-Coon J, Ernst E (2013). Artichoke leaf extract for treating hypercholesterolaemia. Cochrane Database Syst Rev. 7:1-28.
27.Wittemer SM, Ploch M, Windeck T, Muller SC, Drewelow B, Derendorf H, Veit M (2005). Bioavailability and pharmacokinetics of caffeoylquinic acids and flavonoids after oral administration of Artichoke leaf extracts in humans. Phytomedicine. 12: 28-38.
28.Zapolska-Downar D, Zapolski-Downar A, Naruszewicz M, Siennicka A, Krasnodebska B, Koldziej B (2002). Protective properties of artichoke (Cynara scolymus) against oxidative stress induced in cultured endothelial cells and monocytes. Life Sci. 71:2897-2808.
29.Zipes DP (2008). Heart-brain interactions in cardiac arrhythmias: role of the autonomic nervous system. Cleve Clin J Med. 75: S94-S96.