

## The Inhibitory Effect of Itraconazole on Atherosclerosis in Hyperlipidemic Rabbits

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Atherosclerosis is a chronic inflammatory disease of the great vessels. The drug Itraconazole, with a full antifungal range has the following important properties: anti-inflammatory feature, its inhibitory effect on the activity of 5-lipoxygenase and Chemotaxis of T-cell and the production of leukotriene, its effect on stopping VEGF, its decreasing effect on LDL -C and its increasing effect on the HDL -C and IL-10. 40 rabbits were divided into 4 equal groups. The day before the experiment the animals were bled and then the first group was fed standard food, the second group was fed a high-cholesteroldiet, the third group was fed standard food and Itraconazole and the fourth group was fed a high-cholesterol diet and Itraconazole, at the end of the twelfth week the animals were bled and information was reviewed. Significant reduction in serum levels of TC, TG and LDL-C and a significant increase in HDL-C in the fourth group compared to the second group at the end of the experiment, indicates the effectiveness of this drug on the adjustment mode of Dyslipidemia caused by the consumption of high cholesterol foods. In the third group compared to the control group, triglyceride, total cholesterol and LDL-C have significantly reduced and HDL-C was significantly increased, which indicates the negative effect of drug with a dose of 80 mg per kg at the end of the twelfth week (05 / 0P <). Itraconazole by reducing serum level of cholesterol will slow the process of Atherosclerosis.

**Key words:** Itraconazole, Atherosclerosis, Rabbits, Hyperlipidemic.

Atherosclerosis is a chronic inflammatory disease and starts with dysfunction of the endothelial layer of the vessels and continues by changing the nature of the area beneath Intima and accumulation of lipoproteins in this area and, by erosion, rupture of the Intima layer and creation of thrombosis, the process of the atherosclerosis is complete (Higashi Y 2010). The initial step in the pathogenesis

of Atherosclerosis is endothelial dysfunction layer (Higashi Y 2009). Moreover, activation of endothelial cells of vessels by vascular endothelial growth factor (VEGF) which is an angiogenesis factor may also increase the mechanisms of evolution pathophysiology and plaque instability of atherosclerotic (Holm 2009). Inflammation plays an important role in the development of Atheroma. Inflammatory mechanisms cause the Dyslipidemia and this disorder in fat accumulation causes the formation of Atheroma (Libby P. 2002). Leukocytes migration beneath endothelial and the activation of T-Cells are considered among the most important steps in beginning Atherosclerosis and its pathophysiology and plaque formation (Bogdanski P. 2007; Libby P. 2002). It has been

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well documented that from the onset of initial damage to plaque formation, several molecular and cellular inflammatory cytokines are involved in the disease process (Kleemann R. 2008).

One of these proinflammatory cytokines is Interleukin 8 (Gustafson B. 2010). Recently, Han et al reported wide anti-atherogenic role for Interleukin in macrophages and include increased excretion of harmful lipoproteins, inhibition of inflammatory molecules and apoptosis reduction (Han X. 2009). In recent years it has been found that the 5-lipoxygenase pathway may play an important role in the pathogenesis of Atherosclerosis. This information significantly increases the probability of effective diet in treatment of Atherosclerosis by anti-leukotriene drugs (Jawieñ, J., 2009). It is thought that increased serum levels of LDL-cholesterol is one of the major risk factors of Atherosclerosis and cardiovascular illnesses while the opposite can be seen in patients with HDL-cholesterol (Jain, K.S., 2009; Schneider, B., 2007). Numerous studies show that diets rich in carbohydrates and fats increase harmful lipids and lipoproteins of plasma and will increase serum level of triglycerides, total and bad cholesterol and reduce the level of good cholesterol while increasing the risk of cardiovascular disease (Albrink, 1986).

Itraconazole with a wide range of antifungal features has the important feature of being an anti-inflammatory (Vlckova-laskoska, 2009), specifically, this drug is a potent inhibitor of the activity of 5-lipoxygenase and by the formation of leukotriene prevents chemotaxis of neutrophil and interleukin eight production (Jaschonek, K., 1989). After 6 months of treatment with Itraconazole an increase in interleukin 10 was observed (Gimenes, V.M. 2006). Han et al have reported that interleukin 10 increases cholesterol removal by macrophages to protect against poisoning of the cholesterol accumulation in the cells (Han, X., 2009). Itraconazole in particular prevented the progression of endothelial cell cycle in G1 phase in the laboratory and stops the vascular endothelial growth factor or dependent base of fibroblasts growth factor- to angiogenesis (Chong, C.R.2007). In addition, Itraconazole has an inhibitory effect on the synthesis of cholesterol (Lütjohann, D., 2009). This drug causes a significant reduction in serum levels of LDL-

cholesterol and compared with ketoconazole causes significant increase in HDL-cholesterol (Schneider, 2007).

With respect to the following items: 1-anti-inflammatory activity of Itraconazole 2- inhibition effect on 5-lipoxygenase activity 3- its inhibitory effect on chemotaxis of T-cell 4- inhibitory effect on the production of leukotriene 5- its effect on stopping the VEGF 6- its reducing effect on the (LDL-cholesterol) level 7- its increasing effect on the (HDL-cholesterol) level 8- its increasing effect on the IL-10 level, the study was conducted.

## METHODS

According to obtained information from the researches previously conducted, the rabbit is a good animal model for Atherosclerosis and results from this induced Atherosclerosis are similar to human atherosclerosis (Duff G.L.1935; Constantinides, P.,1961; Wissler and Vesselinovith, 1968). In this study, 40 New Zealand white male rabbits weighing  $5/0 \pm 2/2$  kg were purchased and transferred to Experimental Animal Center of Jahrom Medical University and were kept separately in individual cages and standard conditions (standard food, adequate water, temperature of  $2 \pm 23$  and humidity of  $5 \pm 55$  per cent). One week after the animals' adaptation to the new environment, the rabbits were randomly divided into 4 groups of 10 rabbits. Then, while the rabbits were kept 12-15 hours in fasting condition, they were weighed, blood was taken from the artery of rabbit ear, (day zero) and in laboratory after the clotting of blood samples, the serum was separated by centrifugation at 3000 rpm for 15 min. Until the pathology tests, serums were stored at  $-20^{\circ}$  C. Then, by using a triglyceride kit (Zist Shimi Company) and cholesterol (Pars Azmoon Company), levels of total cholesterol, triglyceride, LDL-C and HDL-C were determined. The next step was performed one day after blood sampling. The first group was considered as control group and daily received 130 g of standard food and enough water for 12 weeks. The second group was considered as a high cholesterol group and received 130 g of high fat diet daily and enough water for 12 weeks. 2 g of cholesterol was dissolved in 20 ml of sunflower oil which was then mixed with 100 g of standard powdered rabbit

food and poured in a case to produce pellets; a rate of 130 g per day was given to the rabbits. The third group was determined as the group to receive Itraconazole. This group received standard food and enough water each day in addition to 80 mg oral capsules of Itraconazole of each kilogram body weight in which every ten milligrams of it was dissolved in one milliliter of distilled water by gavage feeding for 12 weeks (Jehangir, K., 2000; Perfect, J.R. 1986). The fourth group like the second group received high-fat and adequate water diet and, furthermore, received Itraconazole like the third group. At the end of the twelfth week while rabbits were kept 12-15 hours in fasting condition, first they were weighed and then about five milliliters of blood was taken from the ear of the fourth group. After providing serum, the samples were sent to the laboratory to determine the concentration rate of total cholesterol, triglyceride, LDL-C, HDL-C.

#### Statistical analysis

Results were expressed as mean  $\pm$  standard deviation. The method of statistical analysis of serological data was a two-factor design with repeated measures on one factor. To compare the means, SPSS software and one-way ANOVA test and Duncan's post hoc was used. Significant differences were considered in the level of  $P > 0.05$ .

## RESULTS

#### Blood fat and lipoproteins

- A) Comparison of the mean concentration change of triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and blood low-density lipoprotein cholesterol (LDL-C) between the four groups at day zero or the day before the start of the experiment (group 1 or control group, group 2 or group received high-cholesterol diet, group 3 or group received Itraconazole and group 4 or group received Itraconazole plus high-cholesterol diet) (Table 1). Comparison of the mean concentration change of the same variables (TG, TC, HDL-C, LDL-C) between the four groups at day zero, significant difference with  $P < 0.05$  was not observed.
- B) Comparison of the mean concentration change of triglyceride, cholesterol, high

density of lipoprotein cholesterol and blood low-density lipoprotein cholesterol between the four groups at the final day of the experiment or the end of the twelfth week (Table 2 and Fig. 1).

Comparison of the mean concentration change of similar variables between the four groups at the final day of experiment except high density lipoprotein cholesterol in fourth group toward the control group in the remaining groups, a significant difference was observed with  $P < 0.05$  and according to Table 2:

- 1) The mean concentration change in blood triglyceride (TG) in the fourth group at the end of the twelfth week about 4 times reduced and about 81% in the third group; in the second group it is about 11 times more than the control group. In the fourth group, its concentration change is 5 times more than the third group while the concentration change in the fourth group is about 37% and the concentration change in the third group is 7.5% that of the second group.
- 2) The mean concentration change in blood cholesterol (TC) in the fourth group at the end of the twelfth week is about 4 times more, is about 70% in the third group, and about 9 times more in the second group compared to the control group. In the fourth group, its concentration change is 5.7 times more than the third group while the concentration change in the fourth group is about 44% and the concentration change in the third group is 8% that of the second group.
- 3) The mean concentration change of high density lipoprotein cholesterol in blood (HDL-C) in the fourth group at the end of the twelfth week is about 1.1 times more than the control group and the difference between the two groups is not significant with  $P < 0.05$ . The third group is about 1.66 times more than control group, the second group is 60% of control group, and the concentration of the fourth group is 67% that of the third group while the concentration in the fourth group is about 1.8 times and concentration variations in the third group is 2.8 times more than second group and

**Table 1.** Comparison of mean and standard deviations of studied parameters of blood serum of the day before the experiment (day zero), in which four groups of rabbits were randomly divided and were considered as control group (Group 1), high-cholesterol diet group (Group 2), normal diet and Itraconazole drug group (Group 3) and high-cholesterol diet plus Itraconazole drug group (Group 4)

Groups Parameters	Group1	Group2	Group3	Group4
Triglyceride (mg/dl)	112/00±2/55	113 /00±4/27	112/00±2/55	112/80± 5/12
Total Cholesterol(mg/dl)	136/400±5/33	134/40±4/07	134/40±5/06	138/00± 9/44
Low-density Lipoprotein(mg/dl)	40/60± 2/408	39/20± 3/83	40/60±4/77	40/60 ±3/91
High-densityLipoprotein (mg/dl)	83/80± 4/27	8520±5/26	84/60±4/16	84/80±7/56
Weight(gr)	1894/0± 62/29	1722/20±78/55 ★	2070/0 ±211/90/	2323/0±96/88*

This symbol ★ indicates that this parameter is significantly different with the same parameter in the other three groups ( $P < 0.05$ ). This symbol \* indicates that this parameter is significantly different with the same parameter in the first group ( $P < 0.05$ ).

**Table 2.** Comparison of mean and standard deviations of studied parameters of blood serum groups 2,3 and 4 of New Zealand white rabbits compared to control group, and compared to each other at the end of the twelfth week (end of treatment)

Groups Parameters	Group1	Group2	Group3	Group4
Triglyceride (mg/dl)	121/20±3/72	1312/20± 87/72	98/00±2/74	48960/±53/03
Total Cholesterol(mg/dl)	147/80±5/24	1340/0±56/21	103/40±3/83	589/40±48/07
High-densityLipoprotein(mg/dl)	38/00±1/41	23/00± 00/2	63/20±2/63	42/20±2/46 *
Low-density Lipoprotein (mg/dl)	83/40±4/53	1151 /0±41/12	32/20±3/44	464/40±38/90
Indisaterogenic AIP	0/504±0/026	1/759±0/042	0/1884±0/013	1/058±0/043
Weight(gr)	2248 /0±29/22	2966/0±53/44	2230/0±81/30 *	2495/0±83/82 <sup>△</sup>

This symbol ★ indicates that this parameter is not significantly different with the same parameter in the first group ( $P < 0/05$ ). This symbol <sup>△</sup> indicates that this parameter, is not significantly different with the same parameter in the third group ( $P < 0/05$ ). Note: The remaining parameters were significantly different compared to the same parameters in the control group and compared to each other ( $P < 0/05$ ).

**Table 3.** Comparison of mean and standard deviation of studied parameters of serum of rabbits in each of the four groups at the end of the twelfth week compared to the day before the experiment (day zero)

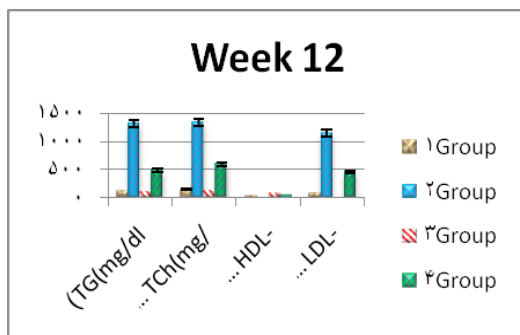
Groups Parameters	Group1	Group2	Group3	Group4
Triglyceride A	112/00±5/15	113/00±4/27	112/0±5/43	112/80±5/12
(mg/dl) B	121/20±3/72*	1312/20±87/72	98/0±6/29	489/60±53/03
Total A	136/40±5/33	134/40±4/07	134/40±5/06	138/00±6/44/
Cholesterol(mg/dl) B	147/80±5/24	1340/0±56/21	103/40±3/83	589/40±48/07
High-density A	40/60±2/41	39/20±3/83	40/60±4/77	40/60±3/91
Lipoprotein(mg/dl) B	38/0±1/41*	23/02/00	63/20±2/63	42/20±2/46*
Low-density A	83/80±4/27	85/20±5/26	84/60±4/159	84/80±7/56
Lipoprotein (mg/dl) B	83/40±4/53*	1151/0±41/12	32/20±3/44	464/40±38/90
Weight(gr) A	1894/0±62/29	1722/0±78/55	2070/± 211/9	2323/0±88/96
B	2248/0±29/22	2966/0±53/44	2230/±81/30	2495/0±83/82

A- Parameters measured at day zero (before the experiment).

B- Parameters measured at the end of the twelfth week (end of experiment).

This symbol <sup>△</sup> indicates that the related parameter to the end of the twelfth week (B) compared to the day before the experiment (A) in a specified group (6 cases in group 1 and one case in group 4) were not significantly different ( $P < 0/05$ ). While the difference between B and A is significant in the rest ( $P < 0/05$ ).

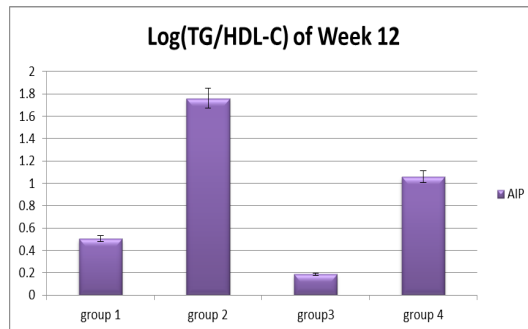
- the difference between the two determined groups is significant with  $P < 0.05$ .
- 4) The mean concentration change of low-density lipoprotein cholesterol (LDL-C) in the fourth group at the end of the twelfth week is about 5/6 times more than the control group. The third group is about 38% of control group, while in the second group it is about 14 times more than control group. The concentration of the fourth group is 14/5 times more than the third group while the concentration in the fourth group is about 40% of the second group and concentration changes in the third group are 3% of the second group.
  - 5) In comparing the Indisaterogenic (AIP = Indisaterogenic =  $\text{Log}(\text{TG} / \text{HDL-C})$ ), which is an indicator of atherosclerotic waste. All groups are significant with  $P < 0.05$ . This Indis is about 1.76 in the second group that had high cholesterol diet which shows a significant increase compared to the other three groups. Group with a high-cholesterol diet plus Itraconazole by the number of 1/06 ranked in the next step and in the group with the standard diet plus Itraconazole this Indis is 0.19 which is lower than the control group (0.5) (Figure 2).
  - C) Comparison of the concentration of triglyceride, total cholesterol, high density lipoprotein cholesterol and low-density



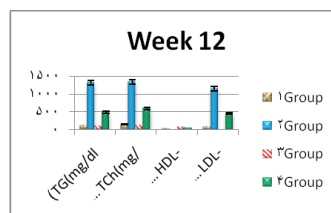
**Fig. 1.** Comparing the mean value of similar variables among the four groups at the end of the experiment (end of the twelfth week), except for high density lipoprotein (HDL-C) of fourth group (group of high-cholesterol diet plus Itraconazole drug) compared to group 1 (control group) show significant difference in the remaining group with ( $P < 0.05$ )

lipoprotein cholesterol in the blood at day zero with the final day of experiment in all four groups is shown based on Table 3 and Figs. 3-6.

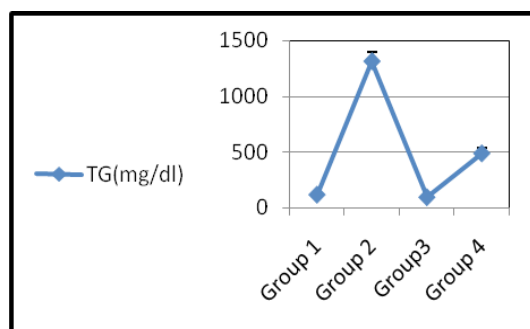
- 1) The mean concentration change of the same variables ((TG, TC, HDL-C, LDL-C) between day zero and the end of the experiment in the control group except for the total cholesterol in the remaining groups,



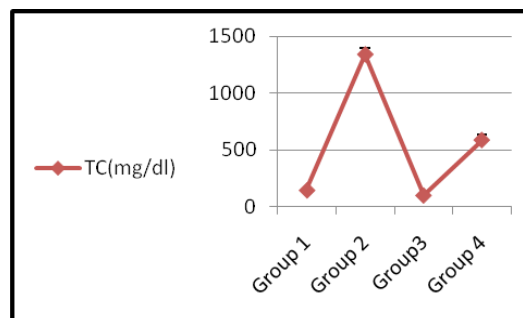
**Fig. 2.** Comparing Indisaterogenic which is an indicator of the lesions rate of Atherosclerosis each group has significant difference with each other with ( $P < 0.05$ ) and this Indis in group 2 (group of high cholesterol diet) compared to the other three groups show a significant increase. Group 4 (group of high-cholesterol diet plus Itraconazole drug) is ranked in the next position and in group 3 (group of standard diet plus Itraconazole drug) its value is even less than the control group



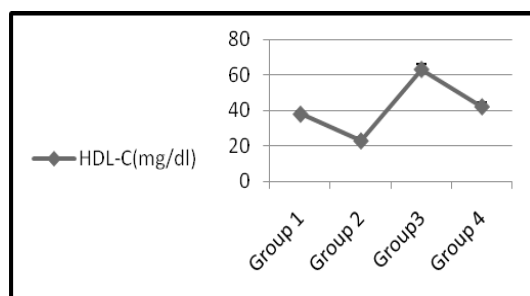
**Fig. 3.** Comparing the mean weight at the end of the experiment compared to one day before the experiment in four groups: Group 4 (group of high-cholesterol diet plus Itraconazole drug), group 3 (group of standard diet plus Itraconazole drug), group 2 (group with high cholesterol diet) and group 1 (control group) significant difference is observed with ( $P < 0.05$ ). In group 4 at the end of the twelfth week compared to Day Zero 7 per cent, in third group 8%, in second group 70% and in the control group 19% was added to the weight of the animals and this increase is quite obvious in Group 2.



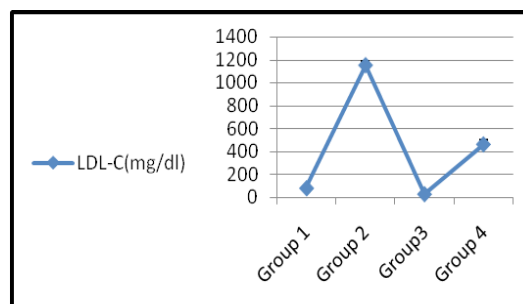
**Fig. 4.** Mean concentration comparison of triglyceride in the four groups at the end of the twelfth week



**Fig. 5.** Mean concentration comparison of total cholesterol in the four groups at the end of the twelfth week



**Fig. 6.** Mean concentration comparison of high-density lipoprotein cholesterol in the four groups at the end of the twelfth week



**Fig. 7.** Mean concentration comparison of low-density lipoprotein cholesterol in the four groups at the end of the twelfth week

- showed no significant difference with  $P < 0.05$ .
- Changes in total cholesterol concentration of the control group at the end of the twelfth week was 8% higher than day zero.
- 2) In the mean concentration the change of variables between day zero and the end of the twelfth week in the second group, significant differences were observed between all the same variables with  $P < 0.05$ .  
In the second group at the end of the twelfth week, the concentration of triglyceride was about 11/6 times, total cholesterol changes were about ten times, the concentration of high-density lipoprotein cholesterol was about 59% and the concentration of low-density lipoprotein cholesterol was about 13/5 times more than day zero.
  - 3) The mean concentration change of the

same variables between the day before the experiment and the end of the experiment in the third group have significant difference with  $P < 0.05$ .

At the end of the twelfth week, the concentration change of triglyceride was about 88%, the concentration change of total cholesterol was about 77%, the concentration change of high density lipoprotein cholesterol was 1/6 time more and the concentration change of low-density lipoprotein cholesterol was about 38% that of day zero.

- 4) The mean concentration change of the same variables between the day before the experiment and the end of the experiment in the fourth group except high density lipoprotein cholesterol (HDL-C) have significant difference with  $P < 0.05$  in the remaining groups.



At the end of the twelfth week, the concentration change of triglyceride was about 4/3 times more, the concentration change of total cholesterol was about 4/3 times more and the concentration change of low-density lipoprotein cholesterol at the end of the twelfth week is about 5.5 times more than day zero.

#### **The animal weight**

The mean concentration change of the animals' weight at the end of the experiment compared to one day before the experiment, significant differences in all four groups were observed with  $P < 0.05$ . At the end of the twelfth week 7% weight added to the fourth group, 8% weight added to the third group, 72% weight added to the second group and 19% weight added to the control group compared to day zero to the weight of the animals and this increase is obvious in the second group (Table 3 and Fig. 7).

### **DISCUSSION**

Significant reduction of concentration in triglyceride, total cholesterol, low-density lipoprotein cholesterol of blood (LDL-C) and a significant increase in high density lipoprotein cholesterol (HDL-C) in rabbits receiving a high-cholesterol diet plus Itraconazole drug compared to rabbits receiving a high-cholesterol diet (group 4 compared to group 2) was observed, indicating the effectiveness of this drug on the adjustment mode of Dyslipidemia caused by the consumption of high cholesterol foods ( $P < 0.05$ ). Also, such condition in the third group that received normal diet plus Itraconazole drug compared to the control group that only received normal diet ( $P < 0.05$ ) indicates that Itraconazole probably reduces atherosclerotic lesions by lowering the level of triglyceride and total cholesterol, which may be caused by age and increases in body. Because direct relationship has been reported between age increasing and fat disorders (Heimbürger, D.C., 2000).

Indisatrogenic in fourth group was about 76% that of second group and was about 36% in the third group of the control and this represents a reduction of atherosclerosis lesions because of Itraconazole drug consumption. Numerous studies show that diets rich in carbohydrates and fats increase harmful lipids and lipoproteins of

the plasma and increase levels of triglyceride, total cholesterol and bad cholesterol, reduce the level of good cholesterol and increase the risk of cardiovascular disease. (Albrink, 1986 & West, 1990). Dyslipidemia adjustment in the fourth group compared to second group and significant reduction in concentration of triglyceride, total cholesterol, low-density lipoprotein cholesterol of blood and a significant increase of high density lipoprotein cholesterol in the third group compared to the control group may be due to the anti-inflammatory feature of Itraconazole (Vlekova-laskoska, 2009), in particular, this drug is a potent inhibitor of the activity of 5-lipoxygenase (Jaschonek, K., 1989) that prevents the formation of leukotrienes, chemotaxis of neutrophils, interleukin eight and free radicals. According to Jawien, J., (2009), in recent years 5-lipoxygenase path can play an important role in the pathogenesis of atherosclerosis. This information considerably increases the probability of effective treatment regimens of anti-leukotrienes in atherosclerosis. Increase of interleukin was observed after 6 months of treatment with Itraconazole (Gimenes, V.M., 2006). Recently, Han et al have reported wide anti-atherogenic role for interleukin 10 in macrophages and include increased excretion of harmful lipoproteins, inhibition of inflammatory molecules and decreased apoptosis (cell death). Further, Han et al have reported that IL10 increases cholesterol removal by macrophages to protect against the toxicity of cholesterol accumulation in cells (Han X. 2009), thus cholesterol reduction in the group receiving Itraconazole may also be due to the mentioned reason. In addition, Itraconazole has an inhibitory effect on cholesterol synthesis (Lutjohann, 2009). In the study of Itraconazole, total cholesterol was reduced 92% and LDL-C was reduced 17% and risk factor of atherogenic was reduced to thirty percent. These researchers have concluded that Itraconazole has inhibitory effect on the cholesterol synthesis and using it at high dose (400mg/d) resulted in a significant reduction of LDL-C and has significant increase in HDL-C concentration changes compared with ketoconazole (Schneider, 2007). According to Morrell, 1993, cholesterol synthesis is done by a series of enzymes and one of which is HMG-CoA reductase that can reduce HMG-CoA reductase activity and prevent cholesterol synthesis (Morel,

I. 1993). Itraconazole may also effect the synthesis of cholesterol and reduce it in this research through this mechanism.

### CONCLUSION

In this study Itraconazole drug with a high cholesterol diet reduces the concentration of cholesterol, triglyceride and harmful lipoproteins and increased the good lipoproteins compared to the high cholesterol group, but the parameters rate increased compared to the control group with this therapeutic dose and 12 weeks consumption. In the third group compared to the control group, triglyceride, total cholesterol and LDL-C is reduced and HDL-C was significantly increased, indicating the negative effect of drug with a dose of 80 mg per kg at the end of the twelfth week ( $P < 0.05$ ). After further investigation and research on humans and determining the dosage it is suggested this drug be introduced as an anti-atherosclerosis.

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