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The Effects of Hydroalcoholic Extract of Chicoree on atherosclerosis plaque formation of Cardiovascular Diseases in Rabbit.

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ABSTRACT

Plants productions have relative effect as compared with medical chemical compositions and also have the least complications. The use of plants and their medical productions has had historical records in Iran and other countries. So The most important object of the present study is to investigate the effect of Chicoree extract on atherosclerosis plaque formation of cardiovascular diseases in rabbit. Twenty eight rabbits were randomly divided into four groups, normal diet as control group, sunflow oil as sham group, high cholesterolemic group (1% cholesterol), high-cholesterol + Chicoree extract (500 mg/kg/bw) group. Components were given to sham and all 2 experimental groups as gavage. Obtained results of present study indicated that there wasnot significant changes in the rate of body weight in Sham as compaired with control group. There was significant decrease in body weight in 4, 5 groups as compared with control group ($p < 0/01$). The results of present study indicate that the extract of Chicoree extracts can probably prevent from atherosclerosis prevalence, It plays this role because of presnt flavonoids and vitamins

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INTRODUCTION

High levels of circulating fat is considered as an important factor in atherosclerosis and investigations show that coronary artery disease-induced mortality is higher in countries with high consumption rate of fat than countries such as China and Japan [1,2].

Atherosclerosis stiffens arterial wall and hence decreases its elasticity and narrows blood path which ultimately leads to decreased blood supply to main organs of the body including heart and brain. Clinical syndromes of heart coronary diseases are mainly due to the underlying atherosclerosis of epicardial coronary artery which is identified by an atheroma or plaque in the inner wall of arteries [3].

Although increased plasma lipids is a specific factor for vascular disease, they do not change in about half of the patients, therefore, increased coronary vascular disease cannot be explained. However, the disease is better diagnosed through measurement of apolipoprotein levels [4].

Apo-A usually acts a cofactor for lecithine cholesterol acyl-transferase (LCAT) which results in an increase in cholesterol uptake from tissues and their accumulation in HDL for transferring to the liver [5].

Physical structure of the coronary artery wall: The coronary artery supplies the heart in a highly twisted path providing appropriate points for formation of fibrous plaque or atheroma. The main cause of cardiac disease is coronary artery atherosclerosis which results in blood supply decrease [6].

Blood lipid disorder is an important risk factor for atherosclerosis and coronary vascular disease. Cholesterol was firstly identified in human atherosclerotic plaque by known German pathologist, Virchow, in 1850. Hyperlipidemia is classified according to the levels of lipids into 1) hypercholesterolemia; 2) hypertriglyceridemia; and 3) combined (type 1 + type 2) forms [7].

Hypertriglyceridemia (familial hyperlipidemia, FH) is another type of lipid disorder; an autosomal dominant disease in which LDL receptor and apo-B-100 genes are mutated resulting in increased total cholesterol and LDL levels, in turn, increased coronary vascular disease and early death [8].

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One percent increase in LDL results in one percent increase in coronary vascular disease, while, one percent increase in HDL results in 2%-3% decrease in coronary vascular disease. HDL exerts its protective effect on atherosclerosis in levels higher than 75 mg/dL; this increase leads to increased longevity. Increased atherosclerosis [8]. apo-A-I has also a protective impact on

Smoking is the main factor of early death in 35-69 years old people in developed countries and as estimated, it is the cause of 30% of deaths in this age range. Heart-induced death risk is increased 18% in men and 31% in women for each 10 cigarettes smoked [9].

Diabetes and hyperglycemia: Strong epidemiologic evidence shows that both types of diabetes (insulin-dependent and insulin-independent) are main and important risk factors for atherosclerosis. Atherosclerosis is the cause of death in 80% of diabetics. The probability of death due to narrowing of coronary artery in type I diabetes is three times greater than non-diabetic peers. Diabetic patients develop atherosclerosis in lower ages when compared with non-diabetic people. Hyperglycemia results in higher accumulation of platelets and may lead to formation of thrombosis. Increased insulin levels (in some types of adult's diabetes) may damage covering cells of vessels walls, helping creation of atheroma. However, diabetes is not recognized as the sole risk factor, since many of these people suffer from obesity and hyperlipidemia as well, which per se are considered as risk factors [9].

Hyperuricemia:

Blood uric acid levels higher than 15 mg/dL results in increased adhesion of platelets and decreased coagulation time. Myocardial infarction and general damages of atherosclerosis is seen more in gout patients [9].

Obesity:

Obesity is mentioned as a risk factor; in some references as a main risk factor and in some others as a less important one. Obesity consists of two groups:

a) Pre-pubertal obesity: this type is seen in most members of family, exists from birth, and is associated with increased number of adipocytes.

b) Post-pubertal obesity: this type is seen at middle ages and is associated with increased number of adipocytes. Blood lipid and cholesterol are elevated in these patients and the risk of myocardial infarction, hypertension, and other cardiovascular diseases is higher in this group. In general, obese people are more prone to diabetes, hypertension, and hyperlipidemia. Meanwhile, normal-weight people with abdominal obesity are at increasing risk of cardiovascular diseases.

Heredity:

This is the most important factor for development of atherosclerosis. Anyone who comes to the world possesses a structural map in the chromosomes which carry personal traits, apparent phenotype, and disease genotype through genes. If an individual's parents develop myocardial infarction before their fifties, the probability of its occurrence in youth ages will be higher in their children. However, social factors such as nutritional status, economics, and other acquired factors have a severing role in this familial potential [9].

Aggregation of lipids and other materials in arteries results in their narrowing and hence difficulty in blood flow; this condition, *i.e.* atherosclerosis or clogged vessels, results in occlusion of most arteries of the body and occurrence of disease in many organs such as heart (heart attack), brain (stroke), kidneys (renal failure), *etc*.

Atherosclerosis thickens arterial wall and results in reduced vascular elasticity and occlusion of blood path which leads to slow circulation within the arteries and even their occlusion. To compensate low blood supply, the heart has to pump blood with higher pressure through these arteries; this result in heart enlargement and hence its damage. In some instances, soluble lipids may increase in blood and elevate blood concentration; this decelerates normal circulation of blood and may develop disease. In atherosclerosis, the inner wall of an artery may be injured, a type of blood cell called platelet aggregates in the injury location where lipid deposition increases as well. Firstly, the deposits consist of only thousands of lipid-containing cells, but platelets and lipids attack into the depth of the arterial wall and cause damage and deposition of platelet and lipid. The main characteristic of atherosclerosis is high amounts of lipid and platelet deposition. The most important hazard of these deposits is narrowing of the arterial canal. This condition reduces the blood flow in tissues supplied by the affected artery. If a section of these depositions is detached, circulates in blood, and occludes the artery somewhere farther, the condition is called arterial emboli [4].

Chicory is a perennial herbaceous plant. Its stalks are short and can reach to half to one meter in the wild type and to two meters in the cultivated type. Its flowers are tomentose and have deep notches. The flowers are blue. Its seeds are small, long, tetrahedral, and gray hazels. The root is direct and with a thickness of 1-3 cm and length of 10-60 cm. A circle exists around the root at the growth plate of stem, like a collar. The root exterior color is brown, while its inner color is white and has white latex; the extract or boiled root is bitter. Chicory is grown in almost most parts of Iran.

Chemical compounds of chicory are water, proteins, lipids, carbohydrates, calcium, phosphorous, iron, potassium, thiamine, riboflavin, niacin, glucoside, chicoriin, a resin called chicoridine, ascorbic acid, copper, mucilage, essence, pectin, lactucin, intibin, arsenic, vitamin A, and vitamin B [10].

Hassanloo *et al*. showed through spectrophotometric methods that *Silybum marianum*, the family which includes chicory, has a large amount of flavonoids with anti-oxidative properties [11].

Khaksar *et al*. showed that in diabetic animals, chicory-containing diet is more effective than bean-containing diet and that the impact of chicory is directly related to its consumption percentage. These diets may be effective as well in treatment of diabetes mellitus type I in human [12].

MATERIAL AND METHODS

In this research, 28 male, mature rabbits of the New Zealand race with an approximate weight of 2-2.5 kg were purchased from the Razi Institute of Shiraz and transferred to the animal house in Azad University of Jahrom. To adapt them with the environment, they received baseline diet and were kept in standard conditions in terms of lighting and temperature (12 h darkness and 12 h light at 24±2 °C) for 2 weeks. The animals were kept in 360 × 450 × 710 mm cages made of poly-carbonate. Cage floor was covered with sawdust and wood chips, and were emptied, cleaned, and disinfected once per day. Water supplied from municipal water of Jahrom was provided in special plastic containers which were cleaned and filled with water every day.

To determine chicory and nettle doses required, the LD50 method was used. To investigate the effect of cholesterol, since it is provided as powder and 1% of total weight of the diet should contain cholesterol, it was dissolved in olive oil. Therefore, a solution was prepared with cholesterol concentration of 0.5 g/mL and the rabbits were received it through a feeding tube according to their weights and diet relative amount.

The rabbits were randomly divided into four groups of seven animals each, as follows; Group I as controls with normal diet; Group II as sham with sunflower oil as cholesterol solvent (2 mL per kilogram of body weight); Group III with high-cholesterol diet (1% of food weight); Group IV with chicory extract (500 mg/kg/bw) and high-cholesterol diet (1% of food weight). All groups received the diet for 60 days during which the animals had access to food and water without limitation. To provide a high cholesterol diet, cholesterol prepared from Merck, Germany, was fed to rabbits by stomach tube based on 1% of the diet weight. The extracts of plants with the mentioned dose were also fed to the samples through stomach tube at a specified time after ingestion of high cholesterol every day.

The rabbits were anesthetized by chloroform at the end of experiment, after blood sampling; their chests were then dissected, the aortas were removed and washed with physiologic saline; the aortas were then placed in 10% formalin to prepare them for tissue sections. The sections were stained with hematoxylin-eosin. Atherosclerotic plaques were graded according to the ratio of plaque thickness to media thickness in a 1-4 scale [9].

The results in both serology and histology are presented as mean ± standard deviation. To statistically analyze the serological data, the two-factor design with repeated measures on one factor was used and the results were compared in each time unit between the groups and at different time units within each group. For statistical analysis of histological data, the results were compared between groups using a completely randomized design. SPSS-17 was used to compare the means in both sectors, and within and between experimental groups through one-way ANOVA and Duncan's post-test methods. Differences at the level of $p<0.05$ were considered significant.

Results:

Body weight had not significantly changed in Group III (high cholesterol) compared with the control groups ($p<0.05$). Body weight was reduced significantly in Group IV compared with the control groups and Group III (high cholesterol) (P<0/05) (Table 1).

Table 1: Comparison of various groups on basis Body weight and Plaque scale.

			IV	III	II	Control I	Group / Parameter
			-0.667 ± 0.216 a	0.76 ± 0.76 b	0.48 ± 0.023 b	0.428 ± 0.024 b	Body weight
			2.5 ± 0.223 b	3.333 ± 0.210 c	0.166 ± 0.166 a	00±00 a	Plaque scale

The means in each row having at least one common letter are not significantly different at the 5% level by Duncan test. This table compares all studied parameters in different groups.

Histological results showed that in the group treated with normal diet (control), the vessel was completely normal and did not show any lesion in the intima and media (Figure 1).

In the slices prepared from the aorta of 1% cholesterol-treated group, atherotic plaques were detectable. The plaques were formed of lipid-laden macrophages, foam cells, with smooth muscle cells within the plaques. The plaque thickness was increased and was more than half the thickness of the media (Figure 2, 3)

Pathology results showed that the extracts reduced significantly the damage in the arterial wall compared with the high-cholesterol group in whom atheroma was fully raised and observable in the inner surface of the vessel.

In addition to oxidation of lipids, blood platelet activity is another important factor that could accelerate the formation of atherosclerotic plaque. Increased cholesterol is associated with increased coagulability and increased platelet count [13].

In addition to antioxidative properties, flavonoids exert also anti-platelet and anti-inflammatory properties. Lale *et al*. (1996) showed that flavonoids have inhibitory effects on platelet and leukocyte functions and protective effects on endothelial cells and thus prevent the interaction between vessel wall and blood which can initiate thrombosis. Flavonoids perform this action through effects on tissue factor of human monocytes which is per se a blood clotting factor starter [14].

In the groups with high-cholesterol and chicory and nettle extracts, the severity of lesion was decreased in comparison with the high-cholesterol group and the thickness of plaque was half the thickness of media (Figure 4, 5).

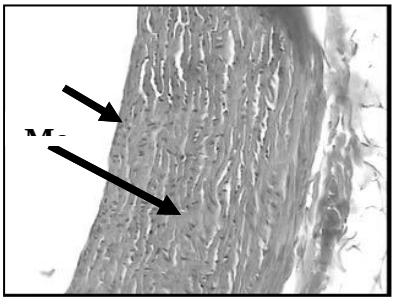

Fig. 1: Aorta tissue in control group (x40).

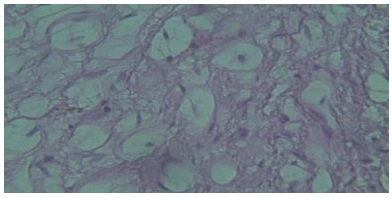

Fig. 2: Aorta tissue in high-cholesterol diet group (x100).

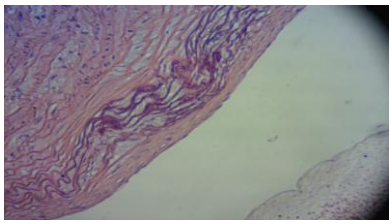

Fig. 3: Aorta tissue in high-cholesterol diet group (x40).

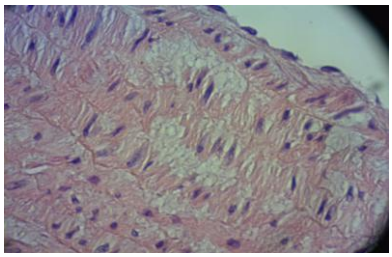

Fig. 4: Aorta tissue in Chicoree extract and high-cholesterol diet group (x100).

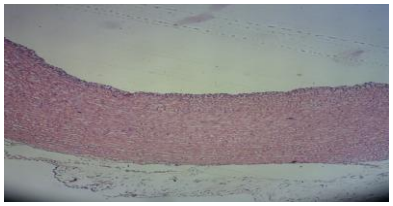

Fig. 5: Aorta tissue in Chicoree extract and high-cholesterol diet group (x40).

Disscusion:

Today, hyperlipidaemia and its side effects are known as a health system problem in most communities. Myocardial ischemic diseases are currently the main causes of death in industrialized and developing societies and atherosclerosis is their most common etiology which occurs naturally in all people to some degree. Atherosclerosis has a higher rate and extent and more serious morbidity in certain groups and leads to myocardial ischemia and its related incidents even at an early age. Causes that trigger the disease in these groups are taken into consideration as risk factors from years ago. The effects of these factors, such as hypertension, diabetes, hyperlipidemia, and smoking are fully proven [15, 16, 17, 18].

According to the table 1, a significant reduction in the final weight of laboratory animals was achieved in Group IV. Previously performed research stated that a positive relationship exists between leptin and plasma cholesterol and triglyceride [19].

Leptin acts as a satiety factor and hence affects appetite and satiety center in the brain. This hormone is released in the blood and circulates toward hypothalamus where it binds to its specific receptors and reduces food intake and increases energy use in the body [20,21].

In fact, leptin conveys the information about body fat storage and energy status to the hypothalamus and leads to regulation of food intake and energy expenditure in order to stabilize body weight [22, 23].

The effects of this hormone is probably exerted through its actions on hypothalamus and include most importantly reduction of body fat mass, reduction of hyperglycemia, and increasing of fat metabolism and hence weight loss [24,25].

Since in the present study, total cholesterol, triglycerides, and LDL were significantly increased in Groups III, IV, and given the positive relationship between leptin and blood lipids, one can state that leptin reduced appetite and resulted in weight loss through increasing blood fat. However, factors such as nausea and maintenance conditions of laboratory animals may affect body weight and should not be ignored.

Various biological activities such as anti-oxidative, antimicrobial, and anti-inflammatory are observed in plants which are mainly due to flavonoids and other phenolic components [26].

It was stated in some research that plants similar to those examined in this study such as *Silybum marianum* contain flavonoids and exert a positive influence on improvement of several diseases including hyperlipidemia [27].

It also stated that the *Silybum marianum* can lower blood cholesterol in patients with hypercholesterolemia. In a study conducted at Shariati Hospital, Tehran, flavonoids-containing *Silybum marianum* reduced total cholesterol, LDL, and triglycerides [28].

Specific mechanism or mechanisms that determine the improvement of lipid profile or reduction of the risk of coronary artery disease is unknown.

Hetrog *et al*. found in their studies that regular consumption of flavonoids reduces the risk of death for cardiovascular disease in elderly men [29].

Cook reported that flavonoids can reduce LDL oxidation through reducing lipid peroxidation, reduction of free radicals, supporting α-tocopherol-LDL or reduction of oxidized α-tocopherol-LDL, and separation of metal ions that participate in oxidation reactions [30].

The anti-oxidative effect of flavonoids on the affinity of LDL to its receptor was studied by Safari. The results showed that flavonoids with good anti-oxidative property increase the affinity of normal and oxidized LDL to its receptor and thus have beneficial effects in treatment of atherosclerosis and reduction of plasma cholesterol.

Borradail *et al*. showed that flavonoids may reduce plasma lipids and atherosclerosis. It was identified that the cholesterol lowering effect of naringnin flavonoids is associated with a decrease in hepatic HMGCoA reductase enzyme, as well as reduced secretion of apo-B from hepatocytes which is related to reduction in acyl-cholesterol acyl transferase (ACAT) activity and reduced ACAT expression. HMGCoA reductase is the rate-limiting enzyme of cholesterol formation in liver and other tissues and decreases the reductase gene expression through negative feedback regulation [31].

Vitamins and herbal antioxidants reduce the risk of cardiovascular diseases probably through decreasing free radicals; they improve endothelial function in hyperlipidemic patients [32].

Free radicals may oxidize LDL in vessel walls and thus reduce vascular endothelial-related vasodilatation [33].

In hyperlipidemic patients, antioxidant requirements increase and adding these vitamins to their diet or medication may lower their blood lipids. As an antioxidant, vitamin C found in plant reduces lipid peroxidation and vascular oxidative damage [34].

Since the use of lipid-lowering drugs at high doses is associated with side effects, and vitamin C and antioxidant-rich diets maintain health and reduces the risk of heart disease, and according to the results, it seems that vitamin C exerts its favorable changes in HDL and LDL levels through two main mechanisms: 1) decreasing LDL oxidation and increasing its recognition by its receptor; 2) competition with glucose (due to structural similarity) in the HDL and LDL glycation process which results in increased LDL catabolism and decreased HDL excretion [35].

Conclusion:

According to the results obtained in this study, it can be stated that chicory extracts was somewhat effective in reduction of blood lipids in the experimental groups with high-cholesterol diet. The results of this study can be partially extended to humans.

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