EC PHARMACOLOGY AND TOXICOLOGY
Research Article

Evaluation of Antihyperlipidemic Activity of *Artemisia herba*-alba Asso in New Zealand Rabbits

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Abstract

Aims: Hyperlipidemia is a well-documented risk factor for cardiovascular diseases which are the leading cause of death in the world. This study aimed to evaluate the effect of *Artemisia herba-alba* Asso (AHA) on hyperlipidemia in the rabbit model.

Methods: The study was conducted on 18 New Zealand rabbits, adult males, randomly divided into 3 groups of 6 each. The first followed a standard diet and served as a normolipid control (CRL), the 2nd was gaved by 10 ml of egg yolk, and considered hyperlipidic control (HYP), the third was treated as the previous lot; rabbits in this group were then treated with AHA infusion at a dose of 300 mg/kg body weight orally. Egg yolk and AHA infusion were applied (6/7 days) for 6 weeks. At the 45th day of the experiment, the biochemical profiles (biochemical and hepatorenal assessments) were determined and the animals were sacrificed and anatomopathological and histological studies were performed.

Results: The results of the lipid assessment showed an increase in lipid parameters in the group treated with egg yolk. The administration of the plant in the AHA group resulted in a significant decrease in cholesterol ($P < 0.05$) and atherogenicity index ($P < 0.05$) compared to HYP group. Regarding the hepatorenal assessment, a significant increase in ALT and not significant for AST in the group (HYP) was recorded, for AHA treated group, no significant variation was observed. A significant decrease of relative organ weights was recorded in gall bladder ($P < 0.001$), adrenal and testicular weights ($P < 0.01$) in AHA group compared to CRL. Micrographs of liver, kidneys and testes have not showed abnormalities in different animal groups.

Conclusion: Finally, it appears from this study that *Artemisia herba-alba* Asso may be used to prevent hyperlipidemia.

Keywords: *Artemisia herba-alba;* Lipids; Cholesterol; Atherogenicity; Hypolipaemia

Introduction

Cardiovascular disease is the leading cause of death in the world. They are responsible each year of death. According to data from the World Health Organization (WHO), an estimated 17.1 million deaths from cardiovascular disease, or 29% of total global mortality. Among these deaths, it is estimated that 7.2 million are due to coronary heart disease and 5.7 million to a stroke. More than 82% of deaths occur in middle- and low-income countries and almost equally affect men and women. By 2030, nearly 23.6 million people will die from cardiovascular disease, mainly heart disease or stroke [1].

In Algeria, more than 14,000 deaths each year, more than 20% of these deaths are due to atherosclerosis caused by dyslipidemia, one of the major risk factors for cardiovascular diseases that may be related to changes in lifestyle related rural exodus, smoking, food, stress [2].

Dyslipidemias also called hyperlipoproteinemia are the main disorders of lipid metabolism. They are typified by quantitative or qualitative changes in plasma lipoproteins. They can be manifested by one or more disturbances: elevation of total cholesterol, low density lipoprotein (LDL) and triglycerides or a decrease in high density lipoprotein (HDL). Dyslipidemia is one of many factors that increase the risk of cardiovascular disease (CVD) with hypertension, smoking and obesity, diabetes [3,4].

Given the considerable increase in the number of people who have these problems as well as the side effects of drugs, many researchers have evaluated the pharmacological action of traditional plants and therefore their interest in traditional medicine.

Artemisia herba alba, or desert wormwood, is a greyish perennial dwarf shrub growing in arid climates belonging to Asteraceae family [5]. This species has been used in traditional medicine in various diseases and some properties were investigated scientifically as: stomachic, antispasmodic, analgesic, vermifuge, antimicrobial, antidiabetic, anti-tumor, disinfectant and ovicidal activities, it is used also as coagulant agent, to treat wounds, and respiratory and digestive disorders [6-11].

Aim of the Study

The present study aimed to evaluate the antihyperlipidemic properties of *Artemisia herba alba* Asso.

Materials and Methods

Preparation of *Artemisia herba-alba* Asso infusion

The plant *Artemisia herba alba* Asso "White wormwood" (Voucher Specimen: AHA-1702ZD) was purchased from a local supplier in Skikda according to the herbalist, this plant is harvested in the mountain of Arris (wilaya of Batna) whose altitude is about 1600m. The sample is then washed and dried in open air shaded place for 21 days. After drying, the aerial parts of the plant were recovered, stored in jars sealed and placed in a place protected from light and heat until use.

The aerial parts of *Artemisia herba alba* Asso were grounded with a coffee grinder, a quantity of 22g of powder was added to 250 ml of boiled distilled water and then left for 30 minutes for infusion with stirring from time to time. The infusion obtained is then filtered on filter paper. After filtration, the final volume is recorded for the calculation of the different doses administered.

Eggs

The eggs were bought from the local market. Egg yolks were separated manually, grouped in a clean container and mixed one hour before gavage.

Animals and housing conditions

This study was carried out on 18 healthy New Zealand rabbits, white, adult males, weighing between 1600g and 2000g at the beginning of the experiment. The animals were purchased from a local supplier (Hama Bouziane, Constantine, Algeria). The rabbits were fed a standard diet (EL-Kseur Agri-Food Complex, Livestock Feeding Unit, Bejaia). Food and water were provided ad libitum. The animals were kept in wire cages in standardized environment at room temperature with a 12-h light-dark cycle. The animals were acclimatized to the conditions of the animal house for a period of 7 days before the start of the experiment. All the experimental procedures adopted were approved by the Scientific Committee of Department of Nature and Life Sciences, Faculty of science, University of August 20th, 1955 Skikda.

Experimental design

The animals were divided into three groups of six rabbits each so that the weight is homogeneous between the different batches.

a) **Normal Control (CRL):** This group received a standard diet during the entire duration of the experiment.
b) **Hyperlipidemic control (HYP):** This group received a standard diet + 10 ml of egg yolk.
c) **Hyperlipidemic + infusion of Artemisia herba-alba Asso (AHA):** This group was treated as the previous batch, rabbits in this group were then treated with AHA infusion at 300 mg/kg.

AHA infusion was applied 20 min after egg yolk administration to avoid interaction. The preparations (eggs, AHA infusion) were given orally by gavage to rabbits using a gastric tube, once a day (6/7 days) for 45 days.

General state and body weight of animals

Rabbits were evaluated clinically every day, the observation focused on clinical signs (appetite, behavior change... etc.) and the state of faeces (solid, liquid, presence of blood... etc). The body weight gain, the temperature, the heart rate and the respiratory movements of the rabbits were performed once a week throughout the duration of the experiment.

Biochemical Assays

At the end of the experiment, the animals were fasted overnight and for biochemical analysis, samples of blood from the marginal ear vein were collected into heparinized tubes. The blood is then centrifuged (centrifugal eppendorf 5810) at 35,000 rpm for 3 minutes and then the plasma was recovered and used for biochemical assays. Biochemical analyzes were performed using an automatic analyzer (mindray D5-3304).

The analyzed parameters are: total cholesterol (CH), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate amino transferase (AST), alanine amino transferase (ALT), blood creatinine, urea and uric acid (UA).

Pathological anatomy and histology

After slaughter, the animals were dissected to examine the internal organs: the liver, kidneys, lungs, spleen, heart, testes and adrenals. These organs were subjected to a macroscopic and microscopic examination of qualitative and quantitative order which includes the macroscopic observation of the external structure, the color, the consistency and the microscopic texture of the organs which have been conserved in a suitable medium (formaldehyde 10%). Histological sections were taken in the pathology laboratory at Skikda hospital.

Statistic analysis

The data obtained from measurements of body weight and those of the various organs, as well as biochemical analyzes were expressed on means with the corresponding standard deviation. All statistical analyzes were performed using the ANOVA test, the level of significance was set at $P < 0.05$. The software used for this study is Origine version 6.I.

Results

General state and body weight of animals

Throughout the experimental period, no mortality was recorded, and no serious clinical signs of toxicity were observed in the animals. All the rabbits remained healthy, and they were available for evaluation. The average weight of the control group (CRL) evolved progressively from 1816.6 ± 137.24g to 1944.4 ± 384.858 g towards the end of the experimental period with a weight gain of 258.4 ± 288.548g. The group gavaged with egg yolk (HYP) showed a progressive increase until the 6th week (from 2111.94 ± 157.69g to 2344.57 ± 287.36g) with a weight gain of 375 ± 146.471g (Figure 1). While the AHA group experienced an increase in weight during the first 3 weeks, followed by a slight decrease, but this decrease was not significant with a body weight gain of 365.6 ± 21.314g. Statistical analysis of animal weights as well as body weight gains obtained showed no significant difference between the three groups of animals.

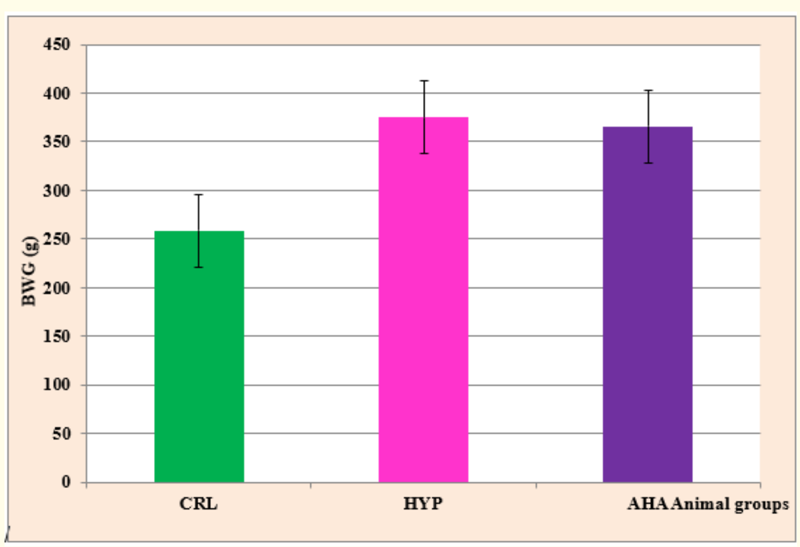

Figure 1: *Body weight gains of rabbits from the three lots.*

Values are expressed as mean ± standard deviation (n = 6). CRL: Control Group, HYP: Hyperlipidemic Group, AHA: Group treated with the infusion of *Artemisia herba alba*, n = 6, CRL vs HYP (P = 0,443); AHA vs HYP (P = 0,890); AHA vs CRL (P = 0,431).

Biochemical results

Lipidemic profile

The results concerning the lipid profile were recorded in table 1. Rabbits treated with egg yolk (HYP) showed a highly significant (P < 0.00001) increase in total cholesterol versus control (CRL). While infusion administration of *Artemisia herba alba* showed a significant reduction in yolk-induced hypercholesterolemia (P < 0.05) in AHA group.

Animal groups	CH (mg/dL)	HDL-C (mg/dL)	LDLC (mg/dL)	TG (mg/dL)	AI
CRL	0,43 ± 0,173	0,108 ± 0,037	0,277 ± 0,076	0,445 ± 0,220	2,956 ± 0,962
HYP	2,855 ± 0,225	0,37 ± 0,089	1,662 ± 0,924	2,02 ± 0,529	6,946 ± 1,281
AHA	1,59 ± 0,604	0,301 ± 0,017	0,985 ± 0,371	1,533 ± 0,232	4,723 ± 2,079
ANOVA (P value)					
	CH	**HDL-C**	**LDL-C**	**TG**	**IA**
HYP Vs CRL	0.000002627	0.00164	0.049	0.00089	0.0025
AHA Vs HYP	0.01463	0.397	0.196	0.072	0.0488
AHA Vs CRL	0.02	0.0239	0.053	0.00329	0.138

Table 1: *Lipidemic profiles of different animal groups at the end of experiment.*

Values are expressed as mean ± standard deviation (n = 6). CT: Cholesterol; HDL-C: High density lipoproteins; LDL-C: Low Density Lipoproteins; TG: Triglycerides; AI: Atherogenicity Index; CRL: Control Group; HYP: Hyperlipidemic Group; AHA: Group Treated with the Infusion of Artemisia herba-alba Asso.

The results also showed a highly significant increase (P < 0.001) of triglycerides in the group (HYP) versus control (CRL). While the hypertriglyceridemia induced was reduced, but not significantly in the group treated with the infusion of white mugwort (AHA). HDL-C was increased very significantly (P < 0.01) in the group (HYP) compared with (CRL). The administration of *Artemisia herba alba* infusion in the AHA group resulted in a significant decrease in this parameter (P < 0.05) compared to CRL. While the differences between the two groups HYP and AHA were not statistically significant. A significant increase (P < 0.05) in LDL-C and atherogenicity index (P < 0.01) in HYP group versus control group (CRL) was recorded. In the AHA group, this risk was significantly reduced (P < 0.05) compared to the yolk-fed group (HYP), noting that the difference with normal lipid control (CRL) was not significant.

Hepatorenal profiles

Liver enzymes (Table 2) showed an increase in the HYP group. The results obtained showed no significant variation (P > 0.05) in the concentration of Aspartate Amino Transferase (AST) in the three batches of rabbits. Alanine amino transferase (ALT) was significantly increased in the (HYP) group compared with the CRL group (p < 0.01). No significant differences were found (P > 0.05) for urea and creatinine in the HYP group versus CRL. But the AHA group recorded a significant decrease in creatinine compared to the HYP group (P = 0.033) and highly significant compared to the CRL (P = 0.0007).

Anatomopathological and histological study

The general appearance of rabbit organs of various batches and their relative weights were normal (Table 3). Relative weights of liver, heart, lung, kidneys, and spleen showed no significant variation (P > 0.05) in all three lots. The relative weight of the gall bladder that underwent a very highly significant (P < 0.001) decrease in the AHA group compared to CRL, with a highly significant decrease in relative adrenal and testicular weights (P < 0.01). The results of the structural architectures of organ micrographs (liver, kidneys, testes) were normal (Figures 2-4). The kidney micrographs show that interstitial tissue, tubular, and glomerular compartments are not affected in all experimental animals (Figure 2). The testicular parenchyma is divided in lobules containing several seminiferous tubules covered by stratified epithelium of spermatogenic cells (which form spermatozoids) and Sertoli cells. The lobules are delimited by a connective tissue septum which takes its origin from albugineous tunic (Figure 3). Figure 4 shows also normal hepatic parenchyma. No abnormalities were observed as fatty change, portal inflammation, necrosis or ballooning degeneration in all liver micrographs of different rabbit groups.

Animal groups	AST (UI/L)	ALT (UI/L)	Crea (mg/L)	Urea (g/L)	UA (mg/L)
CRL	33,285 ± 17,591	61 ± 17,606	11 ± 1,490	0,4966 ± 0,115	1,315 ± 0,597
HYP	48,324 ± 20,245	88,066 ± 20,948	10,182 ± 1,772	0,494 ± 0,086	1,494 ± 0,817
AHA	44,243 ± 21,105	75,3383 ± 22,266	7,8983 ± 1,251	0,3983 ± 0,077	1,0566 ± 0,681
ANOVA (P values)					
HYP vs CRL	0,132	0,017	0,3626	0,964	0,656
AHA vs HYP	0,752	0,357	0,0336	0,085	0,357
AHA vs CRL	0,243	0,163	0,000793	0,091	0,465

Table 2: *Hepatorenal profiles of different animal groups at the end of experiment.*

Values are expressed as mean ± standard deviation (n = 6). CRL: Control Group; HYP: Hyperlipidemic Group; AHA: Group Treated with the Infusion of Artemisia herba alba; ASAT: Aspartate Amino Transferase; ALAT: Alanine Amino Transferase.

	Kidneys (2)	Heart	Lung	Gall bladder
CRL	0,00518 ± 0,00034	0,00274 ± 0,00018	0,00656 ± 0,00438	0,00022 ± 0,00005
HYP	0,00664 ± 0,00109	0,00236 ± 0,00022	0,00611 ± 0,00114	0,00173 ± 0,00097
AHA	0,00547 ± 0,00051	0,0025 ± 0,000093	0,00622 ± 0,0017	0,00102 ± 0,00014
	Liver	**Adrenals (2)**	**Spleen**	**Testicle (2)**
CRL	0,03494 ± 0,00349	0,000255 ± 0,000038	0,000361 ± 0,00025	0,00345 ± 0,000201
HYP	0,03257 ± 0,0024	0,000182 ± 0,000016	0,000627 ± 0,000047	0,00281 ± 0,00065
AHA	0,03299 ± 0,0001	0,000118 ± 0,000023	0,000504 ± 0,000034	0,00246 ± 0,00024
	ANOVA (P values)			
	Kidneys (2)	**Heart**	**Lung**	**Gall bladder**
HYP vs CRL	0,0916	0,08275	0,8723	0,05565
HYP vs AHA	0,16742	0,36597	0,93117	0,28017
AHA vs CRL	0,47079	0,11071	0,90662	0.000874
	Liver	**Adrenals (2)**	**Spleen**	**Testes (2)**
HYP vs CRL	0,38695	0,03879	0,1487	0,17565
HYP vs AHA	0,91604	0,01926	0,02233	0,43906
AHA vs CRL	0,65515	0,00629	0,38766	0,00574

Table 3: *Relative organ weights of different batches of rabbits.*

Values are expressed as mean ± standard deviation (n = 6). CRL: Control Group, HYP: Hyperlipidemic Group, AHA: Group treated with the infusion of Artemisia herba alba.

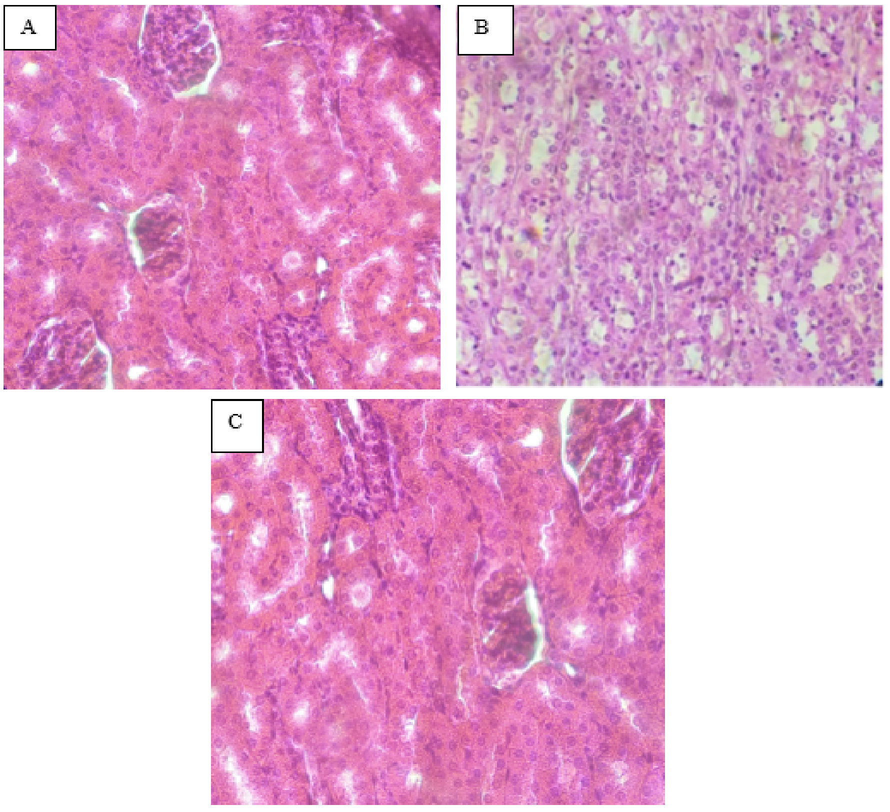

Figure 2: *Kidney histology stained with Hematoxylin-Eosin, A: Hyperlipidemic group HYP, B: Group treated with infusion of Artemisia herba alba AHA, C: Normolipid control group CRL (G X 40).*

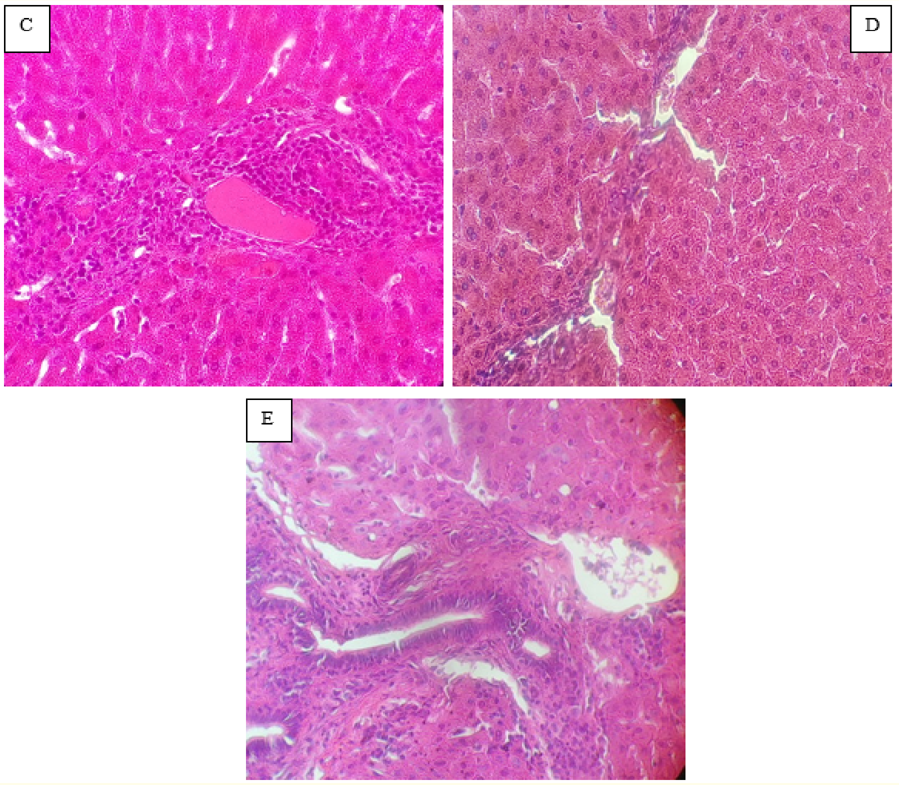

Figure 3: *Liver histology stained with hematoxylin-eosin, C: In hyperlipidemic group rabbit, D: In the group treated with the infusion of Artemisia herba alba, E: Normolipid control group CRL (G X 40).*

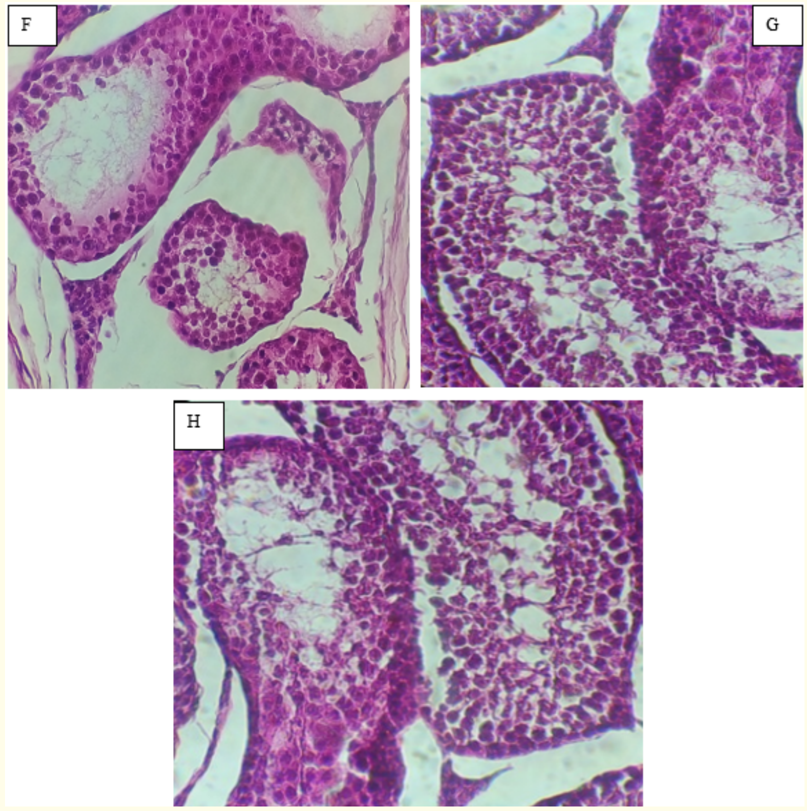

Figure 4: *Testis histology stained with Hematoxylin-Eosin, F: In hyperlipidemic group rabbit, G: In Artemisia herba alba infusion group, H: Normolipid control group CRL (G X 40).*

Discussion

The current study aimed to investigate the effect of Artemis herba-alba infusion on induced hyperlipidemia in rabbit model. This animal represents the first model of experimental atherosclerosis. Numerous studies have shown that atherosclerosis can be induced experimentally by administering hypercholesterolemic diets to animals [12]. Indeed, in animal models (rat, rabbit) as in humans, a high cholesterol diet causes many metabolic alterations; severe hypercholesterolemia, an inflammatory response [13] and oxidative stress [14].

In our study we induced hyperlipidemia by a high cholesterol diet which is egg yolk which is used in several ancient and recent scientific works; the average composition of this latter per 100g is 16.1g proteins, 34.5g lipids, 22.9g triglycerides, 10g phospholipids, 13g saturated fatty acids, 20.7g unsaturated fatty acids, 1,2g cholesterol [15-17].

Some nontoxic plants can have a harmful effect on various human or animal organs, because of their use in excessive doses or their absorption for a long time. In our case, the dose of *Artemisia herba alba* administered to rabbits (300 mg/kg) was chosen because it shows no toxicity as reported elsewhere [18].

In our study the body weight results show a significant increase in the group HYP compared to CRL. These results are consistent with those of Djerrou., *et al.* [19] who found significant difference in rabbits rendered hyperlipidemic by egg yolk at a dose of 7 ml/kg for 4 weeks. While the administration of the plant infusion in the group (AHA) shows a slight decrease towards the 21st day following another increase at the end of the experiment.

Numerous studies have reported the beneficial effects of medicinal plants on the improvement of the lipidemic profile in rats fed a cholesterol-enriched diet.

Hypertriglyceridemia and hypercholesterolemia appear to be one of the major effects of excessive cholesterol consumption. Indeed, the cholesterol-enriched diet is responsible for elevated serum and hepatic cholesterol and triglycerides [20].

In this work, the rabbits subjected to the cholesterol-rich diet show an increase in the level of lipid parameters whose cholesterol increases 6.6 times in the group gaved by the egg yolk (HYP) compared to the control group (CRL), the triglycerides increase 4.5 times, HDL 3.4 times, LDL 6 times, and increase atherogenic risk 2.3 times. We suggest that there is a release of free fatty acids (Cholesterol) that will be oxidized in the liver to "Acetylcoenzyme A" which causes hyperlipidemia in the cholesterol group.

These results are similar to that of Aminian., et al. [21] and confirmed by Djerrou., et al. [19] who observed an increase in lipid parameters whose cholesterol increased 8.3 times in the group gaved by egg yolk compared to the control group, triglycerides increase 1.5 times, HDL 0.8 times, LDL 20.7 times and the increase in atherogenic risk 8.4 times.

The application of the *Artemisia herba alba* infusion at a dose of 300 mg/kg caused a decrease in cholesterol 3.7 times, and improvement of the atherogenicity index 1.6 times, whereas HDL, LDL and triglycerides have not been significantly modified.

The hypocholesterolemia effect of *Artemisia herba alba* is well confirmed in alloxan diabetic rats treated with this plant [22]. Abid., *et al*. [23] reported that a decoction of AHA lowers triglycerides and cholesterol levels in rats fed subcutaneous fat from sheep and animal butter. The differences observed between the results obtained in the present study and the previous studies could be explained by the modifications made to the experimental protocol (animal species, sex, dose of egg yolk, duration of application as well as the dose of *Artemisia herba alba*).

The possible mechanism of this antihyperlipidemic activity of AHA extracts may be related to increased mobility of plasma glucose to peripheral tissues, as suggested by the decrease in insulin resistance. The observed hypolipidemic effect may also be due to a decrease in cholesterol and fatty acid synthesis and/or depressed fat mobilization [24].

In our study, liver function was assessed by measuring plasma concentrations of ALT and AST. Renal function was assessed by measurement of plasma creatinine and urea and uric acid concentrations [25,26]. With respect to hepatic function, AST activities were found to be slightly elevated but statistically insignificant while ALT concentration was 1.4 times higher in the group gavaged with egg yolk (HYP) compared to the normolipidemic control group (CRL), while there was a decrease in the concentration of these liver enzymes but statistically insignificant in the treated group with plant infusion. The enzymatic function of the liver has not been consecutively altered by plant infusion treatment (AHA group). It is known that damage to the structural integrity of the liver results in an increase in specific liver enzymes (PAL, ALT and AST) in the serum, because they are cytoplasmic enzymes and are circulated after injury [27,28]. It is necessary to mention that these transaminases play an important role in the metabolism of amino acids and in providing intermediates necessary for gluconeogenesis. According to this study, the non-significant decrease in plasma transaminases (ALT and AST) in rabbits treated could indicate an improvement in liver function due to the possible hepato-protective effect of *Artemisia herba alba.* With regard to renal function, In our work, the administration of the plant infusion causes a decrease in creatinine concentration by 1,3 times compared to HYP group and 1,4 times compared to CRL group. While no significant differences were noted in urea and uric acid concentrations. Plasma creatinine concentration is often used as a simple index of glomerular filtration rate, the degree of increase in creatinine and serum creatinine being considered as a reflection of the degree of decrease in this renal function [29].

Moreover, our results indicate that the relative organ weights and the normal architectures observed of kidneys, testes and liver in the different micrographs could indicate that there is no damage due to administration of egg yolk or *Artemisia herba-alba* infusion to rabbits. In a recent study, Bertella., *et al.* [30] have reported that the essential oil of *A. herba-alba* collected from Batna (Algeria) was mainly constituted of oxygenated monoterpenes followed by monoterpene hydrocarbons, the most abundant compound found was camphor. In addition to α-thujone, b-thujone, eucalyptol and chrysanthenone components. However, the mechanisms of actions of these molecules are not yet well documented.

Conclusion

The study concluded that *Artemisia herba alba* infusion may be used in the prevention of hypercholesterolemia and as anti-atherogenic agent. Other studies are required to determine bioactive phytochemical constituents of this plant and to investigate their possible mechanism of action.

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