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Research Article

Hypolipidemic Effect of Hemp Seed Oil from the Northern Morocco Endemic Beldiya Ecotype in a Mice Model: Comparison with Fenofibrate Hypolipidemic Drugs

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Introduction. *Cannabis sativa* is a source of oil seeds for pharmaceutical, cosmetic, and food uses. *Objective*. The aim of this study is to evaluate the hypolipidemic effect of hemp seed oil (HSO) obtained from a local ecotype called "*Beldiya*." *Methods*. The extraction of HSO was carried out by cold press method. Then, the fatty acid and tocopherol composition was analyzed, respectively, by GC-FID and HPLC. The hypolipidemic activity of HSO at a dose of 3.5 and 7 mg/kg body weight was evaluated in Triton WR-1339-induced hyperlipidemic mice by measuring plasma cholesterol (total lipid, HDL, and LDL), plasma triglycerides, and atherogenic index using enzymatic methods. Fenofibrate was used as a standard hypolipidemic drug at a dose of 3.5 mg/kg body weight. *Results*. Analyzed HSO shows a high unsaturated fatty acids' content with the dominance of linoleic acid (48.85%), oleic acid (21.82%), as well as α- and γ-linolenic acid (14.72%). The result demonstrates that this typical vegetable oil contains a high concentration of γ-tocopherol (456 mg·kg^{-1} oil). Furthermore, the administration of HSO decreases plasma total cholesterol, triglycerides, and LDL-cholesterol while increases HDL-cholesterol. Consequently, the HSO reduces the atherogenic index and LDL/HDL ratio. The hypolipidemic effect of fenofibrate is relatively more marked comparatively to that of HSO especially concerning total cholesterol and its LDL fraction. *Conclusions*. The local ecotype HSO has an interesting effect on plasma lipid parameters and might be beneficial for the treatment of hyperlipidemia and prevention of atherosclerosis.

1. Introduction

Cannabis sativa L. is an annual plant belonging to the family of *Cannabinaceae*, widely spread in several countries of the world, especially in Asian countries, Canada, the United States (US), Europe, and Africa [1]. The ecotype "*Beldiya*" is an herbaceous crop endemic to the Rif region of Morocco [2]. It has been traditionally cultivated for centuries and is adapted to its natural and cultural environment. This ecotype is characterized by its high tolerance to biotic and abiotic stress and its capacity to be cultivated in a region with low and irregular rainfall [2]. It is one of the oldest herbs cultivated to provide nutritional and medicinal benefits and a versatile crop that can be cultivated for production of fiber,

seed, and oil [3–5]. Hemp seed oil is deep green oil rich in essential fatty acids, tocopherols, and other secondary metabolites [6–8]. It is characterized by a high amount of unsaturated fatty acids with respect to saturated ones and has a perfect ratio of $\omega-6$ linoleic fatty acid (18 : 2n6) to $\omega-3$ α-linolenic fatty acid (18 : 3n3) [9, 10]. This ratio of 3 : 1 is optimal for healthy human nutrition and confers a high nutritional value to the hemp oil. Further, the presence of micronutrients such as tocopherols particularly γ-tocopherols, polyphenols, and carotenoids with antioxidant, anti-inflammatory, and plasma lipid-lowering activities increases the health benefits of the oil [9].

Cardiovascular diseases (CVD) represent the main cause of morbidity and mortality in many developed and developing countries [11, 12]. The most common underlying cause of onset and complication of such pathologies is hyperlipidemia [13]. Many nutritional reports have recently recommended the intake of edible vegetable oils to provide improvement of lipid metabolism and significantly reduce the risk of CVD complications [14, 15]. In fact, it is reported that numerous oils such as Moroccan argan oil decreases plasma cholesterol and triglycerides [16]. Furthermore Oladapo et al. [17]. demonstrated the beneficial effect of palm, soya, and olive oils on cardiometabolic health regarding total cholesterol, HDL-cholesterol, non-HDL cholesterol, and atherogenic index. On the other hand, it is showed that a blend of soy oil, sunflower oil, and non-conventional flaxseed oil significantly decreased atherogenic circulation lipid including total cholesterol, triacylglycerol, and low-density lipoprotein in high-fat diet-fed rats [18].

So, to demonstrate the beneficial impact of these oils on cardiometabolic health, many studies were conducted to show their hypolipidemic and antiatherogenic properties in different experimental models such as Wistar and Meriones shawi rats [14, 16, 19]. However, no experimental study has been undertaken in Morocco to demonstrate the possible beneficial effect of hemp oil in this field. The TritonWR-1339 mice model is widely used to screen hypocholesterolemic and hypotriglyceridemic activities of natural products [20]. The use of this model was justified especially by a given significant hyperlipidemia in quick time.

The main objective of this study is to support the efforts that Morocco has been making to contribute to local cluster initiatives to support the competitiveness of small- and medium-sized enterprises, provide alternatives solutions to cannabis growers in the Rif, and to break their almost exclusive dependence on accumulating capital, which is based on drug trafficking. To achieve this objective and participate in this project, this study was designed to characterize the hemp seed oil from local endemic ecotype "*Beldiya*" and demonstrate its possible hypolipidemic activity in hyperlipidemic mice and its possible use and valorization as a pharmaceutical product.

2. Material and Methods

2.1. Cold Extraction of Hemp Seed Oil. Hemp seeds of *Cannabis sativa* L, "*Beldiya*" ecotype were collected in the region of Tamrot (Rif, Northern Morocco) at the maturity in July 2020. The collected samples were cleaned by hexane to remove Δ-9-THC [15], which could have contaminated them during the harvest, and stored at $4 \pm 2^{\circ}$C in plastic containers sealed until use. The oil was prepared by triturating in an oil screw press (KOMET Model DD85G); the speed was 70 RPM with a temperature of 100°C. The fine particles and debris were removed by centrifugation at 3000 RPM for 15 min. The obtained hemp oil samples were stored at 4°C until use.

2.2. Fatty Acid Analysis of "Beldiya" Hemp Seed Oil. Fatty acids were converted to fatty acid methyl esters (FAMEs) before analysis by gas chromatography coupled with a flame ionization detector (GC Agilent 6890, Agilent Technologies) as previously described [21]. The samples (1 μL in spitless mode) were separated on a BPX70 capillary column (60 m length, 0.32 mm internal diameter, and 0.25 μm film thickness; SGE Europe). Helium was used as the carrier gas at a flow rate of 1 ml·min^{-1}. The initial oven temperature was 50°C and then it was increased at a rate of 30°C·min^{-1} to 170°C, followed by an increase of 4°C·min^{-1} to 220°C. This temperature was maintained for 10 min.

The results were expressed in percentage, after the identification of fatty acids by comparison with those of standards from Sigma-Aldrich containing 37 FAMEs (Supelco, Bellefonte PA, USA).

2.3. Tocopherols Analysis. The tocopherol compounds were analyzed by HPLC-DAD (Agilent Technologies Series 1200 System) according to the AOCS Method Ce 8–89 (AOCS, 1989) [22]. The samples were dissolved in hexane and separated in an Uptisphere NH_2 column (150 mm × 3 mm, 3 μm) using hexane/2-propanol (99 : 1, v/v) as an isocratic mobile phase. The flow rate was 1 mL/min and temperature was set at 30°C. The detection of separated compounds was carried out at 292 nm using an ultraviolet detector. The compounds were quantified by external calibration using standard tocopherols obtained from Sigma-Aldrich (Steinheim, Germany).

2.4. Total Phenols and β-Carotene Quantification. The amount of total phenols was determined by the Folin–Ciocalteu spectrophotometric method (spectrophotometer, RAYLEIGH UV1800, UV-Visible) according to the procedure described by Moumen et al. [22]. The β-carotene content was determined spectrophotometrically, and the results were expressed with reference to a standard curve established from a range of β-carotene concentrations (Sigma-Aldrich, St-Louis, MO, USA) as previously described [23].

2.5. Experimental Animal Design. Forty *albinos*' mice bred in the animal house of the Faculty of Sciences (Oujda, Morocco) and weighing 30 g were fasted overnight and divided randomly into five groups of eight animals each; the first served as the control group (CG) which received 0.5 ml of 9‰ NaCl by intraperitoneal injection and gavaged with

distilled water. The second, hyperlipidemic group (HG) was injected intraperitoneally with 0.5 ml (200 mg/kg) of Triton solution and gavaged with distilled water. The third and fourth, hemp oil-treated groups (HOG), received Triton by intraperitoneal injection and gavaged with hemp oil at a dose of 3.5 and 7 mg/kg, respectively. The fifth, fenofibrate-treated group (FTG), received Triton and gavaged with fenofibrate solution at a dose of 3.5 mg/kg.

After 24 h, the animals were slightly anesthetized with pentobarbital, and blood was taken from their retro-orbital sinuses using tubes containing trisodium citrate as an anticoagulant. After centrifugation at 2500 rpm for 15 min, the plasma was recovered for determination of lipid parameters.

The mice treatment and handling were used according to the internationally accepted standard guidelines for the use of laboratory animals. The present experimental protocol was approved by the local committee for the use of laboratory animals (Faculty of Medicine, University Mohamed I; approval number: 002016).

2.6. Enzymatic Dosage of Plasma Lipid Parameters. The plasma total cholesterol was enzymatically oxidized by cholesterol oxidase to produce hydrogen peroxide which reacts with 4-amino-antipyrine and phenol to produce a red-colored quinoneimine. 10 μL of plasma was mixed with 1 mL of an enzymatic reagent (Biosystems Kit, Barcelona, Spain, REF: 12505). After incubation at 37°C/10 min, the absorbance was recorded at 510 nm. The amount of plasma total cholesterol (TC) was calculated according to the kit manufacture as follows: TC (mg/dL) = (absorbance sample/absorbance standard) × concentration of the standard.

Plasma triglycerides were also quantified by using the enzymatic method (Biosystems Kit, Barcelona, Spain, REF: 12528). So, after hydrolyzing triglycerides by lipases, formation of a chromophore from H_2O_2, 4-aminophenazone, and 4-chlorophenol under peroxidase catalysis was measured spectrophotometrically. 10 μL of plasma samples was reacted with 1 mL of the enzymatic reagent for 10 min at 37°C. Then, the absorbance was measured at 510 nm. TG concentration was calculated as follows: TG (mg/dL) = (absorbance sample/absorbance standard) × concentration of the standard.

The HDL and LDL cholesterol contents were determined enzymatically using Biosystems kits as described in the kit manufacture (Biosystems Kit, Barcelona, Spain, REF 12557 for HDL and REF : 12585 for LDL-cholesterol).

The atherogenic index (AI) and LDL-C/HDL-C ratio were calculated according to formulas previously described by Harnafi et al. [24].

2.7. Statistical Analysis. The obtained experimental data were analyzed using Student's *t*-test. One-way ANOVA statistical analysis and Tukey's post-hoc test were employed to evaluate the difference between the treated groups using SPSS for Windows. The *P* values less than 0.05 were considered as statistically significant. The results are expressed as mean ± SEM.

3. Results and Discussion

3.1. Fatty Acid, Tocopherol, β-Carotene, and Total Phenol Content of "Beldiya" Hemp Seed Oil. The analysis of the hemp oil fatty acids (Table 1) shows that linoleic acid (48.85%) is the main fatty acid followed by oleic acid (21.82%), α-linolenic acid (14.17%), and palmitic acid (8.03%). It is also noted from several studies that the presence of γ-linolenic acid (0.55%) has beneficial effects on human health [23]. These results are widely comparable to that of other hemp seed oils previously reported in the literature [4, 7, 25]. In addition, the balance of saturated, monounsaturated, and polyunsaturated fatty acids brings out values of 12.46%, 23.71%, and 63.83%, respectively. In comparison with cannabis seed oils from Morocco or other origins described in the literature, no discrepancies were found [15].

On the other hand, the polyunsaturated fatty acid/saturated fatty acid ratio of this oil was evaluated at 5/1; this fairly high ratio could be favorable for reducing hyperlipidemia and preventing atherosclerosis [14, 26]. Finally, the $\omega 6/\omega 3$ ratio of our oil was estimated at 3.48 which is very close to those reported by previous works studying cannabis oil from different regions [10, 15, 25, 27, 28]. According to the nutritional recommendations, this ratio lower than 5 could be ideal and nutritionally beneficial compared to those given by the current alimentation ranged between 10 and 30 [23, 29].

Minor oil fractions analysis (Table 2) showed a high content of total tocopherol (498.64 $mg \cdot kg^{-1}$ oil) with a dominance of γ-tocopherol (456 $mg \cdot kg^{-1}$ oil). The hemp seed oil is rich in β-carotene (17.73 $mg \cdot kg^{-1}$ oil) and total phenols (39.02 $mg \cdot kg^{-1}$ oil).

The amounts obtained are within the range of values usually found in the literature [15]. This richness in antioxidants, especially, γ-tocopherol, could constitute a considerable asset in the use of Moroccan hemp oil as an important source of natural tocopherols as well as a protective agent against oxidation [30, 31]. Also, during the last 25 years, research has revealed that γ-tocopherol has antioxidant and anti-inflammatory activities relevant to disease prevention compared to α-tocopherol [32].

3.2. Hypolipidemic Effect of Hemp Seed Oil. The induction of hyperlipidemia in animal models by using the nonionic surfactant Triton WR-1339 is a strategy widely used in experimental studies in order to search for novel hypolipidemic substances [24]. This surfactant can inhibit the enzymatic activity of lipoprotein lipase (LPL) and lecithin cholesterol acyl transferase (LCAT), resulting in the accumulation of plasma total cholesterol, triglycerides, and very low-density lipoprotein [24]. The concentrations of plasma total cholesterol and triglyceride in Triton-treated mice and controls are summarized in Figure 1. As can be seen, in comparison with the normal control group, Triton WR-1339 caused a marked increase in cholesterol and triglyceride levels measured 24 h after injection. The plasma total cholesterol was increased by 234% ($P < 0.001$) and triglycerides by more than 660% ($P < 0.001$). After 24 h, the

Table 1: Fatty acids' composition of hemp seed oil (Beldiya ecotype) cultivated in the Tamrote region (north of Morocco).

Fatty acids	(g/100 g fatty acids)
C14 : 0	0.05 ± 0.00
C15 : 0	0.02 ± 0.00
C16 : 0	8.03 ± 0.04
C16 : 1n7	0.04 ± 0.00
C16 : 1n9	0.13 ± 0.00
C17 : 0	0.05 ± 0.00
C17 : 1	0.03 ± 0.00
C18 : 0	3.13 ± 0.02
C18 : 1n9	21.82 ± 0.12
C18 : 1n7	1.24 ± 0.04
C18 : 2n6	48.85 ± 0.08
C18 : 3n6	0.55 ± 0.01
C18 : 3n3	14.17 ± 0.08
C18 : 4n3	0.07 ± 0.00[b]
C20 : 0	0.84 ± 0.01
C20 : 2n6	0.19 ± 0.00
C20 : 1n9	0.45 ± 0.00
C22 : 0	0.04 ± 0.00
C24 : 0	0.31 ± 0.01
SFA	12.46 ± 0.05
UFA	87.54 ± 0.05
MUFA	23.71 ± 0.14
PUFA	63.83 ± 0.14
$n-6$	49.60 ± 0.08
$n-3$	14.24 ± 0.08
$n-6/n-3$	3.48 ± 0.02

SFA: saturated fatty acids, UFA: unsaturated fatty acids, MUFA: monounsaturated fatty acids, and PUFA: polyunsaturated fatty acids.

Table 2: Tocopherol, total phenol, and carotene contents of hemp seed oil (Beldiya ecotype) cultivated in the Tamrote region (north of Morocco).

Parameters	Contents
α-tocopherol	23.31 ± 2.22[a]
β-tocopherol	0.20 ± 0.01[a]
γ-tocopherol	456.24 ± 18.80[a]
δ-tocopherol	18.89 ± 0.85[a]
Total tocopherols	498.64 ± 21.07[a]
Seed total phenols	191.20 ± 1.94[b]
Oil total phenols	39.02 ± 4.08[c]
β–carotene	17.73 ± 0.38[d]

[a]mg/kg oil, [b]mg gallic acid equivalent/100 g seeds, [c]mg gallic acid equivalent/kg oil, [d]mg/kg oil.

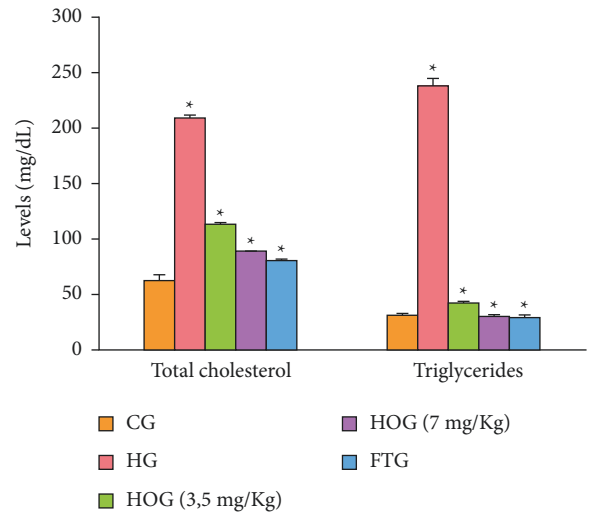

Figure 1: Effect of hemp seed oil on plasma cholesterol and triglycerides in Triton WR-1339-induced hyperlipidemic mice. With (CG: control group; HG: hyperlipidemic group; HOG: hemp oil-treated group; FTG: fenofibrate-treated group; TC: total cholesterol, TG: triglycerides. * $P < 0.001$ (HG vs CG and treated groups vs HG)).

administration of hemp seed oil in Triton-injected mice at a dose of 3.5 mg/kg, respectively, decreases both plasma total cholesterol and triglycerides by 45.7% and 82% ($P < 0.001$), with respect to the hyperlipidemic group. At 7 mg/kg, the hemp seed oil reduced plasma total cholesterol by 57% and triglycerides by 87% ($P < 0.001$) (Figure 1).

The LDL and HDL-cholesterol levels are reported in Figure 2. When the Triton-injected group was compared with control, we observed that the LDL cholesterol was increased by 207% ($P < 0.001$). While the HDL cholesterol was not significantly hindered, LDL cholesterol was reduced by 61% ($P < 0.001$) and HDL cholesterol increased by 324% ($P < 0.001$) after 24 h of the administration of hemp seed oil (Figure 2).

After 24 h, a significant increase was noticed in the atherogenic index (117%, $P < 0.001$) and LDL/HDL ratio (111%, $P < 0.001$) (Figure 3). In addition, the hypolipidemic effect of the studied oil resulted in a significant decrease of the atherogenic index (−50.2%) and LDL/HDL ratio (−90%) compared to the hyperlipidemic control (Figure 3). Furthermore, the LDL cholesterol was 80% reduced and HDL cholesterol 380% increased comparatively to mice received Triton alone ($P < 0.001$). As a consequence, the atherogenic index was reduced by 66% and LDL/HDL ratio by 95%. Thus, from these results, it appears clearly that the hypolipidemic effect of the hemp oil is dose-dependent and affects all lipid parameters which represent a high-risk factor for atherosclerosis and related cardiovascular diseases.

In fenofibrate-treated mice at a dose of 3.5 mg/kg, similar patterns of change were observed. Indeed, total cholesterol was lowered by 61.7% and triglycerides by 87% (Figure 1). Furthermore, the LDL cholesterol was significantly reduced (−87.4%) and HDL cholesterol raised (+408%) in comparison to the hyperlipidemic group (Figure 2). This results in a significant decrease in the atherogenic index (−84.6%, $P < 0.001$) and LDL/HDL ratio (−97%, $P < 0.001$) (Figure 3). It is noted that the hypolipidemic effect of fenofibrate is relatively more marked compared to that of hemp seed oil especially concerning total cholesterol and its LDL fraction. However, the oil can be included in diet as a functional food unlike drugs which can only be taken for therapeutic purposes. Furthermore, the oil is a natural product with ordinary fatty acids, tocopherols, and polyphenols which could be safer compared to synthetic drug fenofibrate.

The hypocholesterolemic effect of the studied hemp seed oil was associated with a significant drop in the atherogenic LDL fraction considered for a long time as the main

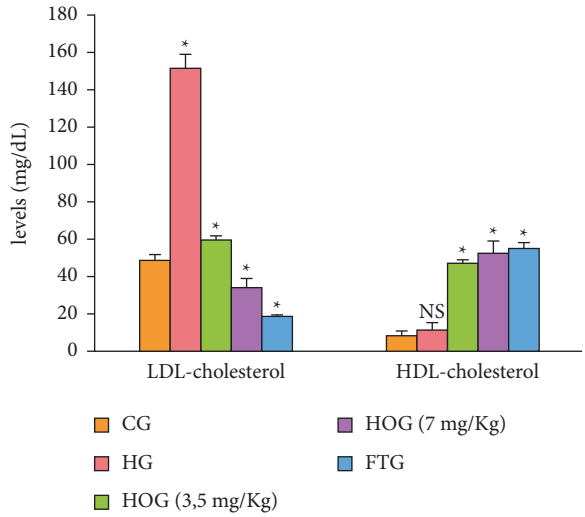

Figure 2: Effect of hemp seed oil on plasma LDL and HDL cholesterol in Triton WR-1339-induced hyperlipidemic mice. CG: control group; HG: hyperlipidemic group; HOG: hemp oil treated group; FTG: fenofibrate treated group; LDL: LDL-cholesterol, HDL: HDL-cholesterol. $^*P < 0.001$, NS: not significant (HG vs CG and treated groups vs HG).

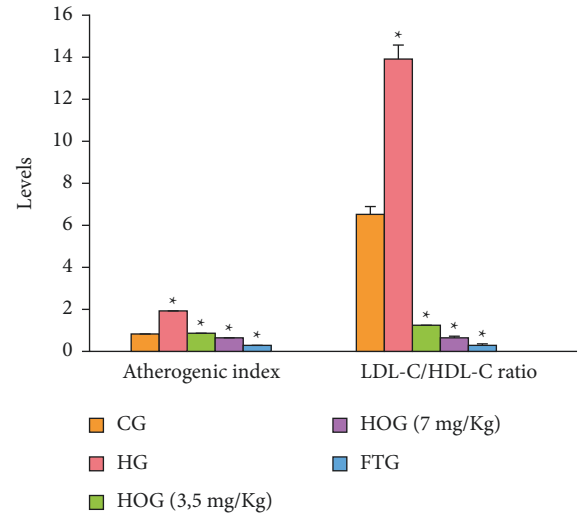

Figure 3: Effect of hemp oil on atherogenic markers in hyperlipidemic mice. (Values are expressed as mean ± SEM. $^*P < 0.001$ (HG vs CG and treated groups vs HG). AI: atherogenic index).

modifiable risk factor for cardiovascular diseases and the therapeutic target of several lipid lowering drugs. This led us to suggest that the hypocholesterolemic effect of hemp seed oil could arise from the activation of LDL receptors responsible to the uptake of cholesterol from plasma to peripheral tissues as described by previous reports [26]. On the other hand, the hypocholesterolemic effect of the studied oil was accompanied by a significant increase in HDL-cholesterol levels. This is a great advantage in lipid metabolism that prevents fat deposition in the vessel endothelium by returning the excess cholesterol from peripheral tissues to the liver via HDL and its elimination in the form of bile acids. Our finding is consistent with several previous reports demonstrating the hypolipidemic activity of edible vegetable oils [33–35]. Indeed, it was recently demonstrated that the use of rice bran oil as edible oil significantly improves lipid metabolism by decreasing total and LDL cholesterol and increasing HDL cholesterol in humans. On the other hand, triglycerides play a key role in maintaining lipid metabolism homeostasis and are independent risk factors of cardiovascular diseases [36]. In the present study, it was found that hemp seed oil significantly reduced plasma triglycerides levels. This suggests that the oil could restore metabolism of triglycerides via the activation of endothelial lipoprotein lipase involved in the hydrolysis of VLDL at a tissue level. This mechanism was previously proposed by others when studying the hypolipidemic effect of natural products [24, 35]. Furthermore, the administration of hemp seed oil to the hyperlipidemic mice results in a significant decrease of the atherogenic index and LDL/HDL ratio which are closely related to the hypocholesterolemic effect. Our findings concord with several studies conducted with vegetable oils and natural substances [17, 37, 38]. This could confirm the beneficial effect of the studied oil on lipid metabolism and related atheromatous diseases.

So, it is recently reported that intake of polyunsaturated fatty acids (PUFAs) decreased total cholesterol, triglycerides, LDL-cholesterol, VLDL, apoprotein B, and increased HDL-cholesterol by increasing liver X receptor alpha (LXRα) gene transcription via peroxisome proliferator-activated receptors (PPARs) [39, 40]. LXRα increases the expression of cholesterol 7α-hydroxylase (CYP7), which converts cholesterol to bile acids; therefore, by stimulating CYP7 activity, PUFAs help to catabolize cholesterol [39]. Furthermore, dietary PUFAs may exert their LDL-C-lowering properties by increasing membrane fluidity, which increases LDL receptor activity and increases LDL catabolism [26, 41]. Concerning triglyceride metabolism, it is suggested that such fatty acids act by decreasing VLDL secretion from the liver and by stimulating lipoprotein lipase, which hydrolyzes triglycerides from chylomicrons and VLDLs [39, 42, 43]. In addition, the $\omega - 6/\omega - 3$ ratio of the studied hemp oil was estimated at 3.48 lower than 4, which corresponds to the nutritional recommendations [43]. Minor oil fractions analysis showed high content of total tocopherol with a dominance of γ-tocopherol. The oil also contains β-carotene and phenols. These compounds could prevent lipoprotein structural alteration, contributing to their normal metabolism [30].

4. Conclusion

It was concluded that the "*Beldiya*" hemp seed oil, native ecotype of cultivated in Morocco, could be considered as a prominent source of polyunsaturated fatty acids characterized by high nutritional and functional values. Besides, its richness in antioxidants, especially γ-tocopherol, could constitute a considerable asset in use of the oil as an important source of natural tocopherols as well as a protective agent against lipoprotein oxidation and prevention of atherosclerosis. This work could contribute as an idea to the

reorientation of exploitation of cannabis in Morocco for the production of commercial value-added oil instead of drugs.

Data Availability

All the data supporting the findings of this study are included in this article.

Ethical Approval

All applicable international and national guidelines for the care and use of animals were followed.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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