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# Effect of *Citrus Limon* Essential Oil on Lipid Profile and Obesity in Wistar Rats

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# تأثير الزيت الأساسي لليمون على الدهون والسمنة في فئران ويستار

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## ABSTRACT

Obesity causes many pathologies; no therapeutic axis has provided an effective solution to this problem. The use of herbal medicine with healthy food and physical activity is recommended, and essential oils are the best known of these natural substances. The objective of this study is to evaluate the effect of *Citrus limon* essential oil on body weight and lipid profile. The plant material is the lemon; the extraction method is hydrodistillation. The experiment lasted 20 days and involved 15 female rats (2 to 3 months old) weighing between 160g and 230g. The rats were divided into 3 groups: the first receiving a standard diet, the second receiving a high-fat diet, and the third receiving a high-fat diet and treated with essential oil. The extraction yield is 1.69%. The physicochemical characteristics comply with AFNOR. This study shows that a high-lipid diet induces obesity characterized by hyperlipidemia. Intraperitoneal administration of the essential oil caused a decrease in body weight, abdominal circumference, plasma total cholesterol, and triglycerides and an increase in HDL-cholesterol. Considering this study, we found that lemon essential oil has beneficial effects on metabolic alterations. Its inclusion in the diet may help improve the metabolic profile and reduce the incidence of obesity and its long-term complications.

## الملخص

سبب السمنة المفرطة العديد من الأمراض، ولم يقدم أي محور علاجي دراسي علاجا فعالا ودائمًا لهذه المشكلة. لقد تبين أن الزيوت الأساسية المستخرجة من النباتات الطبيعية ذات فعالية معتبرة لهده الحالة. هدفنا من هذه الدراسة هو تقييم أثر زيت قشرة ثمرة الليمون على وزن الجسم ودهونه المعتبرة. يتم استخراج الزيوت الأساسية النباتية من قشرة الليمون بطريقة التقطير المائي. استمرت التجربة 20 يومًا على 15 أنثى من فئران التجارب البيضاء، أعمارهن بين شهرين وثلاثة أشهر. أوزانها بين 160 إلى 230 جرام. قسمت الفئران إلى ثلاثة مجموعات: المجموعة الأولى غير معاملة تتلقى نظامًا غذائيًا كاملا. المجموعة الثانية غير معاملة تخضع لنظام غذائي عالي الدهون. أما المجوعة الثالثة فخضعت لنظام غذائي عالي الدهون وبمعالجة بزيت الليمون الأساسي (30 ميكروجرام/كحجم/ يوم). أعطى المستخلص عائدا علاجيا بمقدار 1.60%. تتوافق الخصائص الفيزيائية والكيميائية مع معاييرAFNOR. تسبب النظام الغذائي الغني بالدهون بالسمنة لدى الفئران التي تميزت بقرط السمنة وتشحمات الدم. إن إعطاء الزيت الأساسي داخل الصفاق تسبب في انخفاض في وزن جسم الفئران ومحيط البطن، وتركيز الكوليسترول الكلي في البلازما، والدهون الثلاثية الكربون، وزيادة تركيز كوليسترول-HDL. أن الزيت الليمون الأساسي له تأثيرات فعالة على التغيرات الأيضية. قد يؤدي تضمينه في النظام الغذائي إلى تحسين المظهر الأيضي وتقليل حدوث السمنة ومضاعفاتها على المدى الطويل.

**KEYWORDS**
**الكلمات المفتاحية**
Abdominal circumference, animal model, body weight, citrus, hyperlipidemia
الحمضيات، فرط شحميات الدم، محيط البطن، نموذج حيواني، وزن الجسم

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## 1. Introduction

The prevalence of obesity has increased significantly over the past three decades. Algeria is not spared by this modern-day scourge. In 2012, the prevalence of obesity among adults in Constantine was 30.9%, 20.8% of men and 38.3% of women (Dalichaouch, 2015). Obesity is a metabolic disorder characterized by an excessive accumulation of body fat due to a state of dysregulation of energy reserves by external and/or internal factors (Basdevant, 2004). Experimental and epidemiological data suggest a direct correlation between lipid intake and the degree of obesity (Ailhaud, 2008).

Obesity is a risk factor for several diseases and a major public health problem that must be treated. Currently the World Health Organization places its prevention and management as a priority in the field of nutritional pathology. None of the therapeutic approaches have proven to be effective, and all of them reveal an unfavorable benefit–risk balance. The failures of obesity drugs are, above all, linked to their side effects, which are significantly greater than the expected benefits (Favre, 2019). In some traditional societies (China and some African countries), the medical management of so-called chronic pathologies is largely performed using medicinal plants (Ait Ouakrouche, 2015). The search for new herbal treatments with minimal side effects is a current challenge in this field. Essential oils extracted from aromatic plants are beginning to be of great interest as a potential source of natural bioactive molecules with a wide range of applications (Yavari kia, 2014). Lemon (*Citrus limon*) of the *rutaceae* family, the most important citrus fruit after orange and tangerine, is cultivated today in all Mediterranean regions, and its essential oil (EO) is used for several applications (Khan et al., 2010). Lemon peels are rich in nutritional ingredients (water, proteins, sugars, and minerals) and functional ingredients (essential oils, fibers, carotenoids, vitamin C, and phenolic compounds), which give them different properties (Khan et al., 2010). Citrus essential oil contains different types of flavonoids and limonoids, which could have an anti-obesogenic and lipid-lowering effect (Khan et al., 2010). Studies in animals have shown that they lower cholesterol and blood triglycerides (Miceli et al., 2007).

## 2. Materials and Methods

### 2.1. Extraction Process of the Essential Oil:

The essential oil of *Citrus Limon* (Eureka) is extracted by hydrodistillation (Clevenger, 1978), and the distillate (essential oil

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plus water) is recovered in a separating funnel for separation of the mixture by density difference. The extraction time is measured from the fall of the first drop of distillate into the separatory funnel. The boiling temperature is lower than the most volatile solvent (water). The oil is recovered then treated with a desiccant – sodium sulfate. The essential oil yield (EOR) is defined as the ratio between the mass of essential oil obtained after extraction (M1) and the mass of plant material used (M0) (Benouli, 2016).

### 2.2. Experimental Animals:

The experiment lasted 21 days and involved 15 white female rats (*Rattus norvegicus*) aged 2 to 3 months and weighing between 160g and 230g. These rats were subjected to a period of adaptation to the conditions of the animal house: a temperature of 25±2°C and a humidity of 50–55%. The rats were placed in plastic cages, which were lined with a litter made of wood shavings. The cages were cleaned, and the litters were changed every day until the end of the experiment, and the rats had free access to water.

The rats were divided into three groups, each composed of 5 animals (n=5).

- Group 1 (negative control RT-): received 75g/day of standard laboratory food
- Group 2 (RT+ positive control): subjected to the hyperlipidic diet (composed of 50% standard diet and 50% palm oil 8ml/day) administered directly into the stomach by intragastric gavage.
- Group 3 (RH: treated with essential oil): subjected to the hyperlipidic diet administered directly into the stomach by intragastric gavage (50% standard diet and 50% palm oil) and received an EO treatment by an intraperitoneal injection at a dose of 30µl/kg per day for each rat.

### 2.3. Measured Parameters:

2.3.1. Body Weight and Abdominal Circumference

The body weights were taken with a scale in grams (g). The growth rate of the rats is expressed in percentages (%). Abdominal circumference was measured by placing the tape measure around the waist (between the last rib and the top).

2.3.2. Blood Parameters

Blood sampling was performed by capillary tubes through the retroorbital sinus at eye level. The rats were anesthetized with chloroform for 2–3 minutes. Whole blood, collected in dry tubes, was centrifuged at 3000 rpm for 15 minutes; the tubes containing serum were immediately transported in a cooler to the laboratory for analysis of biochemical parameters (total cholesterol, triglycerides, and HDL cholesterol).

2.3.3. Statistical Analysis

Statistical calculations are often useful for the determination of normal values (or more precisely, reference values) as well as for the evaluation of precision and accuracy of analysis. The statistical analysis of the results was performed using Microsoft Office Excel, 2010. The results are represented as a mean more or less than the standard deviation (Mean±ET). The statistical evaluation is performed by the student T-test. This test compares two averages (Table 1).

**Table1: Difference between two averages**

| | | | | |
|---|---|---|---|---|
| *p-value* | <0.05(*) | <0.01 (**) | <0.001(***) | <0.0001 (****) |
| | Insignificant | Significant | Very significant | Highly significant |

## 3. Results and Discussion

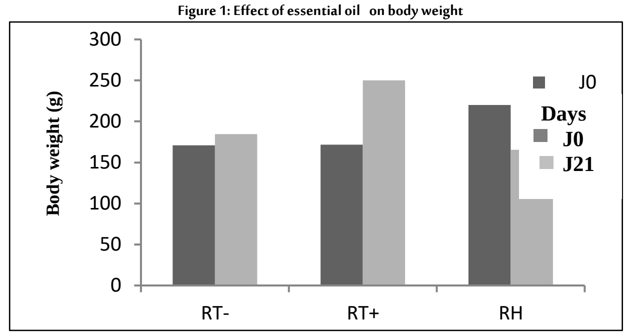
### 3.1 Organoleptic Characteristics and EO Yield:

The essential oil has a yellow to transparent color with a fresh smell and a fluid and mobile appearance. The yield is of the order of 1.69±0.03%. The pH plays a determining role during chemical and biochemical reactions and can influence the stabilizing properties of an essential oil. Our essential oil is acidic (pH6, 2) These results showed that our essential oil is in conformity with the standard of the French Standardization Association (AFNOR, 2000).

### 3.2 Effects of EO on Body Weight and Abdominal Circumference:

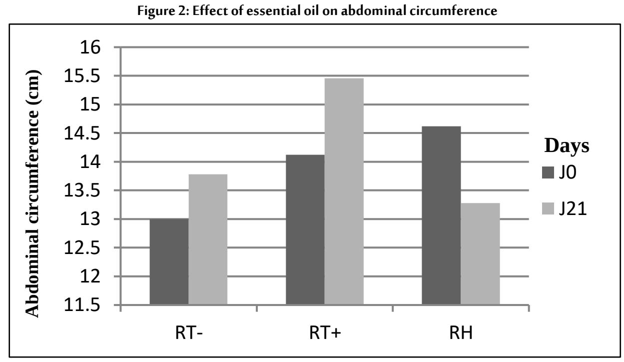
The administration of the hyperlipidic diet induced a very highly significant increase in the body weight of the animals. Indeed, the weight increased from 171.7±4.16g to 250.2±12.53g in group 2 (RT+) rats compared to the weight of group 1 (RT-) which increased from 170.89±4.16g to 184.6±4.16g ($p<0.0001$) (Figure 1). The treatment of obese rats with intraperitoneal administration of EO induced a significant decrease in body weight gain ($p<0.05$) and a decrease in food intake in group 3 (RH) compared to group 2 (RT+) (Figure 1).

**Figure 1: Effect of essential oil on body weight**




The results show that the hyperlipidic diet induced an increase in the abdominal circumference of the animals (Figure 2). This increased from 13.0±0.4cm to 13.75±0.64cm in RT- (negative control rats) and from 14.12±0.31cm to 15.02±0.31cm in RT+ (positive control rats). Intraperitoneal administration of lemon EO significantly reduced the abdominal circumference of the rats to normal ($p<0.05$). Indeed, the difference between the final and initial values is approximately 14.12±0.31 to 15.02±0.31 in group 2 (RT+) and 14.62±0.31 to 13.48±0.31 in group 3 (RH) respectively (Figure 2).

**Figure 2: Effect of essential oil on abdominal circumference**




The hyperlipidic diet induced an increase in body weight and abdominal circumference. These results agree with Laissouf's study (Laissouf et al., 2014), which showed that a high-fat diet induces obesity in Wistar rats. Dietary fat has little effect on satiety, and periodic exposure to a high-fat diet, especially when there is a strong feeling of hunger, may be sufficient to cause rats to consume more calories in the form of fat (Laissouf et al., 2014). Most natural anti-obesity products (e.g., algae and medicinal plants) regulate the expression of thermogenin, a key protein of thermogenesis in brown adipose tissue, which converts energy from food into heat.

### 3.3 Effects of Essential Oil on Lipid Parameters:

Plasma concentrations of the blood lipid parameters, total cholesterol (TC) and triglycerides (TG), increased significantly (p<0.001) in group 2 (RT+) compared to the negative control (RT).

Total cholesterol increased from 0.47±0.63g/L (RT-) and 0.58±0.18g/L (RT+) to 0.51±0.34g/L (RT-) and 0.88±0.27g/L (RT+) respectively (Figure 3).

Triglycerides increased from 0.67±0.55g/L (RT-) and 0.68±0.2g/L (RT+) to 0.91±0.97g/L (RT-) and 1.38±0.91g/L (RT+) respectively (Figure 4).

The administration of lemon essential oil in group 3 (RH) resulted in a significant decrease (p<0.05) of these parameters. Total cholesterol decreased from 0.64±0.20g/L to 0.34±1.42g/L (Figure 3) and triglycerides decreased from 0.78±0.09g/L to 0.41±0.13g/L (Figure 4).

Figure 3: Plasma concentration of total cholesterol

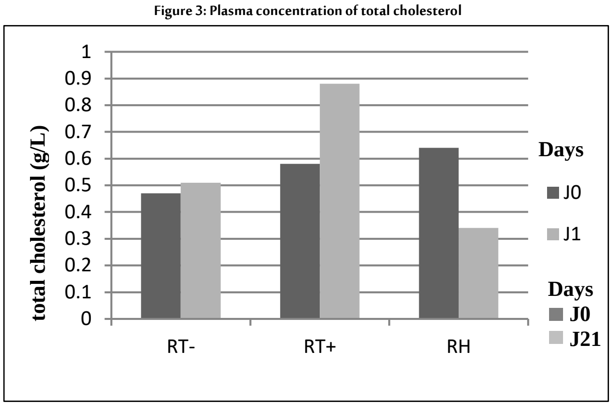
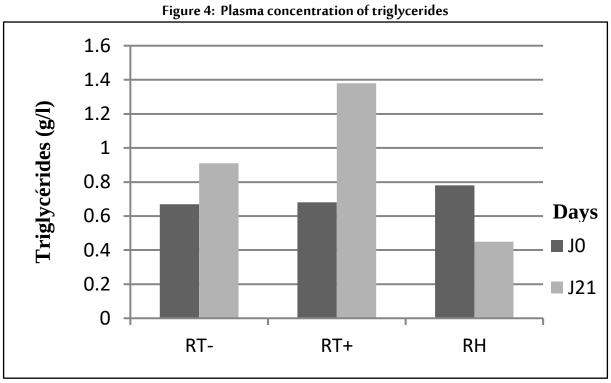
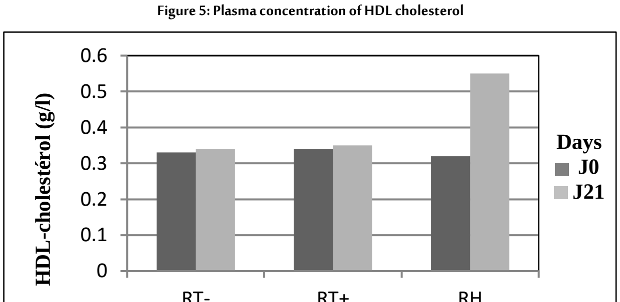



Figure 4: Plasma concentration of triglycerides




HDL cholesterol increased nonsignificantly (p>0.05) in RT- (0.33g/L to 0.34g/L) and RT+ (0.34g/L to 0.35g/L). Administration of lemon essential oil significantly (p<0.05) increased HDL-C in Group 3 (HR) from 0.32g/L to 0.55g/L (Figure 5).

Figure 5: Plasma concentration of HDL cholesterol




In the present study, obesity induced by a hyperlipidic diet led to an increase in plasma total cholesterol and triglycerides but no significant change in plasma HDL cholesterol in RT+ rats compared to RT- rats.

These results are in concordance with those of several authors who have shown that triglyceride and cholesterol levels in obese rats are higher than in negative control rats receiving a standard diet (Mbundu et al., 2018). The hyperlipidemia observed in RT+ rats can be explained by the high lipid content in the diet. Several authors have found that an increase in the lipid content of the diet causes an increase in plasma cholesterol concentration and changes the composition of plasma lipoproteins, including an increase in the portion of cholesterol esters in VLDL and LDL (Abbas, 2015). Arafa (2005) has reported that hyperlipidemia, particularly hypercholesterolemia, can be induced in animals with a cholesterol-enriched diet. Several studies have shown the effect of dietary cholesterol on cholesterolemia. Dietary supplementation with 0.5% cholesterol and 0.5% cholic acid or with two doses of cholesterol (0.5% and 4%) with or without cholic acid (Assini et al., 2013) has shown an increase in serum total cholesterol (TC). Other studies have shown an increase in serum and hepatic TC with 1% cholesterol and 0.5% cholic acid (Assini et al., 2013).

Several studies have highlighted the effect of dietary cholesterol on triglycerides. In rats, dietary cholesterol induces hypertriglyceridemia (Assini et al., 2013). The increase in serum TG may be due to a decrease in low-density lipoprotein (LDL) receptor activity when the diet is supplemented with cholesterol (Assini et al., 2013).

The decrease observed in the lipid profile (cholesterol and triglycerides) of rats supplemented with lemon essential oil is in accordance with the work of Arafa (2005). The constituents of lemon EO can explain this decrease. Assini et al. (2013) showed that submitting mice to a diet supplemented with citroflavonoids could prevent and treat dyslipidemia and hepatic steatosis by inhibiting hepatic fatty acid synthesis and increasing fatty acid oxidation. In addition, *Citrus limon* might be effective against hyperlipidemia because it is rich in vitamin C and contains different types of flavonoids (Khan et al., 2010). Indeed, the antioxidant effects of limonene, which is 60 to 70% of Citrus limon's composition, contribute to the reduction in the cholesterol level (Assini et al., 2013). Moreover, the presence of hesperidin and eriocitrine, the most abundant flavonoids in lemon, would explain this effect and would contribute to improvements in coronary vasodilatation, decrease blood platelet aggregation, and prevent LDL oxidation (Costa et al., 2014; Manish and Mahesh, 2013).

Previous studies have shown that lemon flavonoids and limonites lower blood cholesterol in rats receiving a cholesterol-enriched diet (Boshtam et al., 2010; Wang et al., 2011). These flavonoids are strong inhibitors of the activity of hydroxymethyl-glutaryl-coenzyme A reductase (HMG-COA reductase) and acylated coenzyme A: cholesterol acyltransferase (ACAT) in vivo and in vitro (Choi et al., 2004). HMG-COA reductase is involved in cholesterol synthesis and VLDL cholesterol secretion, and ACAT is involved in intestinal absorption and esterification of cholesterol (Choi et al., 2004).

In addition, Cirico (2006) noted that citrus juice and EO correct the increase in LDL-C in humans by activating LDL receptors, which induce the uptake and degradation of these lipoproteins. Bochtam (2010) confirmed these results in male rabbits consuming a diet enriched in cholesterol (1%) and supplemented with 1g of the aqueous extract of *Citrus limon* bark. Similarly, some authors have shown that lemon flavonoides decrease LDL-C, increase plasma HDL-C, decrease VLDL and LDL cholesterol, and increase HDL cholesterol, thus correcting dyslipidemia (Akiyama et al., 2010; Miceli et al., 2007).

One study showed that the decrease in LDL was associated with overexpression of the LDL receptor gene and a decrease in the expression and activity of the microsomal triglyceride transfer protein (MTP) in vitro, which plays a role in the assembly of lipoproteins, mainly triglycerides and VLDL (Wilcox et al., 2001). It is important to note that the consumption of *Citrus limon* could be responsible, in part, for the decrease in plasma TG levels. Indeed, studies have reported that supplementation with hesperitin and mariginine in rats consuming a cholesterol-enriched diet led to a decrease in plasma triglycerides and an amelioration in hypertriglyceridemia (Akiyama et al., 2010). The hypotriglyceridemic effect may be due to the repression of the sterol regulatory element binding protein-1C (SREBP-1C) pathway in adipose tissue and liver and, consequently, to the decrease in triglyceride synthesis. In addition, this hypotriglyceridemia is concomitant with the reduction of TG-VLDL. Indeed, the mass of VLDL is decreased, reflecting the reduction of their various surface (apo and CL) and center (TG) constituents. This result is in accordance with those of other studies (Green et al., 2013; Wilcox et al., 2001).

## 4. Conclusion

Traditional medicine is widespread and plays a major role in the treatment of various metabolic diseases. The number of research studies for new molecules capable of preventing or delaying the apparition of these diseases is very limited. This work has been performed to evaluate the influence of phytotherapy based on the essential oil of lemon peel (*Citrus limon*) against obesity and its complications in rats made obese by a hyperlipid diet. From our study, we can conclude that the hyperlipidic diet leads to the installation of obesity, associated with metabolic abnormalities such as hyperlipidemia. Our results showed that lemon essential oil reduced body weight gain. Moreover, we observed from our study that lemon EO has a hypolipidemic effect at the plasma level. These results indicate the influence and efficacity of EO on the cellular mechanisms that control lipid metabolism can reduce cardiovascular risk and protect against several diseases.

## Biographies

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