

RESEARCH ARTICLE

PHYSIOLOGICAL STUDY OF OLIVE OIL EFFECT ON IBUPROFEN-INDUCED LIVER AND KIDNEY DYSFUNCTION IN LOCAL MALE RABBITS**Abdulrahman Salem Omer Yaseen^{1,*}, Khaled Saleh Omer Abdulmanea² and Rafat Mohsen Hussein Salem¹**¹ Department of Biology, College of Sciences, Hadhramout University, Hadhramout, Yemen² Department of Food Science & Technology, College of Environmental Science & Marine Biology, Hadhramout University, Hadhramout, Yemen

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Received: 10 December 2020 / Accepted: 18 December 2020 / Published online: 30 December 2020

Abstract

Ibuprofen (IB), is one of the common nonsteroidal anti-inflammatory drugs (NSAIDs), it is mostly used for the management of pain, fever, and inflammations. In addition to its beneficial effects; IB has also been reported to be associated with some adverse effects. Thus, the present study was aimed to investigate the possible beneficial effects of olive oil (OO) against the IB -induced dysfunction of liver and kidney parameters in male rabbits. This study was conducted on 18 local male rabbits weighing between (900 - 1000 g) for 30 days, rabbits were divided into three equal groups; control group (C), ibuprofen group (IB), and ibuprofen +olive oil group (IB + OO), each group included six rats. At the end of the experiment, blood samples were collected for biochemical assessment of the liver and kidney functions. The results showed that IB caused a significant increase ($P < 0.001$) in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), urea (Ur), creatinine (Cr) and uric acid (UA). A significant decrease in the total protein (TP) and albumin (AL) ($P < 0.001$) and ($P < 0.05$) respectively showed in the IB group compared to the control group. Treatment rabbits with OO showed significant improvement in renal and liver functions; the activity enzymes of ALT, AST, and ALP significantly decreased, and the levels of TP and AL significantly increased. The current results were in agreement with other previous studies which informed that the IB has adverse effects on the functional capacities of the liver and the kidney. Further studies are needed to evaluate this ameliorative effect of OO on other medicines and pollutants.

Keywords: Ibuprofen, Olive oil, Liver function, Kidney function, Rabbits.**1. Introduction**

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are used to treat patients who are suffering from acute and chronic conditions such as rheumatoid arthritis, osteoarthritis, dysmenorrhea and post-surgical pain [1-2]. Ibuprofen (IB) is a less expensive NSAIDs, and the most commonly prescribed by doctors [3]. IB exert their anti-inflammatory, analgesic, and antipyretic effects by inhibiting prostaglandins (PGs) synthesis, in addition to suppressing the enzyme cyclooxygenase (COX), which converts arachidonic acid into PGs, thromboxanes, and prostacyclins [4-5].

In spite of their beneficial effects, NSAIDs have been notified to be linked with some adverse effects, such as a toxicity of the gastrointestinal tract [6], IB also causes

hepatotoxicity [7-8], cardiovascular toxicity, especially in people with hypertension [9], damage to the kidney [10-11]; IB can cause renal papillary necrosis and renal tubular toxicity when high doses are used, especially in older patients [12]. In addition to their influence on clotting function [13] and semen quality [14].

Olive oil (OO) is a functional food, besides its high content in mono-unsaturated fatty acids, also contains bioactive compounds such as polyphenols, hydrocarbons, phyosterols, and triterpenes [15-16]. The phenolic compounds of OO have potentially advantageous biological effects such as antimicrobial, antioxidant, and anti-inflammatory properties [17].

OO improved blood profile and renal toxicity [18], cardiovascular and liver damage [19-20], and also have a

low incidence of breast and colon cancer risk [21]. This current study has been designed to determine the effects of OO against IB induced dysfunction of liver and kidney parameters in male rabbits.

2. Materials and methods

2.1. Chemicals:

IB syrup (Each 5ml contains 100mg, Julphar Pharmaceutical, UAE) and OO syrup (Rafael Salgado (RS) brand, Spain) were used. Kits used for the determination of ALT, AST, Ur, UA were obtained from Agappe, India. The assay kits for the determination of Cr, ALP, TP and AL were obtained from Química Clínica Aplicada, Spain. All other chemicals and reagents were of analytical grade.

2.2. Animals and Experimental Design:

18 male rabbits with body weights ranging between 900 - 1000 g were obtained from the local market. The rabbits were free of any congenital disorders and remarkable disease that may cause any problem in the study. The rabbits were kept in a ventilated animal house with a controlled light-dark cycle (12 h light/dark) and constant temperature (25-27°C). Food and water were provided *ad libitum*. After an acclimatization period of two weeks the rabbits were randomly divided into three equal groups, (n=6 for each group) as the following:

Group I (C): The rabbits were administered orally with distilled water once a day for 30 days, and considered as a negative control group.

Group II (IB): The rabbits were administered orally with IB at a dose of 40 mg/kg once a day for 30 days, and considered a positive control group. The dose of IB was selected according to the study of [22].

Group III (IB+OO): The rabbits were administered orally with IB at a dose of 40 mg/kg and 2 ml/kg OO once a day for 30 days. The dose of OO was selected according to the study of [23].

2.3. Estimation of Biochemical parameters:

Twenty-four hours after the last dose of the IB and OO, blood samples were collected. Blood was allowed to coagulate at room temperature for 30 min and then centrifuged at 2000 rpm for 15 min for obtained the serum; serum samples were then stored at -20 °C, until the determination of liver and kidney functions. Serum concentrations of ALT, AST, Ur, UA were determined using commercial kits (Agappe, India), while Cr, ALP, TP and AL were determined using commercial kits (Química Clínica Aplicada, Spain). All parameters were measured spectrophotometrically (APEL PD-303, Japan) according to the manufacturer's instructions.

2.4. Statistical analysis:

The results were represented as mean \pm standard division (SD), differences between control and other experimental groups were tested for statistical significance using the statistical package for social science program (SPSS Inc.,

Chicago, USA) version (20). One way analysis of variance (ANOVA) for comparison between different groups was used followed by Tukey's test, and $P < 0.05$ was considered to be statistically significant.

3. Results

As shown in **Table 1**, there was a significant increase in activity ($p < 0.001$) of ALT, AST and ALP enzymes in rabbits treated with IB alone (group II) compared to the control group (group I), While TP and AL levels were decreased significantly in group II compared to group I. Rabbits treated with OO revealed a notable improvement of these aforementioned parameters in comparison with IB group. The activity enzymes of ALT, AST and ALP significantly ($p < 0.001$) decreased in group III (treated with IB + OO) compared to group II (Fig. 1). Also, OO increased significantly the levels of TP and AL (Fig. 2).

Compared with the control group, there is a significant decrease in kidney functions (Ur, Cr and UA) ($P < 0.001$) and ($P < 0.05$) respectively was observed in rabbits treated with IB alone (Table 2), and the supplementation of OO to IB treated rabbits ameliorated these kidney functions parameters (Fig. 3).

Table 1: Serum activity of ALT, AST, ALP and levels of TP and AL in study groups

Parameters	Groups	I	II	III
	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
ALT (U/L)	29.67 \pm 1.211	36.50 \pm 0.548 ^a	26.50 \pm 1.225 ^{ab}	
AST (U/L)	33.00 \pm 0.894	36.50 \pm 0.837 ^a	25.33 \pm 0.516 ^{ab}	
ALP (U/L)	95.50 \pm 0.548	176.17 \pm 1.472 ^a	67.83 \pm 0.753 ^{ab}	
TP (g/dl)	5.533 \pm 0.206	4.383 \pm 0.204 ^a	5.350 \pm 0.187 ^b	
AL (g/dl)	4.050 \pm 0.137	3.283 \pm 0.116 ^a	3.933 \pm 0.163 ^b	

Result expressed as Mean \pm SD of n = 6 rabbits

a = significant differences between the control group and ibuprofen group, at $p < 0.05$

b=significant differences between ibuprofen group and the olive oil group, at $p < 0.05$

I: control and received distilled water, II: received IB (40 mg/kg), III: received (40 mg/kg IB and 2 ml/kg OO)

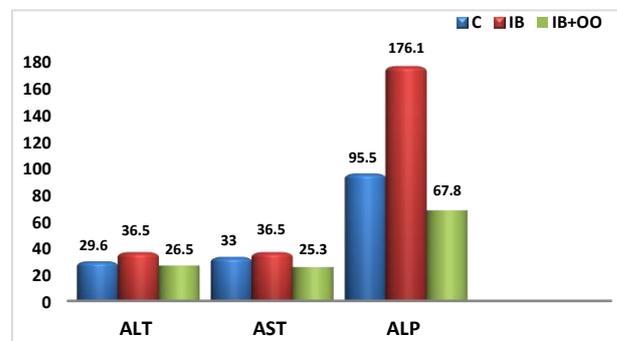


Figure 1 Serum activity of ALT, AST, ALP enzymes in study groups.

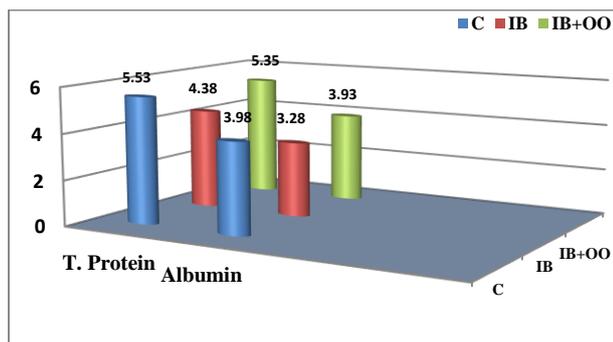


Figure 2 Serum level of TP and AL in study groups.

Table 2: Serum levels of Ur, Cr and UA in study groups

Parameters	I	II	III
	Mean ± SD	Mean ± SD	Mean ± SD
Ur (mg/dl)	53.33 ± 1.633	65.33 ± 1.033 ^a	53.50 ± 1.169 ^b
Cr (mg/dl)	0.717 ± 0.0408	1.250 ± 0.187 ^a	0.850 ± 0.054 ^b
UA (mg/dl)	3.083 ± 0.075	3.317 ± 0.116 ^a	2.950 ± 0.216 ^b

Result expressed as Mean ± SD of n = 6 rabbits

a = significant differences between the control group and ibuprofen group, at p <0.05

b=significant differences between ibuprofen group and the olive oil group, at p <0.05

I: control and received distilled water, II: received IB (40 mg/kg), III: received (40 mg/kg IB and 2 ml/kg OO).

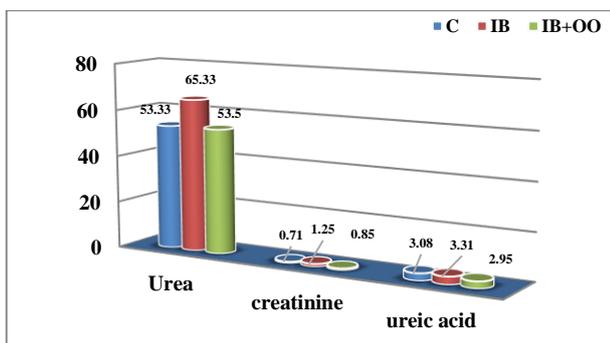


Figure 3 Serum level of Ur, Cr and UA (mg/dl) in study groups

4. Discussion:

NSAIDs such as IB are widely available over the counter and possess effective pain relieving antipyretic, and anti-inflammatory properties. The present study was aimed to test the hypothesis that OO administration could prevent IB induced impairment of liver and kidney function parameters in rabbits. The amount of IB given to animals in this study was equal to the standard therapeutic dose.

The results of the current study showed a significant increase in the levels of Ur, Cr, and UA in the blood serum of rabbits treated with IB compared to the control group. The high level of both Ur and Cr in the animals of this study was consistent with a group of studies that were carried out on albino mice [3, 24] and on rats [10, 22]. In contrast, the study results of [25] showed that IB caused a slight but insignificant decrease in the level of Ur and Cr in the blood of mice, contradicting the results of the current study. This difference may be attributed to the

dose, method of administration, and duration of dose, and the difference in the experimental animals.

The high level of Ur in the blood can be attributed to the fact that poisoning with IB leads to a failure in the kidney function, as the low rate of excretion of Ur into the urine leads to an increased level of Ur in the blood, and therefore IB poisoning leads to a failure in kidney function and an increase in the level of Ur [26]. The study of [27] concluded that IB caused an increase in the level of blood Ur in rats, which was associated with the occurrence of pathological changes in the kidney tissue, represented in the emergence of severe congestion in the blood vessels of the kidneys and tubular necrosis.

The increased level of Cr occurred due to the high levels of the superoxide dismutase (SOD) and Catalase (CAT), and this change is attributed to the oxidative stress associated with the increased generation of free radicals that have the ability to work on lipid peroxidation in the kidney and the decreased level of antioxidants [28]. The prolonged use of NSAIDs, including IB, causes adverse renal effects through two mechanisms: the first mechanism may be partly due to the inhibitory effects of IB in the synthesis of prostaglandins [3], in which the blood flow to the kidneys is not reduced, leading to the occurrence of acute renal injury as prostaglandins regulate vasodilation at the level of the glomeruli of the kidney. The second mechanism is by stimulating acute interstitial nephritis, which is characterized by the presence of infiltration of inflammatory cells in the interstitial substance of the kidney [29].

The elevation of the UA level occurred due to the rise of free radicals in the blood [30]. The study conducted on rabbits treated with IB shown that kidney injury reduces the glomerular filtration rate and increases UA level in the blood and thus it leads to impaired kidney function [23]. Therefore, the high UA resulting from IB in this study may alter the cellular antioxidant balance and affect the biochemical functions of the kidneys [24].

In this study, treatment rabbits with OO resulted in a significant decrease in the concentration of Ur, Cr and UA compared to the group of animals that were given IB alone. The results of the present study are consistent with the results of various studies, including the study of [22], which showed that treating rabbits with OO resulted in a significant improvement in kidney function, and biochemical treatments associated with nephritis caused by IB, and that OO possesses kidney protective properties that reduce the level of Ur and Cr [22, 31]. The reason for this protective role is that the use of OO helps maintain the natural level of antioxidants, including glutathione, as it increases the level of the antioxidant glutathione [22, 32-33].

The results of the present study showed that the administration of IB at a dose of 40 mg/kg day for 30 days led to a significant increase in the levels of liver enzymes: ALT, AST, and ALP in animals treated with IB compared to the control group. The high level of liver enzymes in the present study was consistent with the results of studies

conducted by [34] and [35], which showed a significant increase in AST and ALT enzyme activities in plasma of IB-treated mice. The result study of [24] concluded that IB caused an increase in the level of enzymes (AST, ALT, ALP), and the effect of IB on liver enzyme function was positively related to the amount of dose and duration of exposure. In addition, results of [27] showed that IB caused an increase in the level of enzymes (AST, ALT, ALP) in rats, which was accompanied by pathological changes represented by the occurrence of congestion within the central vein of the liver. On the other hand, the study of [25] showed that IB caused a slight decrease in the level of enzymes AST and ALT in the blood of mice, contrary to the results of the current study. This difference may be attributed to the dose, duration, and type of experimental animal. The increase in liver enzymes in rabbits under study is attributed to the fact that exposure to IB leads to toxicity and breakdown of liver cells, which leads to an increase in the release of enzymes from damaged liver cells and to hepatitis biliary, as well as the resulting hepatic necrosis [34]. More than IB is usually associated with an increase in the level of hepatic enzymes, which is due to cellular leakage, increased harmful activity of free radicals, and loss of integrity of hepatic cell membranes, which leads to leakage of these enzymes into plasma [36], or an increased level of harmful free radicals due to exposure for IB [7].

Results of this study showed that administering IB caused a significant decrease in the levels of serum AL and TP in animals treated with IB compared to the control group, and these results were consistent with the results of the study conducted by [7] and different with a study [37]. The reason for the decrease in the TP level may be due to hepatotoxicity, which leads to a decrease in the level of TP in the blood, or it may be due to the occurrence of inflammation in the small intestine due to IB dosing, which leads to decreased absorption, or the observed decrease in TP level in the plasma may be a result of inhibition of protein biosynthesis and the potential use of available protein as an energy source to repair damaged cells caused by IB [38]. As for the low AL level in the animals under study, it may be caused by cirrhosis and damage to hepatocytes [39], and this indicates conclusively that NSAIDs have a direct effect on the protein synthesis units in Hepatocytes, which are negatively reflected in the low level of AL in blood serum [37].

Treatment with OO led to an improvement of liver enzymes AST, ALT and ALP, as it significantly decreased their concentrations, and improved the level of TP and AL, which significantly increased their concentration in the treated animals compared to the group of animals that were given IB alone. These results are consistent with the results of other studies, including The results of [7] that showed the treatment of female rats with OO led to a significant improvement in liver enzymes, AL and TP levels against hepatotoxicity caused by IB, as the results of [20] the role of OO alone or with honey in improving the concentration of liver enzymes and AL level against the hepatotoxicity caused by methotrexate in rats. The reason for the improvement of

liver enzyme functions by OO is due to the potential mechanism of OO in which it shows great protection against hepatotoxicity caused by IB due to the active ingredients it possesses such as oleic acid and phenolic compounds as well as its activity in removing free radicals as the phenolic compounds have antioxidant activity [40], as phenolic compounds have antioxidant properties due to their ability to break down free radicals, active oxygen species and hydroxyl radicals [41-42].

In conclusion, the OO has significant protective activity against IB- induced impairment in liver and kidney function in male rabbits.

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مقالة بحثية

دراسة فسيولوجية لتأثير زيت الزيتون على خلل وظائف الكبد والكلى المستحدث بالأيبوبروفين في ذكور الأرانب المحلية

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استلم في: 10 ديسمبر 2020 / قبل في: 18 ديسمبر 2020 / نشر في: 30 ديسمبر 2020

المُلخَص

يُعد الأيبوبروفين أحد العقاقير غير الستيرويدية المضادة للالتهابات، ويستخدم في الغالب لإدارة الألم والحمى والالتهابات. بالإضافة إلى آثاره المفيدة تلك؛ تم الإبلاغ أيضًا عن ارتباط الأيبوبروفين ببعض الآثار الضارة. لذلك، كان الهدف من الدراسة الحالية التحقق من الآثار المفيدة المحتملة لزيت الزيتون ضد الخلل الوظيفي الذي يحدثه الأيبوبروفين في معايير كبد وكلى ذكور الأرانب. أجريت هذه الدراسة على ثمانية عشر من ذكور الأرانب المحلية التي تزن ما بين (900 - 1000 جم) لمدة 30 يوم، تم تقسيم الأرانب عشوائيًا إلى ثلاث مجموعات متساوية: المجموعة الضابطة، مجموعة الأيبوبروفين، ومجموعة الأيبوبروفين + زيت الزيتون، كل مجموعة ضمت ستة أرانب. وفي نهاية التجربة تم جمع عينات الدم من أجل التقييم البيوكيميائي لوظائف الكبد والكلى. بينت النتائج أن الأيبوبروفين تسبب في زيادة معنوية في انزيمات الكبد (الأنين أمينو ترانس أمينيز، الأسبارتات أمينو ترانس أمينيز والفوسفاتيز القاعدي)، وفي وظائف الكلى (اليوريا، الكرياتينين وحمض البوليك)، كما أظهر الأيبوبروفين أيضًا انخفاض معنوي في البروتين الكلي والألبومين في مجموعة الأيبوبروفين مقارنة بالمجموعة السيطرة. في حين أن علاج الأرانب بزيت الزيتون أظهر تحسنًا ملحوظًا في وظائف كل من الكبد والكلى المدروسة مقارنة بالمجموعة التي أعطيت الأيبوبروفين لوحده. أتفقت نتائج الدراسة الحالية مع ما أوردته عدد من الدراسات السابقة في أن الأيبوبروفين يمتلك تأثيرات سلبية على القدرات الوظيفية للكبد والكلى، بينما قلل زيت الزيتون من هذه التأثيرات. هناك حاجة إلى مزيد من الدراسات لتقييم هذا التأثير التحسيني لزيت الزيتون على الأدوية والملوثات الأخرى.

الكلمات الرئيسية: الأيبوبروفين، زيت زيتون، وظائف الكبد، وظائف الكلى، الأرانب.

How to cite this article:

A. S. O. Yaseen, K. S. O. Abdulmanea, and R. M. H. Salem, "Physiological Study of Olive Oil Effect on Ibuprofen-Induced Liver and Kidney Dysfunction in Local Male Rabbits", *Electron. J. Univ. Aden Basic Appl. Sci.*, vol. 1, no. 4, pp. 218-224, Dec. 2020. DOI: [10.47372/ejua-ba.2020.4.59](https://doi.org/10.47372/ejua-ba.2020.4.59)



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