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Research Article

# Possible Protective Effects of Saw Palmetto Extract in Indomethacin Treated Rats

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**Abstract**

**Background:** Indomethacin is a widely used nonsteroidal anti-inflammatory drug for treating pain and fever. It is coupled with oxidative stress and an inflammatory response, which accounts for several detrimental effects on the body's organs.

**Objectives:** This study aimed to assess the potential of using Saw palmetto extract to counteract the oxidative stress and inflammatory response resulting from Indomethacin treatment in rat models.

**Methods:** The study involved 20 male albino rats, arbitrarily sorted into four groups of 5 animals each group. Group 1 (control group) was neither induced nor treated. Groups (2-4) were treated with oral Omeprazole (20 mg/kg/day) and Saw palmetto extract (20 mg/kg/day) suspensions, respectively, for 15 days. On day 15 of the study, blood samples were taken by heart puncture for the determination of superoxide dismutase, glutathione peroxidase, tumor necrosis factor-alpha, and interleukin-6.

**Results:** Saw palmetto extract treatment was found to elevate serum levels of superoxide dismutase and glutathione peroxidase significantly compared to the Indomethacin-induction group. Conversely, tumor necrosis factor-alpha and interleukin-6 levels were markedly reduced compared to the Indomethacin-induction group. The antioxidant and anti-inflammatory activities of Saw palmetto extract are contingent on its bioactive flavonoids and sitosterols content.

**Conclusion:** The antioxidant and anti-inflammatory influence of Saw palmetto extract could be a promising approach to counteract oxidative stress and inflammatory response due to Indomethacin treatment.

**Keywords:** Inflammatory response; Indomethacin; Omeprazole; Oxidative stress; Saw palmetto extract.

## Introduction

Indomethacin (IND) is a nonsteroid anti-inflammatory drug (NSAID) that is used to alleviate pain and inflammation in clinical medicine(1). IND use produces reactive oxygen species (ROS), thereby favoring oxidative stress and depletion of antioxidant defense enzymes(2). This leads to lipid peroxidation and tissue injury by cleansing enzymes such as those of the superoxide dismutase (SOD) family, catalase (CAT), and glutathione peroxidase (GPX) families (3, 4). Oxidative stress and ROS have also been shown to mediate neutrophil recruitment, leading to an inflammatory response that is accompanied by the release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (5).

During the autumn season, Saw palmetto, also known as Serenoa repens, This palm indigenous to the southern region of the United States, and yields fruit harvested for medicinal purposes (6). The primary application of this treatment has been to manage benign prostatic hypertrophy (BPH)(7). The fruit is mainly composed of fatty acids, esters, sterols (including β-sitosterol, campesterol, and stigmasterol), flavonoids, polysaccharides, and carbohydrates(8). Additionally, Saw palmetto extract can reduce the production of lipid hydroperoxides in the prostate gland of rats, which is an indication of its possible antioxidant properties(9). There are no previous studies that we are aware of that have been undertaken to investigate the possible effects of Saw palmetto extract against the oxidative stress and inflammatory response caused by IND treatments in rats.

This study aimed to evaluate the efficacy of Saw palmetto extract in treating IND-induced gastric ulcers in albino rats by exploring their effects on the level of antioxidant enzymes and inflammatory markers. Furthermore, the possible mechanisms underlying their therapeutic effects were investigated.

## Materials and Methods:

Indomethacin was purchased from Sigma Aldrich; Omeprazole capsules marked by Acino**,** Zurich, Switzerland**.** Saw palmetto tablet, Horbaach, New York, US, and sodium carboxymethylcellulose from Loba Chemie, India.

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**Determination and preparation of doses:**
According to previous studies, an oral administration of 60 mg /kg of IND is needed to induce oxidative damage(3, 10). The suspension had a concentration of 24mg/ml. Experimentation requires a volume of 0.5 mL to provide a dose of 60 mg /kg to rats.
Regarding Omeprazole, previous studies relied on an oral dose of 20 mg/kg(11) . An oral suspension was prepared for administering Omeprazole orally. The suspension was made with 0.5% Na-CMC as the suspending agent, and Omeprazole capsules (20mg) were used as the source of the active component. The suspension had a concentration of 8 mg/ml. To provide a dose of 20 mg /kg for experimental rats with an average weight of 200 ± 15 g, a volume of 0.5 ml is required.
The dose of Saw palmetto extract was determined based on an oral acute toxicity study in which 200 mg/kg was given to rats and showed no toxic signs. Therefore, one-tenth of this was used in the study, confirming its safety according to another study(12). Saw palmetto extract (3600mg) was used as the source of active component in an oral suspension that was prepared for administering Saw palmetto through the mouth. The suspension was made with 0.5% Na-CMC as the suspending agent. The suspension had a concentration of 8 mg/ml. To provide a dose of 20 mg/kg for experimental rats with an average weight of 200 ± 15 g, a volume of 0.5 ml is required.
**Animals Used in the Study:** Twenty male albino rats aged 3 months with an average weight of 200 ± 15 g, were used in this study. The animals were obtained from the animal house at the Iraqi Center for Cancer Research and Medical Genetics– Baghdad – Iraq and housed in it. They were placed in polyethylene cages with stainless steel covers and raised to prevent coprophagy. Rats were kept for acclimatization for one week before the experiment. They were maintained in standard laboratory conditions (232°F, 12-hour light-dark cycle) and had free access to food from a chow pellet and tap water. They fasted for 24 hours before the IND administration and were allowed free access to water. The study was started at the beginning of January 2024 and finished in February 2024. This study was approved by the ethical committee for experimental studies at the College of Medicine / University of Baghdad.
**Experimental design:** Immediately following the acclimatization period of one week, these rats were randomly assigned to four groups of the same size, with a total of five rats in each group. Participants who were a part of the experimental groups included the following individuals:

- Group 1(n=5) is the normal control group, which was kept under normal laboratory conditions and received oral 0.5% Na-CMC suspension for 15 days by oral gavage.
- Group 2(n=5) is the IND-treated group, which received IND suspension in 0.5% Na-CMC (60 mg/kg) at day 0 and oral 0.5% Na-CMC suspension for 15 days by oral gavage.
- Group 3(n=5) is the standard oral Omeprazole-treated group, which received IND suspension in 0.5% Na-CMC (60 mg/kg) at day 0 and Omeprazole oral suspension (20 mg/kg/day) in 0.5% Na-CMC for 15 days by oral gavage.
- Group 4(n=5) is the Saw palmetto extract-treated group, which received IND suspension in 0.5% Na-CMC (60 mg/kg) at day 0 and Saw palmetto extract oral suspension (20 mg/kg/day) in 0.5% Na-CMC for 15 days by an oral gavage

**Estimation of the anti-inflammatory and antioxidant effects of Saw palmetto extract as compared to Omeprazole-treatment**
The animals were put under anesthesia with 87 mg of ketamine/kg of body weight and 13 mg of xylazine per kg at the end of the experiment, which was day 15(13). The samples of blood were taken by performing a direct heart puncture with plastic syringes containing 5 milliliters, and then they were placed into gel tube(14). During the whole process analysis, these tubes were finally centrifuged for 10 minutes at a speed of 3000 revolutions per minute(15). Following full separation of the blood, serum was obtained, poured into untreated plastic tubes (2 mL), and stored at −20 °C until analyzed (15).
SOD and GPx, TNF-α, and IL-6 levels were assessed in the serum of all experimental groups (1-4) after 15 days from the start of the experiment. The ELISA kits used in the present study were commercially available and are performed according to the instructions provided by the manufacturer (Elabscience® Laboratory, China). The absorbance of the samples was measured using 450 nm via a microplate reader spectrophotometer (16, 17).

**Statistical analysis:**
Statistical analysis was performed using Graph Pad Prism version 9. Results were expressed as mean ± SD for all data. Analytical statistics were thus implemented to probe the significance of relationships between the groups through an analysis of variance (ANOVA) test and a post hoc Tukey's multiple-comparisons test. Statistical significance corresponds to having the value of $P < 0.05$.

**Results**
Figure 1 showed the serum levels of SOD and GPX for the control, IND-treatment, Omeprazole-treatment, and Saw palmetto-treatment groups as reported on day 15 of the experiment.
The serum concentrations of SOD and GPX (G1) in G2 were significantly decreased ($P<0.05$) compared with that of the control group (G1). Additionally, the serum levels of antioxidant enzymes (SOD and GPX)

in G2 were significantly lower means ($P$<0.05) when compared to the control group, Omeprazole treatment groups, and Saw palmetto treatment groups. Conversely, the mean serum levels of the antioxidant enzymes (SOD and GPX) in G4 isolated to the Saw palmetto treatment group were highly demonstrated compared with other treated groups especially G3 which received Omeprazole.

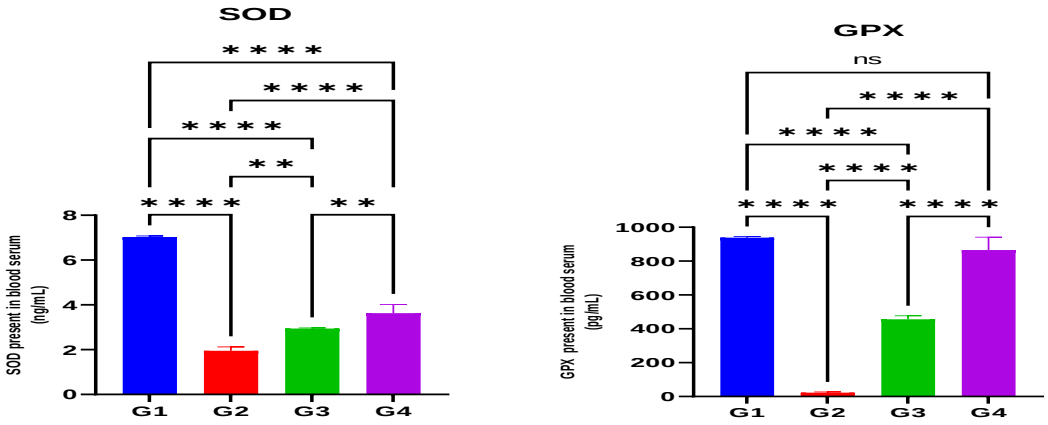


**Figure 1: SOD and GPX Serum Levels measured on day 15 of the experiment for control (G1), IND treatment (G2), Omeprazole treatment(G3), and Saw palmetto treatment(G4) groups.**

Serum TNF-α and IL-6 levels for the control, IND treatment, Omeprazole treatment, and Saw palmetto treatment groups, as recorded on day 15 of the experiment, are shown in Figure 2.

It was noted that the serum levels of pro-inflammatory cytokines (TNF-α and IL-6) of IND treatment (G2), Omeprazole treatment (G3), and Saw palmetto treatment group (G4) were significantly high ($P$<0.05) in comparison with the control group (G1). Moreover, TNF-α and IL-6 levels (G2) were significantly higher than all the other groups (G1, G3, and G4; $P$<0.05). Compared to the Omeprazole treatment group (G3), TNF-α and IL-6 levels in the Saw palmetto treatment group (G4) were also significantly decreased.

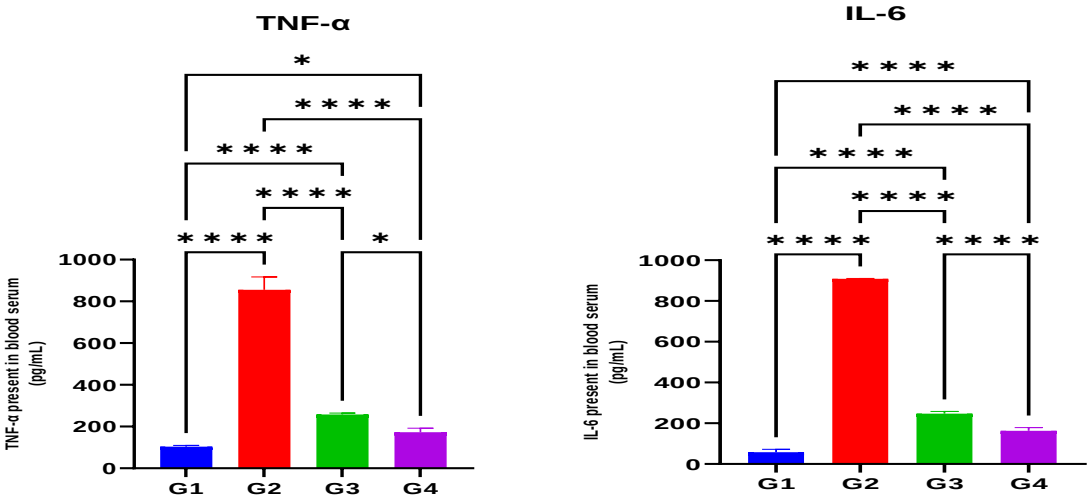


**Figure 2: Day 15 serum levels of the inflammatory mediators TNF-α (A) and IL-6 (B) as estimated for G1 (control), G2 (IND treatment), G3 (Omeprazole treatment), and G4 (Saw palmetto treatment) groups.**

## Discussion

Oxidative stress and inflammation are known to be crucial factors in the pathogenesis of IND-induced toxicity (18, 19). Thus, statistically significant differences detected between experimental groups in G2 compared with other groups G1, G3andG4for SOD, and GPX were reported ($P$ < 0.01). Under homeostatic conditions, there is an equilibrium between the oxidant and antioxidant defense systems of the body(20). The ingestion of IND produces ROS since it promotes oxidative stress (21). It was discovered that IND interacts with a location that is close to the complex and ubiquinone of the mitochondrial electron transport chain. This interaction results in the uncoupling of the oxidative

phosphorylation process and the formation of ROS (22). The ROS inactivate mitochondrial aconitase, which leads to the synthesis of free iron, which in turn leads to the generation of more mitochondrial hydroxyl (OH) (23). There is a correlation between oxidative stress and mitochondrial malfunction, the creation of mitochondrial permeability transition pores, and the generation of mitochondrial oxidative stress (MOS) (24, 25).

About the Omeprazole treatment group (G3), the levels of SOD and GPX were significantly higher when compared to G2. The findings of this investigation, which were documented in another study, indicate that omeprazole possesses antioxidant action independent of its antisecretory characteristics (26). Also, another research was conducted to investigate the in vitro antioxidant effects of Omeprazole along with several proton pump inhibitors to test their ability to quench ROS. It was proved that omeprazole and Esomeprazole showed the highest ability to scavenge free radicals and exert antioxidant effects that are independent of their antisecretory effects (26).

Saw palmetto treatment group (G4) had increased SOD and GPX levels vs. the G2, respectively. Saw palmetto extract is comprised of bioactive compounds, such as flavonoids and phytosterols, which are major antioxidants (27). β-sitosterol, the primary phytosterol in Saw palmetto attract, has been widely researched for its antioxidant bioactivity (27)

To evaluate the antioxidant activity of β-sitosterol, in a study, it was found that oral administration of β-sitosterol increased SOD and GPX activities in diabetic rats concerning control and metformin standard treatment (28). Collectively, these actions helped mitigate the damage done by excess ROS production (29).

Furthermore, the antioxidant properties of Saw palmetto extract are attributed to its flavonoid content. Several bioactive lavonoids, such as quercetin, are present in Saw palmetto extracts. Quercetin, the most potent antioxidant flavonoid, studies demonstrated that it has a beneficial effect in attenuating oxidative stress by increasing the antioxidants enzymes activity (Catalase, SOD, and GPX) in IND-treated rats (30). The antioxidant effect that flavonoids have is attributed to the proven fact that flavonoids can transfer electrons and free radicals, chelate metal catalysts, activate antioxidant enzymes, decrease alpha-tocopherol radicals, and inhibit oxidases (31).

Alongside oxidative stress, inflammation is also a crucial factor in the pathophysiology of gastropathy that is caused by NSAIDs (32, 33). It was observed that the levels of TNF-α and IL-6 increased in G2 compared to the control (G1) and the other treatment groups (G3, G4). The formation of ROS is directly linked to this finding since oxidative stress leads to a rise in the expression of TNF-α and IL-6 genes, which in turn leads to an increase in their levels through the nuclear factor kappa (NF-κB) dependent pathway.

Regarding the Omeprazole-treatment group, there was a significant decrease in TNF-α and IL-6 levels compared to G2. This indicates that Omeprazole has an anti-inflammatory effect independent of suppressing gastric secretion. As documented by previous researchers, the mechanism that is thought to be responsible for these effects is hypothesized to be associated with the down-regulation of nuclear factor kappa (NF-κB), which is followed by the inhibition of pro-inflammatory cytokine(34, 35).

In contrast, the group that received Saw palmetto extract treatment (G4) showed a significant reduction in the levels of TNF-α and IL-6 when compared to the IND treatment group (G2). This finding is related to the anti-inflammatory actions of Saw palmetto extracts reported by several studies (36). The anti-inflammatory actions of Saw palmetto extract are related to its phytosterol and flavonoid contents (27). As previously mentioned, the activation of transcription factors involved in the production of proinflammatory cytokines is triggered by oxidative stress, while flavonoids and β-sitosterol, being antioxidants, can counteract the buildup of free radicals, leading to attenuating the oxidative stress inhibited NF-κB activation (37).

**Limitation**

The current study could be summarized by the small number of animals used and the lack of estimation of the exact molecular mechanism through which Saw palmetto extract exerts its effect. Estimation of Malondialdehyde (MDA) tissue levels, being the product of lipid peroxidation and the expression level of Nrf2 mRNA, is usually used to predict the pathways of enhancing antioxidant activity, while the NF-κB mRNA to estimate the anti-inflammatory activity of the extract.

**Conclusion**

As a result of its anti-inflammatory and antioxidant capabilities, Saw palmetto extract was found to be effective as a potential treatment for oxidative damage that was brought on by NSAIDs, according to the findings of the current study.

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**Conflict of Interest:** None.

**Funding:** None

**Authors' contributions:**
Study conception & design: (Mohammed Qasim Yahya Malallah A. Al-atrakji.). Literature search: (Ziad Mahmood Abdul Majeed). Data acquisition: (Ziad Mahmood Abdul Majeed). Data analysis & interpretation: (Ziad Mahmood Abdul Majeed). Manuscript preparation: (Mohammed Qasim Yahya Malallah A. Al-atrakji & Ziad Mahmood Abdul Majeed). Manuscript editing & review: (Mohammed Qasim Yahya Malallah A. Al-atrakji & Ziad Mahmood Abdul Majeed)

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# التأثيرات الوقائية المحتملة لمستخلص نخيل المنشار في الفئران المعالجة بالإندوميثاسين

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**الملخص**
**الخلفية**: إندوميثاسين هو دواء مضاد للالتهابات غير الستيرويدية يستخدم على نطاق واسع في علاج الألم والحمى. يقترن الإندوميثاسين بالإجهاد التأكسدي والاستجابة الالتهابية، والتي تفسر العديد من الآثار الضارة على أعضاء الجسم.
**الهدف**: هدفت هذه الدراسة إلى تقييم إمكانية استخدام مستخلص نخيل المنشار لمقاومة الإجهاد التأكسدي والاستجابة الالتهابية الناتجة عن علاج الإندوميثاسين في نماذج الفئران.
**الطرق**: شملت الدراسة 20 فأرًا أبيضًا ذكرًا، تم تصنيفهم بشكل تعسفي إلى أربع مجموعات من 5 حيوانات لكل مجموعة. لم يتم تحريض المجموعة 1 (مجموعة التحكم) أو علاجها. عولجت المجموعات (2-4) بمعلقات أوميبرازول عن طريق الفم (20 مجم / كجم / يوم) ومستخلص نخيل المنشار (20 مجم / كجم / يوم) على التوالي، لمدة 15 يومًا. في اليوم الخامس عشر من الدراسة، تم أخذ عينات الدم عن طريق ثقب القلب لتحديد مستويات إنزيم أكسيد الفائق ديسميوتاز، وغلوتاثيون بيروكسيديز، وعامل نخر الورم ألفا، وإنترلوكين 6. وقد تم وصف النتائج باستخدام المتوسط±الانحراف المعياري كما تم تحليلها باستخدام تحليل التباين ANOVA متبوعًا باختبار المقارنات المتعددة لـ Tukey باستخدام Graph Pad Prism الإصدار 9.
**النتائج:** وجد أن علاج مستخلص نخيل المنشار يرفع مستويات إنزيم أكسيد الفائق ديسميوتاز وغلوتاثيون بيروكسيديز في المصل بشكل ملحوظ مقارنة بمجموعة تحريض الإندوميثاسين (القيمة الاحتمالية = 0.000012 والقيمة الاحتمالية <0.000001، على التوالي). وعلى العكس من ذلك، انخفضت مستويات عامل نخر الورم ألفا وإنترلوكين 6 بشكل ملحوظ مقارنة بمجموعة تحريض الإندوميثاسين (القيمة الاحتمالية <0.000001 والقيمة الاحتمالية <0.000001، على التوالي). تعتمد الأنشطة المضادة للأكسدة والمضادة للالتهابات لمستخلص نخيل المنشار على محتواه من الفلافونويدات النشطة بيولوجيًا والسيتوستيرول.
**الاستنتاج**: يمكن أن يكون التأثير المضاد للأكسدة والمضاد للالتهابات لمستخلص نخيل المنشار نهجًا واعدًا لمواجهة الإجهاد التأكسدي والاستجابة الالتهابية بسبب علاج الإندوميثاسين.
**الكلمات المفتاحية:** الاستجابة الالتهابية، إندوميثاسين، أوميبرازول، الإجهاد التأكسدي، مستخلص نخيل المنشار.