DOI: https://doi.org/10.31351/vol32iss1pp283-289

Study of the Anti-Inflammatory Effect of Tamsulosin in Rat by Evaluating IL-4, IL-6 and TNF-α: An airway Model

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Abstract

Inflammatory airway disease is a known worldwide health problem. Current medications are accompanied by serious side effects and it provides only temporary symptom control. Aim: To investigate the effect of tamsulosin, on the inflammatory cytokines IL-4, IL-6, and TNF-α, which are associated with airway inflammation. 30 male, albino rats, weighing 150-250 gm were allocated into 5 groups, each group with 6 rats; Group A: normal control group, rats were given commercial pellets and distilled water for 14 days. Group B: negative control group, rats were exposed to airway sensitization only. Group C: positive control group, rats were treated with prednisolone (4.12mg/kg/d) orally plus airway sensitization. Group D: rats were treated with tamsulosin (35 mcg/kg/d) orally plus airway sensitization. Group E: rats were treated with tamsulosin (17.5 mcg/kg/d) orally plus airway sensitization. Investigation of inflammatory cytokines IL- 4, IL-6, and TNF-α in serum samples by enzyme-linked immunoassay (ELISA). There was a significant reduction (*P*-value<0.05) of IL- 4 and TNF-α in serum for tamsulosin treated group (D) and group (E) when compared with the positive control group (B) but only group (D) (35mcg/kg/d) tamsulosin showed significant reduction (*P*-value<0.05) in IL-6 level when compared with the positive control group (B). Tamsulosin has an anti-inflammatory effect by reduction of IL-4, IL-6, and TNF-α in the rat airway model.

Key words: Tamsulosin, Airway inflammation, Inflammatory cytokines, IL-4, IL-6, TNF-α.

دراسة تأثير علاج التامسولوسين كمضاد لألتهابات المجاري التنفسية المستحدثة في الجرذان

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الخلاصه

التهاب المجرى الهوائي هو مشكلة صحية معروفة في جميع أنحاء العالم. الأدوية المتاحة مصحوبة بآثار جانبية خطيرة ولا توفر سوى السيطرة المؤقتة على الأعراض. دراسة تأثير عقار التامسولوسين على السيتوكينات (انترلوكين اربعة (IL-4) , انترلوكين ستة (IL-6) و عامل نخر الورم-ألفا(TNF-α) المصاحبة لاتهاب مجرى الهواء. تم استخدام ثلاثون جرذا من الذكور، وزنها ١٥٠-٢٥٠ جم قسمت إلى ٥ مجموعات ، كل مجموعة تحتوي على ٦ جرذان. المجموعة الاولى: مجموعة السيطرة ، أعطيت الفئران الماء المقطر لمدة ١٤ يومًا. المجموعة الثانية: تم تعريضها لتحسس مجرى الهواء فقط. المجموعة الثالثة: اعطيت علاج البريدنيزولون (٤،١٢ مجم / كجم) عن طريق الفم بالإضافة إلى تحسس مجرى الهواء. المجموعة الرابعة: اعطيت علاج التامسولوسين (٣٥ ميكروجرام / كجم) عن طريق الفم بالإضافة إلى تحسس مجرى الهواء. المجموعة الخامسة: اعطيت علاج التامسولوسين (١٧،٥ ميكروجرام / كجم) عن طريق الفم بالإضافة إلى تحسس مجرى الهواء. تم قياس تركيز السيتوكينات في مصل الجرذان بواسطة المقايسة الامتصاصية المناعية المرتبطة بالانزيم. انخفاض معنوي (*P*-value <0.05) لـ انترلوكين اربعة ومعامل نخر الورم-الفا للمجموعتين الرابعة والخامسة عند اعطاء علاج التامسولوسين. لكن المجموعة الرابعة فقط أظهرت انخفاضًا معنويًا-(*P*-value <0.05)في مستوى انترلوكين ستة. علاج التامسولوسين له تأثير مضاد للالتهابات عن طريق تقليل انترلوكين اربعة, انترلوكين ستة و عامل نخر الورم-ألفا بعد استحداث التهاب مجرى الهواء عند الجرذان.

الكلمات المفتاحية: تامسولوسين، التهاب المجرى الهوائي، سايتوكينات، انترلوكين أربعة، انترلوكين ستة، عامل نخر الورم-ألفا.

Introduction

Airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are well-known worldwide health problems that significantly affect the quality of life. The common complaints of affected patients include limited lifestyle activities as well as the economic burden. They usually endure frequent hospital admissions, high treatment costs, and even premature death [(1)]. The most common and effective therapy for the management of acute symptoms and preventing exacerbation are corticosteroids [(2)]. Unfortunately, even if they are used as a short course, a wide range of side effects accompany this medical formulation. On the other hand, long term use will lead to a more dangerous impact on human health [(3,4)]. In addition, there is an increase in morbidity and mortality caused by glucocorticoid resistance in asthmatic patients added to the limitation of long-term use of this drug class [(4,5)]. To date, there has been no clinical treatment capable of eliminating the disease or safely controlling it. Therefore, finding an effective medical plan by introducing new medication should be a priority.

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Received: 24/ 6/2022
Accepted: 3/8 /2022

Tamsulosin is an inhibitor of the α1-adrenergic receptor (α_1-AR), and the FDA has approved it for the management of benign prostatic hypertrophy (BPH)[6]. Drugs belonging to this class are inexpensive, common, and well-tolerated [7-9]. Nevertheless, tamsulosin adverse events emerged in 1.1% of treated patients in a previous study conducted by Martin *et al* and the reported adverse events included dizziness, nausea, headache, hypotension, dry nose, pruritus, redness of the skin, increased dyspepsia, and insomnia [10]. In an animal model of hyper-inflammation on mice, prophylactic treatment of cytokine storm is effective via using α_1-AR blocker which is performed by obstructing immune responses [11]. Furthermore, a retrospective study of hospitalized patients admitted for acute respiratory distress syndrome using α_1-AR antagonist had a reduced risk of depending on mechanical ventilation and lower mortality rates compared to non-users [12]. Cytokines have a vital role in regulating the body's immune reaction to infection [13]. IL-4 is one of the important cytokines that drive the allergic inflammatory response. It has an important role in initiating the differentiation of CD4 T-cells into T-helper2 calls, and stimulating the release of a great amount of IgE from B cells. Also, in macrophages, IL4 promotes their activation [14,15]. Another important cytokine is IL-6 which serves as a driving force for chronic inflammatory disease of the airways [16. Tissue injury and inflammation are the main reasons for the formation and release of IL-6. It was initially recognized as B cell stimulatory factor 2 (BSF-2), leading to the differentiation of B-cells into antibody-producing plasma cells [13]. Tumor necrosis factor-alpha (TNF- α) participates in the inflammatory process by causing hyper inflammation in the alveolar cells of the lung [17]. It is released at the beginning of allergen sensitization and continues to stimulate the immune response further at the effector stage [18]. Furthermore, TNF-α acts as a chemoattractant for neutrophils and eosinophils and improves their cytotoxicity on endothelial cells [19]. This research is aimed to investigate the impact of tamsulosin on inflammatory mediators such as IL- 4, IL- 6 and TNF-α that was associated with inflammatory airway disease and comparison with prednisolone.

Materials and method

Materials

Drugs and chemicals that are included in this current study are: Tamsulosin (Astells Pharma, the Netherlands), Prednisolone (Wockhardt, UK), ovalbumin (OVA) (Chadwll Heath ESSEX, England), $Al(OH)_3$ (MERCK Darmstadt, Germany), Normal Saline 0.9% (N/S) (Pioneer, Iraq) and formaldehyde (37-41%)(S.D. Fine Chem Limited, India).

Animals

Thirty healthy, male, rats 150-250 gm were purchased from the College of Veterinary Medicine/Basra University. Rats were housed under an optimum temperature 21±4 °C, light-dark photoperiods (12L:12D) and offered a commercial pellet diet with distilled water throughout the experiment.

Experimental design

Group A: normal control group, rats were given commercial pellets and distilled water (D/W) for 14 days. **Group B:** negative control group, rats were exposed to airway sensitization only. **Group C:** positive (standard drug) control, rats were given prednisolone (4.12 mg/kg/d) orally with airway sensitization [19]. **Group D:** treated control , rats were given tamsulosin (35 mcg/kg, equivalent to 0.4 mg tamsulosin for a 70 kg adult patient) orally with airway sensitization [20,21]. **Group E:** treated control group, rats were given tamsulosin (17.5 mcg/kg, equivalent to 0.2 mg tamsulosin for a 70 kg adult patient) orally with airway sensitization [21,22]. Airway inflammation was induced by sensitization (inhalation of ovalbumin) using a modified model by Zainab et al (2021) [19]. From the 1st to 3rd day, rats were sensitized by 1mg ovalbumin, 100mg $Al(OH)_3$ dissolved in 1ml N/S. On the 6th day, the sensitization dose was increased to 100mg ovalbumin, 100mg $Al(OH)_3$ dissolved in 1ml N/S. Challenge started on the 9th day using a glass chamber (30cm × 30cm × 30cm), which was attached to a nebulizer filled with 1% ovalbumin (1 gm OVA in 100 ml N/S) for 30 minutes each day; the process was repeated for 6 days. Drug doses were administered 60 minutes prior to sensitization in the treated groups. The rats were killed at the 14th day after the first sensitization dose [19].

Statistical analysis

In this study, data were expressed as mean ± (SEM). Comparison among multiple groups was conducted by analysis of Variance (ANOVA) while significance between two groups was assessed by unpaired student t-test. Concerning this work, *P*-values that are less than 0.05 (P-value<0.05) were regarded as significant.

Results

Effect of Tamsulosin on IL-4 in rat serum

Table 1 and Figure 1 elucidate that IL-4 levels (mean ± SEM) for rats that were exposed to airway sensitization (group B) were significantly elevated (P-value<0.05) when compared to the normal control (group A). Serum levels of IL-4 for group B and group A were 93.49±9.49 and 50.47±3.93, respectively.

Furthermore, Table 1 and Figure 1 shows that levels of IL-4 for rats treated with 4.12 mg/kg/d prednisolone (group C), 35 mcg/kg/d tamsulosin (group D) and 17.5 mcg/kg/d tamsulosin (group E) were significantly reduced (P-value<0.05) when compared to the negative control (group B). IL-4 levels for groups C, D and E were 42.88±1.87, 49.03±3.53 and 67.87±5.91, respectively. This data

indicated a significant reduction (*P*-value<0.05) in IL-4 levels when compared to the negative control (group B). Moreover, there was no significant difference (*P*-value>0.05) in IL-4 levels for prednisolone treated group (group C) when compared with tamsulosin 35mcg/kg/d (group D) as illustrated in Figure 1.

Effect of Tamsulosin on IL-6 in rat serum

As shown in Table 1 and Figure 2, IL-6 serum level (mean ± SEM) for OVA-sensitized rats (group B) was significantly elevated (*P*-value<0.05) when compared with the normal control (group A). IL-6 levels in rat serum for group B and group A were 82.5±1.76 and 41±2.44, respectively. Additionally, there was significant reduction (*P*-value<0.05) in IL-6 levels for rat serum after treatment with 4.12 mg/kg/d prednisolone (group C) (60.5 ± 5.53) and 35 mcg/kg/d tamsulosin (group D) (49.16 ± 5.70) in comparison to the negative control (82.5±1.76). However, tamsulosin 17.5 mcg/kg/d (group E) (75.33 ± 4.1) showed no significant difference (*P*-value>0.05) in comparison to the negative control (82.5±1.76), (Table-1). On the other hand, as shown in Table 1 and Figure 2, there was no significant (*P*-value>0.05) difference for prednisolone treated group (group C) when compared with tamsulosin treated group 35mcg/kg/d (group D), Table 1.

Effect of Tamsulosin on TNF-α in rat serum

Table 1 and Figure 3 demonstrate that levels of TNF-α (mean ± SEM) for rats with induced airway sensitization (group B) were significantly raised (*P*-value<0.05) compared to the normal control (group A). Serum level of TNF-α in groups B and A were 242.23±17.24 and 70.74±4.21, respectively.

In addition, Table 1 and Figure 3 shows that levels of TNF-α for rats treated with 4.12 mg/kg/d prednisolone (group C), 35 mcg/kg/d tamsulosin (group D) and 17.5 mcg/kg/d tamsulosin (group E) were 106.76±26.57, 67.56±20.79& 101.76±11.01, respectively. These changes showed significant reduction (*P*-value<0.05) in serum TNF-α level compared to the negative control group (group B) 93.49 ± 9.49.

Table 1. Effectiveness of tamsulosin on the serum levels of interleukin-4 (IL- 4), interleukin-6 (IL- 6) and Tumor necrosis factor-alpha (TNF-α) in rat after airway inflammation.

Treatment group n=6	Type of treatment	IL-4 (ng/L) (means ±SEM)	IL-6 (pg/mL) (means ±SEM)	TNF-α (ng/L) (means ±SEM)
Group A	Normal control/DW	50.47±3.93	41±2.44	70.74±4.21
Group B	Negative control/ OVA-sensitization	93.49±9.49*	82.5±1.76*	242.23±17.24*
Group C	Positive control/ Prednisolone (4.12mg/kg/d)	42.88±1.87 [a]	60.5±5.53 [a]	106.76±26.57 [a]
Group D	Tamsulosin (35mcg/kg/d)	49.03±3.53 [a]	49.16±5.70 [a]	67.56±20.79 [a]
Group E	Tamsulosin (17.5mcg/kg/d)	67.87±5.91 [a]	75.33±4.10	101.76±11.01 [a]

Values were represented as means ± standard error of means (SEM). *= Significantly different (*P*-value< 0.05) concerning the normal control group. Values with symbol superscript (a) are significantly different (*P*-value< 0.05) concerning group B. DW = distilled water; OVA = ovalbumin.

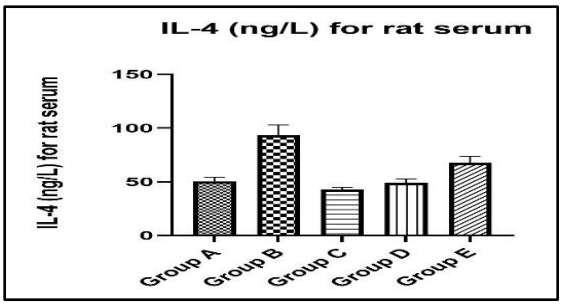

Figure 1.effect of tamsulosin on the serum level of IL-4 in rat. Group A: normal control group, rats given distilled water for 14 days; Group B: negative control group, rats exposed to airway sensitization only; Group C: positive control, treated with prednisolone (4.12mg/kg/d) orally plus airway sensitization; Group D: treated with tamsulosin (35 mcg/kg/d) orally plus airway sensitization; Group E: treated with tamsulosin (17.5 mcg/kg/d) orally plus airway sensitization.

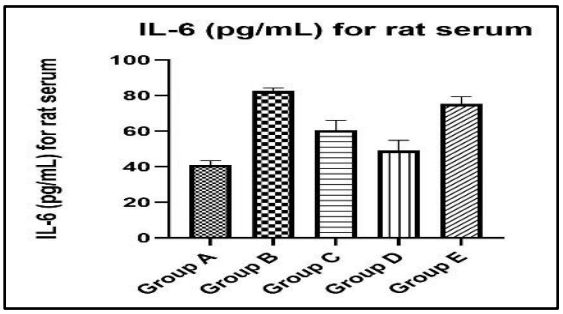

Figure 2 . Effect of tamsulosin on the serum level of IL-6 in rat. Group A: normal control group, rats given distilled water for 14 days; Group B: negative control group, rats exposed to airway sensitization only; Group C: positive control, treated with prednisolone (4.12mg/kg/d) orally plus airway sensitization; Group D: treated with tamsulosin (35 mcg/kg/d) orally plus airway sensitization; Group E: treated with tamsulosin (17.5 mcg/kg/d) orally plus airway sensitization.

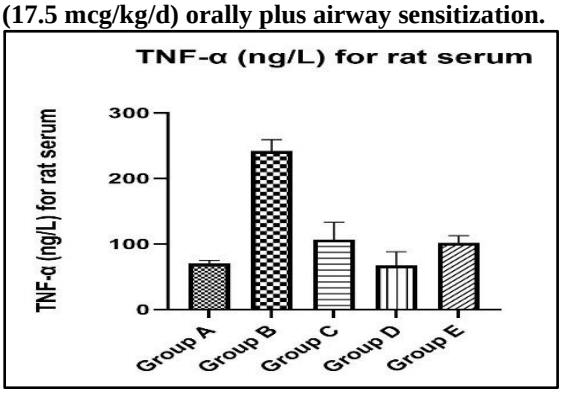

Figure 3. Effect of tamsulosin on the serum level of TNF-α in rat. Group A: normal control group, rats given distilled water for 14 days; Group B: negative control group, rats exposed to airway sensitization only; Group C: positive control, treated with prednisolone (4.12mg/kg/d) orally plus airway sensitization; Group D: treated with tamsulosin (35 mcg/kg/d) orally plus airway sensitization; Group E: treated with tamsulosin (17.5 mcg/kg/d) orally plus airway sensitization.

Discussion

Sustained inflammation of the respiratory tract arises from the pathogenesis of many chronic pulmonary conditions, including COPD and asthma [(23)]. These diseases come with a high case fatality ratio owing to the variable response rates to treatment choices [(5)]. Corticosteroids are the cornerstone of treating inflammation according to their major roles as anti-inflammatory and immunosuppressant. These agents also come with a long profile of dangerous side effects, especially with a long-term administration [(24)]. Prednisolone is a corticosteroid that is traditionally used as anti-inflammatory drug [(25)]. We utilized prednisolone in this research to compare pharmacological action with tamsulosin. Inflammatory cytokines have a leading role in orchestrating respiratory injury in asthma and COPD, making these mediators very attractive targets in treatment [(26)]. The current study was conducted to evaluate the impact of tamsulosin on selected inflammatory cytokines. The tamsulosin effect was then studied via using the OVA-sensitized rat model.

Tamsulosin is commonly prescribed to men as first-line agent for treating benign prostatic hypertrophy (BPH) by approximately 80% of physicians. It belongs to the α1-AR inhibitor pharmacological class [(6)]. Other members of this class have been found to protect against cytokine storm and hyper-inflammation by a previous study [(27)]. Prescribing tamsulosin is very common in men, and we aim to investigate other effects this drug may own.

In the current study, the prolong ovalbumin-sensitization in rats of the negative control (group B) caused airway inflammatory signs in comparison with the normal control (group A). This result is consistent with findings from previous studies [(28-30)]. First, we evaluated IL-4, an inflammatory mediator, which was significantly elevated (*P*-value <0.05) in rats with OVA-sensitization (group B) when compared with the normal control (group A), as shown in Table 1 and Figure 1. These results were in agreement with both Bagnasco *et al* (2016) [(31)] and Zainab *et al* (2021) [(19)], studies which showed that IL-4 level was considerably high when the rats were exposed to repeated OVA-challenge in comparison to the placebo group [(19,31)].

According to Table 1, a reverse airway inflammation reflected by significant (*P*-value <0.05) cytokines level reduction is caused by prednisolone treatment (group C) compared to the negative control (group B), which was also demonstrated by a previous study [(28)]. In this study, both doses of tamsulosin 35mcg/kg/d (group D) and 17.5 mcg/kg/d (group E) had shown the ability to significantly (*P*-value <0.05) reduce levels of IL-4. Moreover, there was no significant difference (*P*-value >0.05) when comparing treated group of tamsulosin 35 mcg/kg/d (group D) to prednisolone 4.12 mg/kg/d (group C) as seen in Table 1 and

Figure 1. Demonstrating that tamsulosin at dose 35 mcg/kg/d had equivalent activity to prednisolone 4.12mg/kg/d regarding the reduction of IL-4 in airway model.

In addition to IL-4, another pro-inflammatory mediator IL-6 was analyzed, which was produced after OVA sensitization in a rat airway model. Evidence showed that IL-6 has a correlation with the pathogenesis of asthma and is associated with the negative outcome after treatment [32]. In the current study, IL-6 concentration in serum was significantly reduced (*P*-value<0.05) by prednisolone treatment when compared to the negative control (group B), which was also observed by a previous study [33]. IL-6 level in serum was significantly downregulated (*P*-value<0.05) in rats treated with tamsulosin (35mcg/kg/d) when compared with OVA-challenged rats (group B). This result is in line with another study conducted by Grzegorz *et al* [34]. On the contrary, tamsulosin in dose 17.5 mcg/kg/d (group E) showed no statistical difference (*P*-value>0.05) in IL-6 level compared to the negative control group, Figure 2, suggesting this dose may be too low to produce a major reduction in IL-6 cytokine. Interestingly, tamsulosin 35mcg/kg/d (group D) was found to have an approximate effect to prednisolone (group C) in reducing IL-6 level, as there was no significant difference (*P*-value>0.05) between the two groups, Table 1.

This anti-inflammatory effect of tamsulosin could be attributed to different mechanisms. In his study, Alain *et al* investigated 26 genes of inflammation markers at mRNA level which resulted in an observed downregulation of mean mRNA expression by 12/26 (46.2%) in the tamsulosin treated group [20]. Additionally, Lin *et al* demonstrated the effect of tamsulosin in blocking the activation of NF-κB, leading to diminishing production of inflammatory cytokines [35]. This finding indicated that tamsulosin may have an equivalent mechanism to glucocorticoids in controlling inflammation at the molecular level. Prednisolone also acts by repressing the gene transcription by interference with the NF-κB family of nuclear transcription factors to diminish the triggering of several pro-inflammatory cytokines [36,37]. Moreover, another mechanism is proposed in an animal study which revealed that by blocking α1 AR pathway, catecholamine ability to augment cytokines production is lost, thus improving the capability to survive inflammatory injury in mice [27].

The other dominant inflammatory parameter in lung injury is TNF-α [38]. In the current study, the level of TNF-α in rat serum of the negative control (group B) was increased significantly (*P*-value <0.05) compared to the normal control (group A) as shown in Table 1. Kumar *et al* (2017) research reported that the TNF-α level is elevated in rats with induced airway sensitization compared to the negative control, which agrees with our study [39]. Treatment with prednisolone 4.12mg/kg/d (group C) showed a significant reduction (*P*-value <0.05) in TNF-α level, compared to the normal control (group A), as seen in Table 1 and Figure 3. This result agrees with other studies that corticosteroids are effective agents which are administered for controlling the release of pro-inflammatory cytokines such as TNF-α and IL-6 [17].

In addition, TNF-α was significantly reduced (*P*-value <0.05) by treatment with tamsulosin 35mcg/kg/d (group D) and this result is in agreement with earlier research by William *et al* (2018) [6]. This result can be explained by the effect of tamsulosin in blocking the activation of NF-κB, therefore reducing the synthesis of inflammatory cytokines [35]. Additionally, another possible mechanism could be described by a previous animal study in which norepinephrine (NE) was found to control the phosphorylation of mitogen-activated protein kinases (MAPK) through AR pathway, which in turn regulated the macrophage production of TNF-α. Therefore, after using an α-AR antagonist, NE role in TNF-α production was blocked [40]. In another research, Sumera *et al* detected a downregulation in the levels of mRNA expression of TNF-α after the administration of α1-AR antagonist in rats, suggesting an immunomodulatory potential for α1-AR blockers [41]. In the current study, it is interesting to note the presence of a superior reduction of TNF-α in the tamsulosin (35 mcg/kg/d) treated group over the prednisolone 4.12mg/kg/d treated group as shown in Table 1 and Figure 3.

This present study has demonstrated that tamsulosin (17.5 - 35 mcg/kg/d) reduce and/or prevents certain inflammatory cytokines release in ovalbumin-challenged rats. In this animal model, the anti-inflammatory action of tamsulosin was detected for the first time; nevertheless, previously reported similar anti-inflammatory response was in other α1 AR antagonist drug-class members [27]. As a final result, according to Table 1, the tamsulosin dose (35mcg/kg/d) had a more pronounced and reliable effect in reducing inflammatory cytokines (IL-4, IL-6 and TNF-α) than the lower dose (17.5mcg/kg/d).

Conclusion

The current research showed that tamsulosin, an α1 AR blocker had an anti-inflammatory effect in airway model that included a reduction in serum concentration of major pro-inflammatory cytokines (IL-4, IL-6 and TNF-α). In the future, more studies with tamsulosin can be conducted for prevention and treatment of other inflammatory lung diseases.

Acknowledgment

This study was abstracted from the master's study that was submitted at the Department of Pharmacology and Toxicology, College of Pharmacy, Al-Basrah University. The authors offer their greatest thanks to the Department of Pharmacology and Toxicology, College of Pharmacy, Al-Basrah University.

Conflict of Interest

The authors of this work had declared no conflict of interest.

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