Original Article

Study of the Anti-Inflammatory Effect of Dipyridamole in Rats Model by Airway Inflammation

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Abstract

Background: Airway inflammation is often caused by pathogens or exposure to pollutants toxins, allergens, and irritants. The lungs are vital organs and excessive inflammation can be life-threatening. Treatment with anti-inflammatory drugs is essential. **Objective:** This study aims to investigate the anti-inflammatory activity of dipyridamole (DP) to improve inflammatory events associated with airway inflammation. **Materials and Methods:** A total of 24 healthy male rats were weighting (150–300 g), which are divided into four groups, each group consists of six rats. Group A: rats were administered distilled water orally, which is considered a control group. Group B: rats were administered distilled water orally with sensitization (by ovalbumin), which is considered a positive control group. Group C: rats were administrated (26.4 mg/kg) DP orally with sensitization. Group D: rats were administrated prednisolone (4.12 mg/kg) orally with sensitization. **Results:** The results revealed that there was a significant reduction ($P < 0.05$) of rat serum levels of interleukin (IL)-6 and tumor necrosis factor-alpha for groups C and D when compared with ova-sensitized positive control (group B). Regarding rat serum levels of IL-4 for groups C and D were reduced, but group C was non-significant ($P > 0.05$) when compared with ova sensitize positive (group B). In addition, group C was non-significant elevated ($P > 0.05$). IL-10 level in rat serum when compared with ova sensitize positive (group B) but group D was significant. **Conclusion:** This study concludes that DP has an anti-inflammatory effect in the airway sensitization model as it reduces inflammatory cytokines levels in rat serum.

Keywords: Airway model, cytokines, dipyridamole, ovalbumin

Introduction

The inflammation of the airway is often related to exposure to pathogens, pollutants, toxins, and allergens.[1] Airway inflammation may be either acute or chronic. Acute inflammation, such as acute respiratory distress syndrome, whereas chronic inflammation, such as asthma and chronic obstructive airway disease (COPD). Bronchial asthma is an obstructive chronic inflammatory illness with only symptomatic treatment.[2] Exacerbations can be fatal. Patients with asthma are synthesized by several allergens like dust, pollutants, and infestation.[3]

Like asthma, COPD is a chronic inflammation usually infiltrated with neutrophils.[4] COPD is the third leading cause of mortality in the United States. The cost of most COPD-related morbidity and health care is owing to acute exacerbations.[5]

Typically, the mechanisms of inflammation are related to pattern recognition receptors (PRRs) to describe the molecular patterns expressed by the pathogens. PRRs receptors can be located on the surface of membranes, such as B-cell Toll-like receptors (TLRs).[6] TLRs explain molecular patterns common to pathogens and enhance inflammatory cells, such as the nuclear factor kappa light chain enhancer of activated B cells (NF-κB), and produce pro-inflammatory cytokines (CKs), and tumor necrosis factor-alpha (TNF-α).[7]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_773_23

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Submission: 17-Jun-2023 **Accepted:** 07-Dec-2023 **Published:** 30-Apr-2026

How to cite this article: Nashmi AD, Hasan JK, Ibrahim MA. Study of the anti-inflammatory effect of dipyridamole in rats model by airway inflammation. Med J Babylon 2026;23:90-6.

As well as CKs interlukin-4 (IL)-4, IL-6, IL-10 and TNF-α. Regarding IL-4, it is secreted by mast cells as well as type 2 T helper (TH2) cells and related CKs.[8] IL-4 indirectly has a significant role in the TH0 cell differentiation process into TH2 cells. In addition, it plays a positive feedback role to further enhance the inflammatory response.[9] In addition, IL-6 CK is induced by inflammatory epithelial cells concerning frequent stimuli, such as viruses, exercise, and allergens.[10] IL-6 is a pro-inflammatory marker and also plays a role in the pathogenesis of many inflammatory conditions like rheumatoid arthritis.[11] Elevated serum IL-6 levels have also been associated with increased COPD mortality.[12] As for IL-10, this CK is manufactured by specific cells, such as macrophages and mast cells, as well as T/B lymphocytes. The main sources of lymphocytes are nuclear cells, macrophages, and B cells.[13] Although IL-10 stimulates the proliferation of certain immune cells, such as B cells and mast cells, it can promote the synthesis of immunoglobulins.[14] As well as TNF-α is a CK storm pro-inflammatory CK that is, crucial for multiple organ failure and systemic inflammation. The severity of the disease was found to be correlated with CK storm or CK release syndrome, which is indicated by higher TNF-α.[15]

These CKs were inhibited by many drugs, of which usually used corticosteroids (CS). Here the use of dipyridamole (DP) in airway inflammation was evaluated in animal models to minimize the routine use of CS. DP as an antiplatelet drug inhibits phosphodiesterase 3 and phosphodiesterase 5, causing accumulation of cyclic adenosine monophosphate and cyclic guanosine monophosphate.[13] DP inhibits the reuptake of adenosine into platelets, erythrocytes, and endothelial cells enhancing extracellular adenosine concentrations.[16] Moreover, DP has reduced pulmonary hypertension without a significant reduction in systemic blood pressure.[16] It has additional benefits as anti-inflammatory and antioxidant activities, in addition to its role as an antiplatelet activity.[17]

The goal behind this research was to investigate whether DP has an effect on pro-inflammatory mediators IL-4, IL-6, IL-10, and TNF-α that are associated with inflammatory airway disease or not when we compare with prednisolone.

Materials and Methods

Materials

The drugs that were used in this study include DP tablets 75 mg (Medochemie Ltd., Limassol, Cyprus), prednisolone (The State Company for Drugs Industry and Medical Appliances, Baghdad, Iraq), phenobarbital (IBN Hayyan Pharmaceutical Co., Homs, Syria), and 0.9% sodium chloride solution (Pharmaceutical Solution Industry, Jeddah, Saudi Arabia), whereas other substances were ovalbumin (OVA) powder (Riedel-de Haen AG, Seelze-Hannover, Germany), aluminum hydroxide [$Al(OH)_3$] powder (MercK, Darmstadt, Germany), and formaldehyde 37% (Aqua Medical, Istanbul, Turkey).

Animals

Twenty-four albino male rats were obtained from Collage of Nahrain, Biotechnology Research Centre, animal facilities at the Baghdad University and Faculty of Pharmacy, Basra University, Basra, Iraq; they were maintained under normal conditions of temperature (21 ± 4°C), humidity, and light/dark cycle (12 h/12 h), and received pelleted feed and reverse osmosis water.

The Research Ethics Committee of the Faculty of Medicine of the University of Basrah approved the research protocol.

Experimental design

The animals were divided into four groups each group consisting of six male rats. Group A represents the negative control group, rats were administered water without sensitization for 14 days. Group B represents the positive control group, rats were administered water with sensitization. Group C treated group, rats were administered orally DP (26.4 mg/kg/day), which dissolved in distilled water (each 1 mL contain 5 mg of DP)[18] with sensitization. Group D treated group, rats were administered orally prednisolone (4.12 mg/kg/day)[19] with sensitization.

Rats in groups B, C, and D were sensitized by OVA.[20,21] Sensitization occurs by intraperitoneal (IP) injection of 1 mg OVA, 100 mg of $Al(OH)_3$ dissolved in 1 mL of 0.9% sodium chloride solution normal saline (N/S) for (1–3) days, then at the sixth day the rats were given IP injection of 100 mg OVA, 100mg Al(OH)3 dissolved in 1 mL of 0.9%N/S. On the ninth day, the rats in groups B, C, and D were nebulized with 1% OVA (1 g OVA) in 100 mL 0.9% N/S for 30 min daily for 6 days. The nebulization method is done by placing the animal in a glass chamber size 20 cm × 30 cm × 40 cm and nebulizing the mixture, prepared previously, in the electric nebulizer through a hole in a glass chamber.

After 24 h of the last dose, animals were anesthetized by IP injection of phenobarbital in a dose of 800 mg/kg IP.[22] Then, the blood was collected directly from the heart, placed in a plain tube, and left to coagulate for 1 h at room temperature, then the blood was centrifuged at 10,000 rpm to separate the serum, then the serum was collected, placed in Ependruff cup and freeze in −70°C. Then frozen serum was thawed and analyzed for IL-4, IL-6, IL-10, and TNF-α detection using an enzyme-linked immunosorbent assay kit from Elabscience Biotechnology Inc., Houston, TX, USA.

Ethical approval

The study was conducted following the ethical principles of the declaration of Helsinki. It was carried out with animal (rats) verbal and analytical approval before the sample was taken. The study protocol was reviewed and approved by Basra University College of Medicine, a local ethics committee according to document number 7/39/5027 on October 26, 2022.

Statistical analysis

In this study, data were expressed as mean ± standard error of the mean (SEM). Comparison between multiple groups was conducted by analysis of variance, whereas significance between two groups was assessed by unpaired Student *t* test. Concerning this work, *P* values that are <0.05 were regarded as significant or otherwise non-significant.

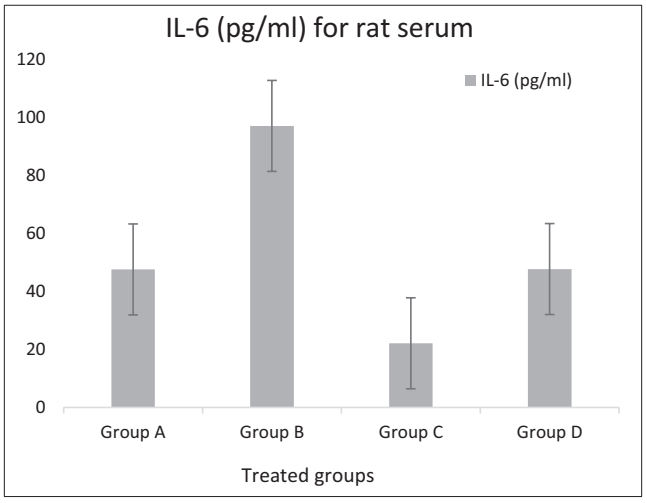

Figure 1: Effect of dipyridamole on level of IL-6 in rat serum. Group A: control group, rats given distilled water for 14 days. Group B: positive control group, rats exposed to airway ova-sensitization only. Group C: treated with dipyridamole (26.4 mg/kg/day) orally with airway ova-sensitization. Group D: treated with prednisolone (4.12 mg/kg/day) orally with airway ova-sensitization

Results

Effect of DP on IL-6 level in rat serum

Figure 1 and Table 1 show serum levels of IL-6 (mean ± SEM) for rats in positive ova-sensitized (group B) were significantly increased ($P < 0.05$) in contrast with normal control (group A), they were 97.16 ± 22.08 and 47.63 ± 15.69, respectively. At the same time, the rat serum levels of IL-6 for DP-treated (group C; 26.4 mg/kg/day) and prednisolone-treated (group D; 4.12 mg/kg/day) were highly significantly decreased ($P < 0.05$) in contrast to positive control (group B), they were 22.14 ± 6.53 and 47.76 ± 16.11, respectively.

Effect of DP on TNF-α level in rat serum

Figure 2 and Table 1 illustrate that the serum levels of TNF-alpha (mean ± SEM) for rats in positive ova-sensitized control (group B) were significantly increased ($P < 0.05$) when compared with normal control (group A), they were 252.05 ± 87.04 and 68.90 ± 21.99, respectively.

Concerning DP-treated (group C; 26.4 mg/kg/day) and prednisolone-treated (group D) (4.12 mg/kg/day) the rat's serum levels of TNF-alpha (mean ± SEM) were 90.65 ± 25.83 and 100.70 ± 34.83, respectively this was indicating a highly significant decrease ($P < 0.05$) in TNF-α in contrast with positive (group B).

Effect of DP on IL-4 level in rat serum

Figure 3 and Table 1 demonstrate that serum levels of IL-4 (mean ± SEM) for rats in positive ova-sensitized (group B) were significantly increased ($P < 0.05$) in contrast with normal control (group A), they were 281.9 ± 73.86 and 113.18 ± 64.68, respectively.

Regarding the anti-inflammatory action for DP treated (group C; 26.4 mg/kg/day), the rat's serum levels of IL-4 were not significantly decreased ($P > 0.05$) it was 189.83 ± 23.59 when compared with the ova-sensitized positive control (group B), whereas in prednisolone-treated (group D; 4.12 mg/kg/day), the rat's serum

Table 1: Effectiveness of dipyridamole on interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) interleukin-4 (IL 4), and interleukin-10 (IL-10) levels in rat serum after airway inflammation

Treatment groups	Type of treatment	IL-6 (pg/mL) for rat serum Mean ± SEM	TNF-α (ng/L) for rat serum Mean ± SEM	IL-4 (ng/L) for rat serum Mean ± SEM	IL-10 (pg/mL) for rat serum Mean ± SEM
Group A	Negative control/DW	47.63 ± 15.69	68.90 ± 21.99	113.18 ± 64.68	210.71 ± 18.36
Group B	Positive control/OVA-sensitization	97.16 ± 22.08*	252.05 ± 87.04*	281.9 ± 73.86*	58.75 ± 14.32*
Group C	Dipyridamole 26.4 mg/kg/day	22.14 ± 6.53¶	90.65 ± 25.83¶	189.83 ± 23.59	48.25 ± 10.54
Group D	Prednisolone (4.12 mg/kg/day)	47.76 ± 16.11¶	100.70 ± 34.83¶	120.33 ± 21.45¶	165.56 ± 40.29¶

D/W: distilled water, OVA: ovalbumin.

Values are represented as means ± standard error of means (SEM).

*Significantly different ($P < 0.05$) concerning the negative control group.

¶Significantly different ($P < 0.05$) concerning group B

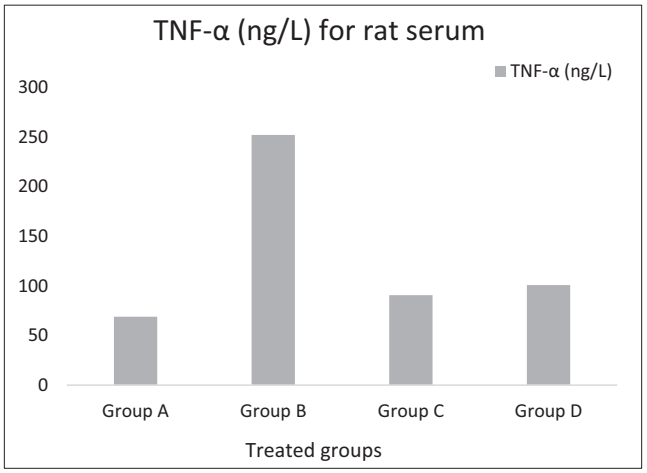

Figure 2: Effect of dipyridamole on the level of TNF-alpha in rat serum. Group A: control group, rats given distilled water for 14 days. Group B: positive control group, rats exposed to airway ova-sensitization only. Group C: treated with dipyridamole (26.4 mg/kg/day) orally with airway ova-sensitization. Group D: treated with prednisolone (4.12 mg/kg/day) orally with airway ova-sensitization

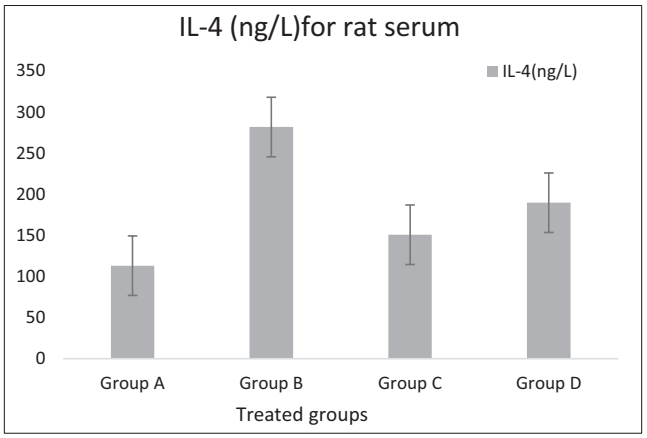

Figure 3: Effect of dipyridamole on level of IL-4 in rat serum. Group A: control group, rats given distilled water for 14 days. Group B: positive control group, rats exposed to airway ova-sensitization only. Group C: treated with dipyridamole (26.4 mg/kg/day) orally with airway ova-sensitization. Group D: treated with prednisolone (4.12 mg/kg/day) orally with airway ova-sensitization

levels of IL-4 was significantly decreased ($P < 0.05$) it was 120.33 ± 21.45 when compared with ova-sensitized positive control (group B).

Effect of DP on IL-10 level in rat serum

Figure 4 and Table 1 show serum levels of IL-10 (mean ± SEM) for rats in positive ova-sensitized (group B) were significantly increased ($P < 0.05$) in contrast with normal control (group A), they were 210.71 ± 18.36 and 58.75 ± 14.32, respectively.

When looking at the rat's serum level for DP treated (group C; 26.4 mg/kg/day) there was no significant increase

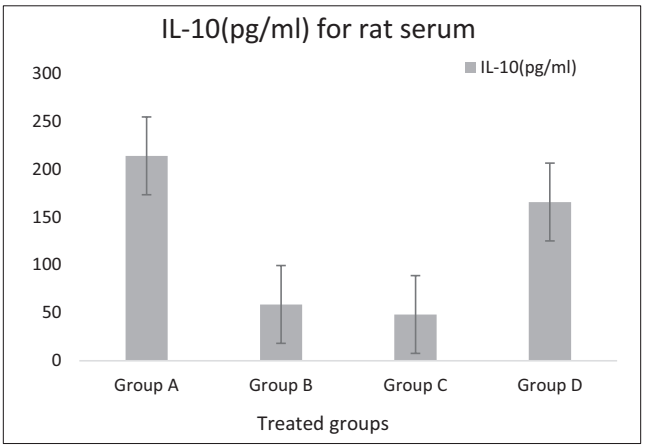

Figure 4: Effect of dipyridamole on level of IL-10 in rat serum. Group A: control group, rats given distilled water for 14 days. Group B: positive control group, rats exposed to airway ova-sensitization only. Group C: treated with dipyridamole (26.4 mg/kg/day) orally with airway ova-sensitization. Group D: treated with prednisolone (4.12 mg/kg/day) orally with airway ova-sensitization

in IL-10 ($P > 0.05$), whereas in prednisolone-treated (group D; 4.12 mg/kg/day) was significantly increased in contrast to positive ova-sensitized (group B), they were 48.25 ± 10.54 and 165.56 ± 40.29, respectively.

Discussion

Despite the advances in treatment, the prevalence of pulmonary diseases has increased. The epidemiological studies indicate that the prevalence of these diseases is underestimated, further increasing the difficulty of their management.[23]

The mechanism of respiratory disease has been related to the enhancement of the inflammatory expression of CKs and certain adhesion molecules. Chemokines play an important role in the differentiation of immune cells. In addition, intercellular adhesion molecule-1, matrix metalloproteinase-9, vascular cell adhesion molecule-1, cytosolic phospholipase A2, and cyclooxygenase-2 have been blamed for inducing pulmonary inflammation related to different stimuli.[24] Various signaling molecules can regulate the target proteins that are involved in pulmonary inflammation.[24]

Regarding the method used to induce airway inflammation in animal models, there was more than one method had been used, but the one used was OVA.

A study done by Andersson *et al.*[25] found that IL-6 CK was dramatically expressed in the lungs of the OVA-treated rats group and the cells obliterating the lumen of the arterioles.[25] Soriano *et al.*[26] found that in sensitized 40 female BALB/c mice with OVA, there was an increase in serum IL-6 and other CKs in the OVA-sensitized group.

IL-6 has described as important regulator of cell to differentiation of CD4 T cells to effector CD4 cells; IL-6 regulates the balance between type 1 T helper and TH2 cells.[27]

When looking at Table 1 and Figure 1, this was parallel with the results in this research that including there was a significant increase in rat's serum IL-6 ($P < 0.05$) for rats in ova-sensitized positive control (group B), when compared with normal negative control (group A).

In another research study done by Halwani *et al.* in 2014[28] on 60 mice found that the serum mice TNF-α was increased in the ova-sensitized group with saline when compared with the normal group given only saline. This is in agreement with this study that ensuring there was a significant increase($P < 0.05$) in rat's serum TNF-α in ova-sensitized positive (group B) when compared with normal control (group A) as shown in Table 1 and Figure 2.

A study done by Chang *et al.* in 2014[29] found that sensitized 50 male Wistar rats with OVA observed a significant elevation in rat serum of IL-4, IL-10, and interferon-gamma in the ova-sensitized group when compared with the normally treated group.

In addition, a study done by Halwani R. *et al.* 2016[26] found that there was an increase in serum IL-4 and other CKs in the OVA-sensitized group.

In addition, a study done by Dong *et al.* 2021[30] on 42 mice in different groups found that IL-4 serum rat level was increased in the ova-induced mice group. The above studies were in agreement with this study as clarified in Table 1 and Figure 3 that involve OVA-sensitization in rats for 14 days, which was associated with airway inflammation. This includes significant elevation ($P < 0.05$) in rat's serum levels IL-4 for positive ova-sensitized (group B) when compared with negative control (group A).

TH cell-derived IL-10 is found to be a significant mediator for tolerance to allergens and may lead to the resolution of allergic inflammation. Whereas, reduced IL-10 induction by T helper cells has been suggested in cases of severe asthma. Genetic mutations that affect IL-10 expression are usually associated with development and increased severity of asthma.[31] In an important study done by Maha Fahad Alenazy and Askari,[32] which induced inflammation by OVA-sensitized BALB/c 40 female mice found that there was a decrease in IL-10 and other CKs in the ova-sensitized group in contrast with the normal control. This is parallel with this study that involved significant reduction ($P > 0.05$) in IL-10 for ova-sensitized positive (group B) when compared with negative control (group A), this is best seen in Table 1 and Figure 4.

From another point of view, when looking at the effect of prednisolone on IL-6 in a study done by Kruif *et al.*[33] on 32 healthy male volunteers, found that IL-6 production was successfully inhibited by prednisolone. This is in agreement with this study that included prednisolone-treated rats (group D), which significantly reduced IL-6 in rat's serum ($P < 0.05$) when compared with the ova-sensitized positive control (group B), as shown in Table 1 and Figure 1.

At the same time in this study, Table 1 and Figure 2 incorporated a significant reduction ($P < 0.05$) in TNF-α for prednisolone-treated rats (group D) when compared with the ova-sensitized positive control (group B) this consent with a mentioned study done by Kruif *et al.*[33] illustrated that TNF-α production was successfully inhibited by prednisolone.

As well as another study done by Liu[34] studied the effects of pretreatment with oral prednisolone on the physiologic and inflammatory responses in 10 allergic asthmatic patients and showed that prednisolone administration reduces the appearance of protein, messenger ribonucleic acid, and CKs, such as IL-4, IL-5, and IL-2. This comes in agreement with the result in this study, Table 1 and Figure 3, which involved significant reductions in serum IL-4 levels for prednisolone-treated rats (group D) in contrast with the ova-sensitized positive control (group B).

Another study done by Negera and Walker[35] on 30 patients pretreated with prednisolone suffering from erythema nodosum leprosum found that there was an increase in serum levels of IL-10. This is parallel with the results found in this study, Table 1 and Figure 4, including IL-10 levels in the serum of rats in prednisolone-treated (group D) was significantly increased ($P < 0.05$) when compared with ova-sensitized positive control (group B).

In addition, in an interesting study done by Alyasiry *et al.*[36] found that DP significantly decreased inflammatory mediators, such as TNF-α and IL-6. This is aligned with this study, Table 1 and Figures 1 and 2 involving significant reductions ($P < 0.05$) in IL-6 and TNF-α for DP-treated (group C) when compared with ova-sensitized positive control (group B).

Moreover, in this study, Table 1 and Figure 3, there was an anti-inflammatory role of DP that included a reduction in rat serum IL-4 level in the rat' serum for DP treated (group C), but this reduction was non-significant ($P > 0.5$).

As well as in this study, in Table 1 and Figure 4, there was no elevation of rat's serum IL-10($P > 0.05$) for the DP-treated group when compared with the ova-sensitized positive control (group B). Although there was an increment in IL-10, this may be related to a reduction in DP dose or a reduction in the duration of administration of DP.[37]

A study done by Macatangay and Jackson[37] found that 35 participants who were randomized, 17 received DP (100 mg four times a day) and 18 received placebo

recipients had baseline and weeks 12 data available for analysis of IL-10. In addition, there was an increase in serum IL-10 in the DP group in contrast with the placebo group.

A study done by Balakumar and WitnessKoe[38] found that in an attempt to decrease renal inflammation in a rat model of acute nephrotoxicity, the study approved that the use of DP 20mg\kg\day for 8 days increased the serum rat's IL-10.

DP prevents the reuptake of adenosine into platelets, erythrocytes, and endothelium and causes more extracellular adenosine concentrations.[23] Adenosine inhibits the activation of various TLRs by suppressing their downstream pathway, NF-κB. Therefore, more than one mechanism has been suggested. $A_{2B}A$ physically binds to p105 (an NF-κB inhibitor) and reduces its degradation and so reduces the production of CKs that act as a pro-inflammatory mediator.[39]

In this study, the anti-inflammatory effect of DP and prednisolone was evaluated concerning the inhibition of NF-κB and some of the ILs related to airway inflammations.

Glucocorticoids are the main anti-inflammatory drugs, that strongly inhibit NF-κB activation probably by mechanisms that are not fully understood like prevention of deoxyribose nucleic acid binding, IκB kinase activity, and transactivation. Glucocorticoids (prednisolone, dexamethasone, and methylprednisolone) can overcome NF-κB activation.[40]

Conclusion

From the results of this study, DP has an anti-inflammatory effect in airway rats model that includes a decrease in serum concentration of major pro-inflammatory CKs (IL-6 and TNF-α) with a slight modulation in IL-4 and IL-10. In the future, more studies on DP must be done, which may help in the prevention and treatment of most inflammatory respiratory diseases and other inflammations.

Financial support and sponsorship

This study was self-funded.

Conflicts of interest

There are no conflicts of interest.

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