

PROTECTIVE EFFECT OF TURMERIC AGAINST ALUMINIUM-INDUCED PROSTATE DAMAGE IN RATS

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Abstract

This study investigates the potential protective properties of turmeric (*Curcuma longa* L.) against aluminium (Al) toxicity-induced prostate damage in male rats. The administration of $AlCl_3$ to rats resulted in decreased body weight, increased oxidative stress markers, hormonal depletion, apoptosis induction, and pro-inflammatory cell infiltration in the prostate tissue. Additionally, histopathological examination revealed various abnormalities. However, co-treatment with turmeric extract improved body weight, increased testosterone levels, reduced apoptosis, and mast cell infiltration. *C. longa* L. exhibited strong antioxidant and anti-inflammatory effects, highlighting its potential as a phytomedicine against reproductive disorders like prostatitis induced by Al exposure.

Key words: aluminium toxicity, antioxidant, anti-inflammatory, prostate damage, turmeric

Introduction. Prostatitis is a chronic disease of the urinary tract that is problematic for many clinicians to treat effectively. It is reported that about half of all men show signs of prostatitis at any time in their lives [1]. Approximately 5% to 12% of infertile men have a history of inflammation of their urogenital system, including prostatitis, epididymitis, and orchitis [2]. Inflammation is associated with multiple cancers, and prostate inflammation, in particular, is a suggested factor in the development and progression of prostate cancer [3]. Various epidemiological studies have investigated the associations between heavy metals exposure

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and prostate cancer risk and different forms of aluminium (Al) are environmental xenobiotics that induce free radical-mediated cytotoxicity and reproductive toxicity [4]. No successful cure has been identified; currently, the most widely prescribed medicines for treatment are antibiotics, alpha-adrenergic antagonists, anti-inflammatories, and neuromodulators, however, all have a minimal clinical impact [5]. At present, the application of herbal products as nutritional antioxidants in diseases related to oxidative stress has received increasing attention. *Curcuma longa* L. which belongs to the family of Zingiberaceae is a perennial herb endemic to Asian countries. The rhizome, the part of the plant that is used medicinally in the form of a yellow powder (turmeric), is used mainly as an anti-inflammatory agent [6]. Curcumin such as the active ingredient of turmeric may function as an antioxidant and medicinal agent without side effects [7]. It also has anti-carcinogenic, anti-inflammatory, and antibacterial effects and serves as an effective chemopreventive agent for cancer [8]. On the other hand, the use of this plant has also proved its effectiveness against heavy metal poisoning. It was reported that curcumin attenuates lead-induced cerebellar toxicity in rats via chelating activity and inhibition of oxidative stress [9]. Despite the potential proven effect of *C. longa* against the toxic effect of Al on the male reproductive system, few or no studies have investigated its effect on the prostatic gland. Based on that, the present study aimed to evaluate the effect of turmeric aqueous extract on Al-induced hormonal depletion, prostatic cell apoptosis, inflammation, and tissue oxidative stress.

Materials and methods. Plant extraction and characterization. Turmeric aqueous extract (TAE) was prepared by grinding dried *C. longa* L. rhizomes into a fine powder, followed by decoction extraction with distilled water (1:10 w/v) in a water-bath reflux system for 15 min. The resulting solution was cooled, filtered, and centrifuged at 4000 rpm for 20 min. The supernatant was concentrated using a rotary evaporator and stored at 4 °C.

Animal experimentation and tissue analysis. A total of twenty-four male Wistar rats with an average weight of 193.9 ± 26.46 g were utilized in the study. The rats were kept under controlled environmental conditions, including humidity, temperature (22 ± 2 °C), and a 12-hour light/dark cycle, with ad libitum access to standard laboratory diet and water. The rats were divided into four groups ($n = 6$ each) and subjected to specific treatments: Group I received oral Aluminium chloride ($AlCl_3$) at a dose of 34 mg/kg BW (body weight); Group II received both $AlCl_3$ (34 mg/kg BW) and turmeric aqueous extract (TAE) at a dose of 200 mg/kg BW, administered one hour apart; Group III received only TAE at the same dose and route as Group II; and Group IV served as a control with no treatment. After a four-week experimental period, the rats were euthanized. Prostate tissues were collected and processed for analysis. Body weight gain and relative organ weight (Relative prostate weight = $[\text{organ weight} / \text{body weight}] \times 100$) were calculated. Tissue biochemical analysis involved measuring malondialde-

hyde (MDA), catalase (CAT), and superoxide dismutase (SOD) concentrations [10]. Hormonal analysis was performed on serum samples to determine testosterone levels using radioimmunoassay methods with commercial kits (VIDAS Assays, BIOMERIEUX) [9]. Histological studies included hematoxylin-eosin staining [11], and toluidine blue staining to assess apoptosis and inflammation levels [12]. The study received ethical approval (No. 0100/2021) under Algerian legislation and guidelines from the Algerian Association of Experimental Animal Sciences (AASEA).

Statistical analysis. Results were expressed as mean $\pm$ standard error (SE) of three or six replicates. Multiple sample comparison was performed using the software SigmaPlot 11.0.1 for Windows. Analysis of variance (ANOVA) followed by Tukey's multiple comparison tests was used. The level of significance was $p < 0.05$.

Results and discussion. Because of their multiple therapeutic properties, such as antioxidant and anti-inflammatory activities, medicinal plants have received more attention in recent years. This study aimed to determine the potential prostate protective properties of turmeric extract against Al toxicity in rats. The current study revealed that the administration of $AlCl_3$ at a dose of 34 mg/kg BW to male rats for 4 weeks led to a decrease in body weight (Table 1), and the appearance of many prostatic disorders including a significant increase of tissue oxidative stress markers (MDA, CAT, and SOD) (Fig. 1), hormonal depletion (Fig. 1), cells apoptosis induction (Fig. 2), and increase of pro-inflammation cells (mast cells) (Fig. 3). Heavy metals are a heterogeneous group of highly reactive substances, which may act as essential cofactors for physiologic processes and/or as toxic elements but the unifying factor in determining metal toxicity is the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [13]. Moreover, the results of the current study indicated that the administration of $AlCl_3$ significantly decreased serum testosterone levels compared to control rats (Fig. 1). These findings are consistent with those of SUN et al. [14], who noticed that Al reduced testosterone, FSH, and LH levels via testicular androgen receptor disruption. Moreover, histopathological examination revealed multiple abnormalities including acini size reduction, an attenuation of the epithelial mucosa membrane, alveolar secretory alteration and stromal degeneration (Fig. 2). DA SILVA et al. [15] indicated that in adult male gerbils, Al toxicity causes histopathological and pro-oxidant damage to the prostate and gonads. In addition, the induction of apoptosis by Al revealed in our research confirms the results of several subsequent studies. HALVAEI et al. [16] state that the induction of oxidative stress is one of the most important mechanisms of acute Al poisoning. Furthermore, the induction of apoptosis was accompanied by mast cell (MC) infiltration (Fig. 3). MCs are inflammatory cells that contain proteases, angiogenic factors, and cytokines. Cell survival, growth, differentiation, and cyclooxygenase-2 expression are all induced when cytokines are increased [17]. MCs are also

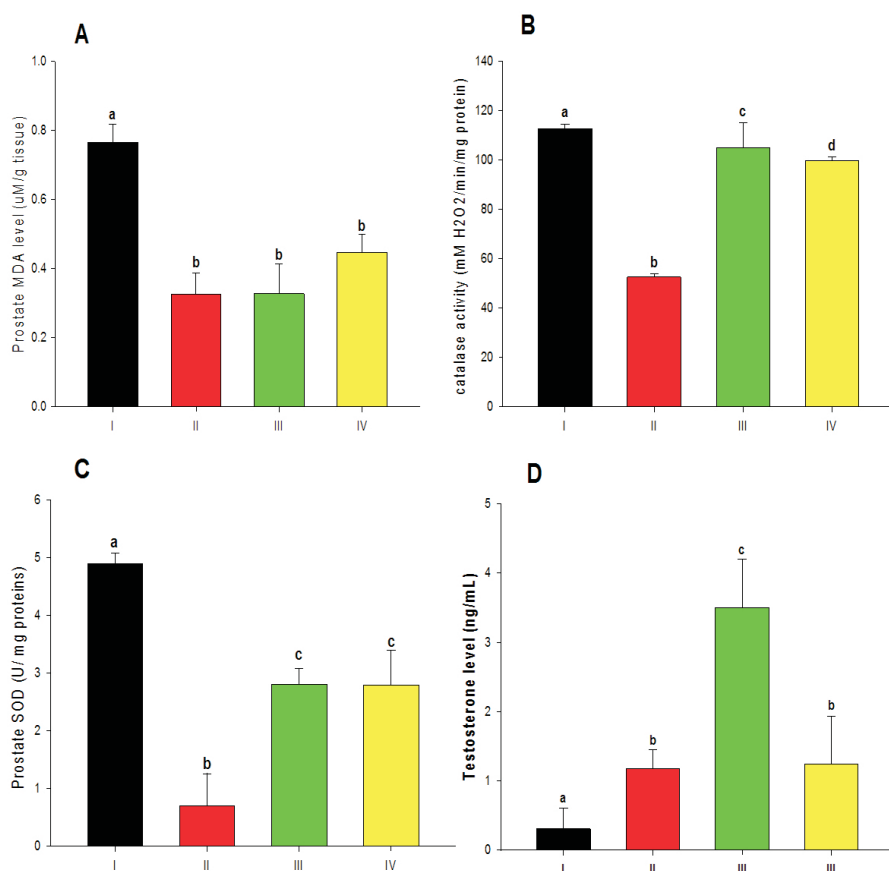


Fig. 1. Evaluation of prostate tissue oxidative stress biomarkers and blood hormonal analysis. A: Tissue malondialdehyde (MDA) levels; B: Catalase activity; C: superoxide dismutase activity (SOD); D: Testosterone levels. I: Aluminum chloride exposed group; II: Al and TAE group; III: Only TAE treated group; IV: Control group

believed to be the primary regulators of inflammatory diseases, since they play an important role in the growth of many tumours, including prostate cancer [18]. On the other hand, concomitant treatment with TAE at a dose of 200 mg/kg BW allowed an improvement of the body weight gain (Table 1), an increase in testosterone level (Fig. 1), and a reduction of apoptosis cells, and mast cell infiltration (Fig. 3). However, various studies have shown that *C. longa* has been shown to have a large range of biological effects including anti-inflammatory, antioxidant, and anticarcinogenic [6]. SOOD et al. [19] conclude that curcumin holds promise as an agent that can potentially mitigate Al-induced toxic effects in the brain by minimizing oxidative stress. Besides the antioxidant and anti-inflammatory effect of *C. longa*, research carried out by BENEDUCI et al. [20], reports that curcumin has a chelating effect on certain metals such as iron and aluminium, and it was

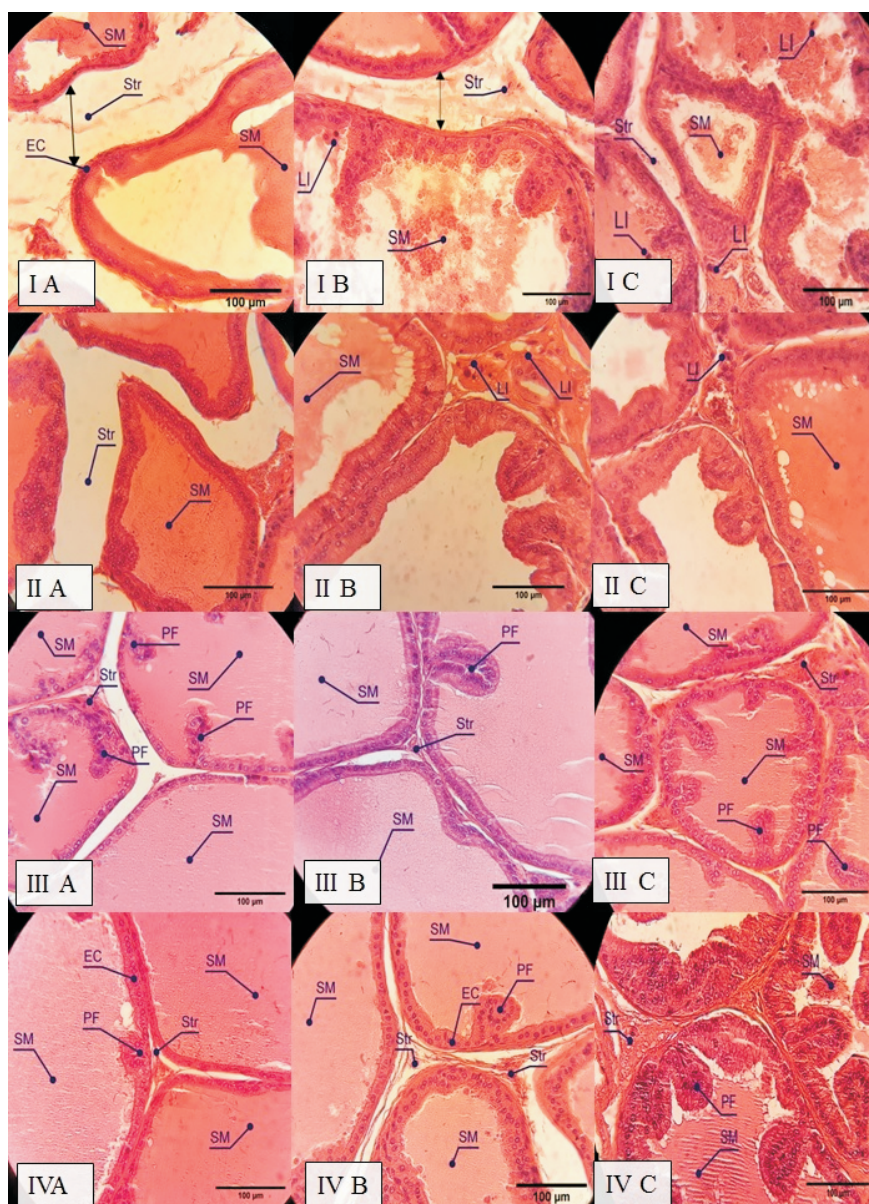


Fig. 2. Histological structure of prostate's lobes (A, B, and C are dorsal, lateral, and ventral lobes, respectively). H&E staining (G $\times 400$). Group I: Exposure to $AlCl_3$ caused multiple abnormalities: a reduction in the size of the acini (double-sided arrow), an attenuation of the epithelial mucosa membrane (EC), secretory alteration characterized by a weak secretory material (SM), and stromal degeneration (Str), with leukocytes infiltration (LI). Group II: Treatment with TAE reduced inflammation by reducing leukocyte infiltration (LI) and maintained normal secretory activity (SM). Groups III & IV: TAE and Control groups with normal appearance of the three prostatic lobes showing acini with significant secretory material (SM) activity. The dorsal lobe presents cuboidal to cylindrical epithelial cells (EC); the normal lateral lobe with a cuboidal epithelial mucosa (EC) and occasional papillary folds (PF); the ventral lobe with normal columnar epithelium with numerous folds (PF)

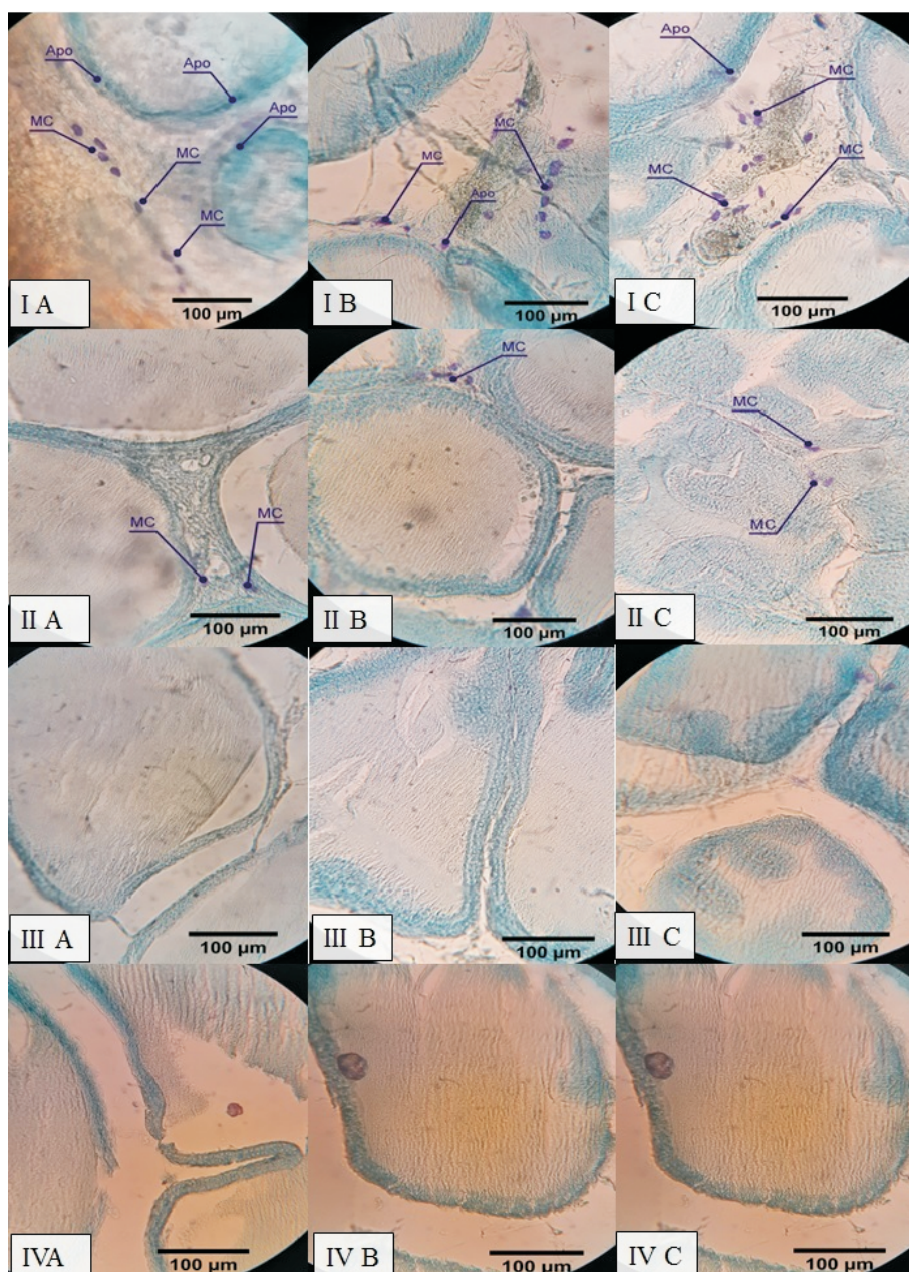


Fig. 3. Histochemical determination of apoptotic cells and mast cell infiltration in prostate's lobes (A, B, and C are dorsal, lateral, and ventral lobes, respectively). Toluidine blue staining ($G \times 400$). Group I: Exposure to $AlCl_3$ causes condensation of chromatin, characteristic of apoptosis state (Apo) and mast cell infiltration (MC). Group II: Treatment with TAE reduced the number of apoptotic cells and mast cell infiltration. Groups III & IV: TAE and Control groups show a normal appearance of the three prostatic lobes with no apoptotic cells or mast cell infiltration

found that Al binds to the keto-enol moiety of curcumin, while Fe binds to the guaiacol (2-methoxyphenol) one.

Conclusion. According to the findings of this study, subacute Al exposure may be responsible for major health concerns related to male reproductive function. Indeed, oral administration of Al to rats resulted in a decrease in testosterone levels, an increase in tissue oxidative stress markers, and a deterioration of the prostate's histological structure with an increase in apoptotic cells and prostate tissue inflammation. Nevertheless, it is important to note that the aqueous extract of turmeric is endowed with a strong anti-oxidant and anti-inflammatory power which explains its remarkable protective influence, against the harmful effects of Al by decreasing tissue oxidative stress, inflammation, induction of apoptosis, and improving the histological state of the prostate. Therefore, this plant should be considered a phytomedicine against reproductive disorders such as prostatitis.

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