Original Article – Andrology
Grand J Urol 2023;3(3):102-8
DOI: 10.5505/GJU.2023.62207

The Effect of Curcumin on Penile Fibrotic Plaque in Rats with Experimental Peyronie's Disease

Deneysel Peyronie Hastalığı Oluşturulan Ratlarda Kurkuminin Penil Fibrotik Plak Üzerine Etkisi

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Cite as: Ulubay M, Kaya A, Ahsen Kaplan A, Kubra Tufekci K, Akdeniz E, Kaplan S. The effect of curcumin on penile fibrotic plaque in rats with experimental peyronie's disease. Grand J Urol 2023;3(3):102-8

Submission date: 13 August 2023 **Acceptance date:** 28 August 2023 **Online first:** 03 September 2023 **Publication date:** 20 September 2023

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Abstract

Objective: No effective medical approach for the treatment of Peyronie's disease (PD) has to date been described. This study was intended to evaluate the antifibrotic, antioxidant, and anti-inflammatory effects of curcumin on fibrotic tissue in the tunica albuginea (TA) in a rat model of PD.

Materials and Methods: Twenty-four male Sprague Dawley rats aged 10 months were randomized into three groups (n = 8 in each). No PD model was induced in the control group. The PD+saline (PD+Ps) group received fibrin injection, followed two weeks later by saline administration by oral gavage for 14 days. The PD+Curcumin (PD+Cur) group received fibrin injection into the TA followed two weeks later by curcumin administration by oral gavage for 14 days. At the end of the experiment, fibrotic activity was evaluated using stereological and histopathological methods. Transforming growth factor-β1 (TGF-β1), one of the most fibrogenic cytokines, was evaluated using immunohistochemistry with an anti-TGF-β1 rabbit monoclonal antibody.

Results: Stereological analysis revealed significantly greater Peyronie-like plaque areas in the TA in the PD+Ps group than in the control and PD+Cur groups ($p<0.0001$). No significant difference was observed between the control and PD+Cur groups ($p=0.35$). The PD+Ps group exhibited strong TGF-β1 immunoreactivity with increased expression in the collagenous connective tissues and fibroblasts around the TA.

Conclusion: Curcumin reduced fibrotic tissue in the TA and may represent a novel therapeutic option in the treatment of PD.

Keywords: Peyronie's disease, curcumin, fibrin, antioxidant

Öz

Amaç: Bugüne kadar Peyronie hastalığı'nın (PH) tedavisi için etkili bir medikal tedavi tanımlanmamıştır. Bu çalışmada, deneysel olarak PH modeli oluşturulan ratların tunika albuginealarında (TA) oluşan fibrotik doku üzerine kurkuminin antiinflamatuar, antifibrotik ve antioksidan etkilerinin değerlendirmesi amaçlanmıştır.

Gereçler ve Yöntemler: On aylık 24 adet erkek Sprague Dawley cinsi rat, eşit bir şekilde üç gruba randomize edildi. Kontrol grubuna deneysel PH modeli uygulanmadı. PH+salin (PD+Ps) grubuna fibrin enjeksiyonu yapıldı ve ardından iki hafta sonra 14 gün boyunca oral gavaj ile salin verildi. PH+Kurkumin (PH+Kur) grubuna TA'ya fibrin enjeksiyonu yapılarak PH modeli oluşturuldu ve ardından iki hafta sonra 14 gün boyunca oral gavaj ile kurkumin verildi. Deneyin sonunda fibrotik aktivite stereolojik ve histopatolojik yöntemler kullanılarak değerlendirildi. En fibrojenik sitokinlerden biri olan Transforming büyüme faktörü-β1 (TGF-β1), tavşan monoklonal antikoru olan anti-TGF-β1 kullanılarak immünohistokimyasal olarak ölçüldü.

Bulgular: Stereolojik analizde PH+Ps grubunda, kontrol ve PH+Kur gruplarına göre anlamlı olarak TA'da daha fazla Peyronie benzeri plakların ortaya çıktığı görüldü ($p<0,0001$). Kontrol ve PH+Kur grupları arasında anlamlı fark izlenmedi ($p=0,35$). PH+Ps grubunda TA çevresindeki kollajenöz bağ dokularda ve fibroblastlarda güçlü TGF-β1 immün reaktivitesi izlendi.

Sonuç: Çalışmamızda kurkuminin TA'daki fibrotik dokuyu azalttığı görülmüştür. Bu nedenle kurkumin PH tedavisinde yeni bir terapötik seçenek olabilir.

Anahtar kelimeler: Peyroni hastalığı, kurkumin, fibrin, antioksidan

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Introduction

Peyronie's disease (PD) is a condition that progresses with fibrosis in the tunica albuginea (TA) layer of the penis and therefore causes penile pain, curvature, and sexual dysfunction. Despite being frequently seen, its aetiology and pathophysiology are not yet fully understood [1,2]. Factors such as trauma, frequency of sexual intercourse, diabetes mellitus, Dupuytren's contracture, family history, gout, plantar facial contracture, radical prostatectomy, tympanosclerosis, Paget's disease, beta-blocker use, advancing age, genetic predisposition, smoking, hypertension, and tissue ischemia may play a role in the aetiology [1,3,4]. The most widely accepted theory involves abnormal collagen and glycosaminoglycan deposition in the TA after inflammation and fibroblast proliferation caused by repetitive microtraumas. Abnormal extracellular matrix production also occurs through increased myofibroblast activity and upregulation of tissue inhibitors of matrix metalloproteinases [2]. The prevalence of PD ranges from 3.2% to 8.9%, with patients being typically aged 50-60 years [5].

PD includes two phases, acute (inflammatory) and chronic (stable). The acute inflammatory phase usually lasts 6-18 months and is characterized by painful erections, the formation of a palpable nodule or plaque in the tunica of the penis and penile curvature. When the lesions stabilize, the chronic phase begins and the penile deformity stabilizes, inflammation decreases, pain improves, and erectile dysfunction symptoms develop [2]. Research has reported that the course of the disease remains stable in 47% of patients and resolves spontaneously in 13%. However, the manifestation worsens in 40% of patients, and these require active treatment [6].

Despite the many alternative treatments (antifibrotic, anti-inflammatory, antioxidant drugs, various vitamins, amino acids, etc.) available in addition to surgical treatment since Francois de la Peyronie's definition of PD in 1743, no entirely satisfactory therapeutic option has still been discovered [1]. Curcumin is a yellow-orange substance obtained from the roots of the plant turmeric. It has occupied an important place in Asia for thousands of years, especially in Indian medicine, and has been the focus of scientific studies for the last 20 years. Studies have shown that curcumin possesses strong antioxidant, anti-inflammatory, antiapoptotic and antidiabetic properties. In addition to its antifibrotic property, it has also been reported to exhibit an antiproliferative effect on fibroblasts. Studies have also observed the protective effects of curcumin on pulmonary, cardiac, and renal fibrosis [7]. Considering that PD is associated with diabetes mellitus at a rate of 18-33%, the antidiabetic effect of curcumin suggests that it may be an important substance in terms of the treatment of the disease [4].

In light of this information, curcumin is worthy of note as a potential therapeutic agent capable of use in the treatment of PD. The purpose of this study was aimed to examine the efficacy of curcumin against abnormal fibrous tissue production in the TA using stereological, histopathological, and immunohistochemical methods. We think that the results obtained will be useful for the development of novel medical methods for the reduction or prevention of penile fibromatosis. This is the first experimental study in the literature to investigate the effects of curcumin in an experimental rat PD model.

Material and Methods

Animals

The experimental protocol adopted in the current study was approved by the Ondokuz Mayıs University, Animal Care and Ethics Committee (HADYEK no. 2018-29-dated 25.05.2018). The animals were obtained from the Experimental Animals Surgical Research and Application Centre of Ondokuz Mayıs University, Samsun, Turkey. Twenty-four male Sprague Dawley rats (weighing 250-300 g, aged 10 months) were divided into three equal groups. The rats were housed instainless-steel cages under a 12-h light/12-h dark cycle at a room temperature of 22±2°C with humidity of 50%±10 in the laboratory. Free access was allowed to food and water. The rats were cared for as specified by the guidelines related to the care and use of laboratory animals issued by the U.S. National institutes of Health (NIH Publication No. 85-23, revised 2011) [8]. This study was also conducted in conformity with the ARRIVE animal experiments guideline [9].

Peyronie's Disease Model

Physiological saline solution was injected into the TA of the rats in the control group. In the PD+saline (PD+Ps) group, 30 µL of fibrin (TISSEELVH Sealer; Baxter, Glendale, CA, USA; 30 uL each of human fibrin and thrombin solution) was injected into the TA in order to induce the formation of Peyronie-like fibrous plaques of rats, two weeks after which, saline solution was administered for 14 days by oral gavage [10]. In the PD+Curcumin (PD+Cur) group, 30 µL of fibrin was injected into the TA, two weeks after which curcumin was administered by oral gavage for 14 days [11]. Curcumin was obtained from Sigma-Aldrich Company (Sigma Aldrich, USA, Catalog number: BD9137). Curcumin was given as 30 mg/kg per day, similar to study of Huyut et al., which investigating the effects of curcumin on liver fibrosis [12]. The bioavailability of curcumin is poor due to its rapid metabolism. It has therefore been used by dissolving it in olive oil to increase oral and gastrointestinal absorption and to reduce clearance from the body in previous research [13]. At the end of the experimental procedure, all rats were anesthetized with intramuscular ketamine (50 mg/kg)/xylazine (10 mg/kg) and subjected to transcardiac perfusion. The penile tissues were removed and examined using stereological, histopathological, and immunohistochemical methods.

Tissue Preparation

Tissue samples were subjected to routine histological tissue processing and embedded in paraffin for stereological and immunohistochemical analysis. The penile tissue of one rat from each group was embedded in resin blocks for electron microscopic analysis.

Stereology

For stereological analysis, sections 5 µm in thickness were taken using the systematic random sampling method and stained with Masson's trichrome to determine histometric changes.

Images were captured at 40x magnification under a microscope with a camera attachment for the analysis of plaque areas in the TA. The fibrous plaque surface areas were estimated using the planimetry method of the Cavalieri principle on Image J (Image Processing and Analysis in Java, NIH, USA) software. Coefficient of error (CE) and coefficient of variation (CV) values were calculated to determine whether the number of animals per group and sampling intervals were appropriate for each animal.

Histopathology

Semi-thin sections (500 nm) were taken from the resin blocks for light microscopic examination and stained with 1 % toluidine blue. Images were captured at 10x, 40x and 100x magnification for histopathological evaluation. Thin (70 nm) sections were also taken from the resin blocks for electron microscopic examination and stained with 0.5 % uranyl acetate and 3% lead citrate (Leica Ultrostain II). After staining, the sections were examined ultrastructurally under a transmission electron microscope (JEOLJSM-7001F, Japan).

Immunohistochemistry

For immunohistochemical evaluation, 5 µm-thick sections from each group were placed onto positively charged slides. Sections were immunestained for transforming growth factor-β1 (TGF-β1) to determine whether fibrin injection induced TGF-β1 expression and formed a Peyronie-like fibrous plaque in the TA. TGF-β1 was evaluated by immunohistochemical analysis with an anti-TGF-β1 rabbit monoclonal antibody (1:100; Abcam). Sections were cross-stained with Mayer's hematoxylin. Immunohistochemical staining was performed by the Department of Pathology at Ondokuz Mayıs University.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 9.0 software (GraphPad, CA, USA). All data are presented as mean ± standard error of the mean. The data were found to be normally distribution using the Shapiro-Wilk normality test. A p values less than 0.05 were considered statistically significant and all groups were analyzed using One-way ANOVA.

Results

Stereology

When all three groups had been evaluated in terms of Peyronie-like plaque areas in the TA, the plaque area in the PD+Ps group was significantly higher than those in the Control and PD+Cur groups ($p<0.0001$). However, no significant difference was observed between the Control and PD+Cur groups ($p=0.35$) (**Figure 1**).

Histopathology

Light microscopic images taken from semi-thin (500 nm) sections were evaluated to determine morphological changes between groups. The histological structure of the tissue was

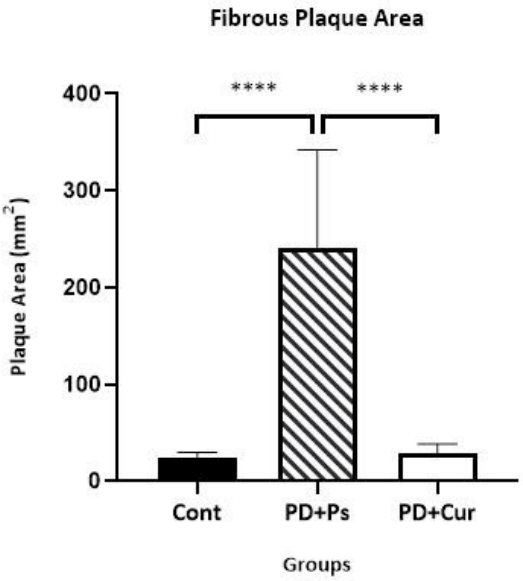

Figure 1. A statistical comparison of fibrous plaque areas induced by fibrin injection in TA between three study groups. Plaque areas were expressed as mean±standard deviation. Significant differences at the level of p <0.0001 between the groups are indicated by (****)

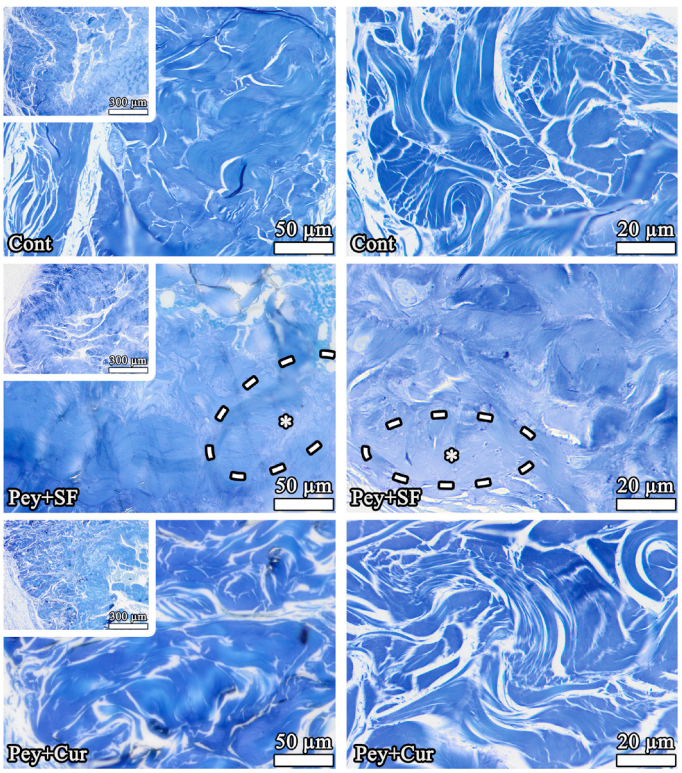

Figure 2. Light microscopic images of semi-thin sections from all groups. The TA and corpus cavernosum parts of the penile tissue are seen at small magnification (x10). The histological structure of the tissue is normal in the control group. Plaque structures were remarkable in the high magnification (x40 and x100) images of the TA in the PD+Ps group. Morphology is similar to that of the control group can be seen in the images from the PD+Cur group. Sections were stained with toluidine blue. Asterix (*); plaque.

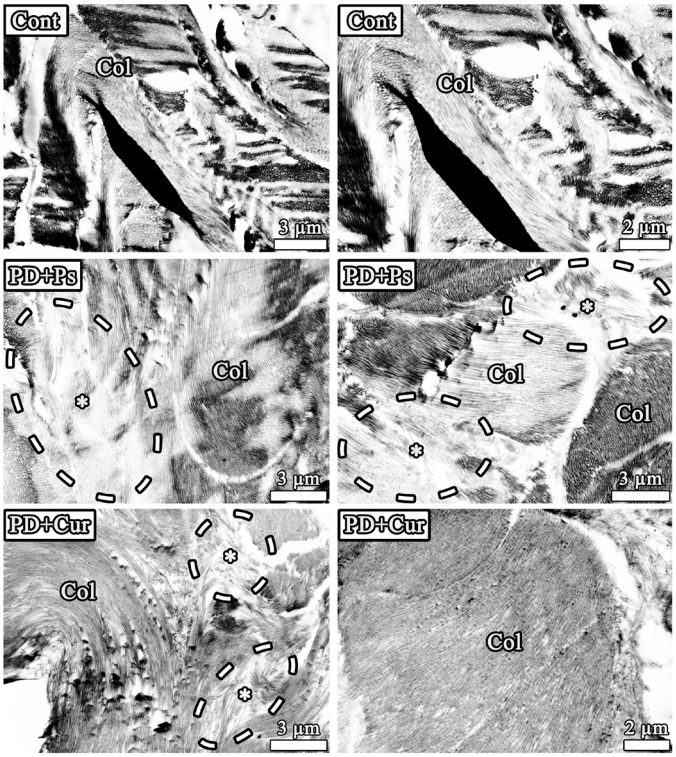

Figure 3. Electron microscopic images of the penis taken from three groups that are the Cont, PD+Ps and PD+Cur groups were seen. Tunica albuginea of the Cont group has a normal structure in that collagen fibres (Col) are organised as parallel and compact in the fascicules. In the PD+Ps group, the uniformity of collagen bundles in the tunica albuginea region was seriously impaired. In most of the areas, there are no collagen fibres in the dashed line (*) or a very weak arrangement is observed. In the PD+Cur group, although some regions have a non-collagenous area (*), most places in the tunica albuginea have a well-organised collagen (Col) fibres.

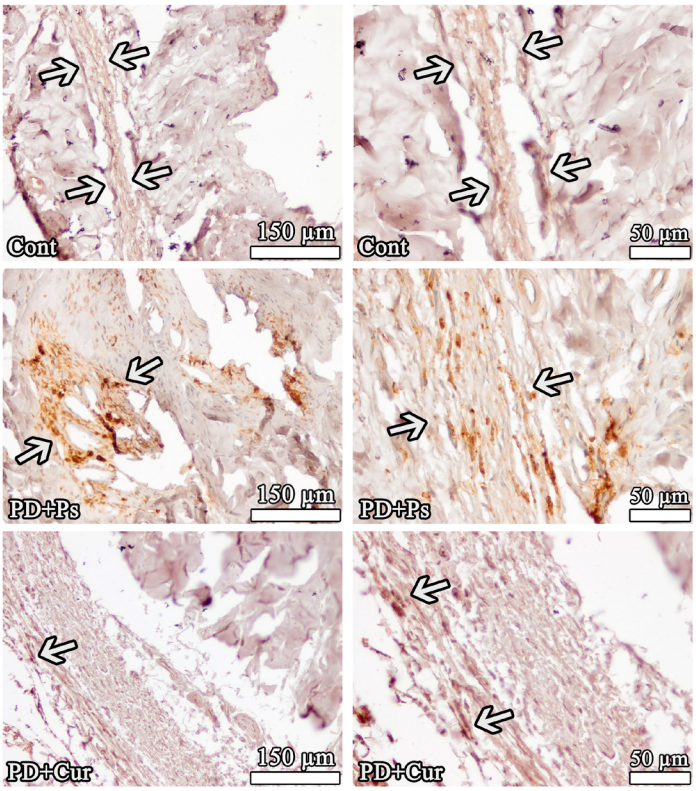

Figure 4. Immunohistochemical staining for TGF-β1 in all groups. In the control group, opposed arrows indicate the presence of non-severe staining. In the PD+Ps group, severe TGF-β1 expression was observed in Peyronie-like plaques extending over a wide area in the TA. Very slight staining can be seen in the areas at the ends of the arrows in the PD+Cur group. Sections were cross-stained with Mayer's hematoxylin. Arrows; TGF-β1 expression.

normal in the Control and PD+Cur groups, whereas abundant Peyronie-like fibrous plaques were observed in the PD+Ps group (**Figure 2**).

Electron Microscopy

Thin sections of penis tissues from the animals, the Control, the PD+Ps, and the PD+Cur groups were examined by electron microscopy. The collagen fibres in TA of the Control group have a well-organised arrangement; there is no interruption of the fibres in their tunica. In the PD+Ps group, most area in the TA lost its collagen fibres, for this reason many of area in the tissue are observed as white area i.e. plaque structures. In this group, it is hard to see fasciculation of collagen fibres in the TA since pronounced collagen degeneration and formation of plaque structures. In the PD+Cur group, collagen fibres of TA are well protected after curcumin treatment except few areas in the tissue and these areas would be evaluated as plaque structures. Protective effects of curcumin in this group were observed since parallel arrangement of collagen fibers are found in the tissue (**Figure 3**).

Immunohistochemistry

Sections were immunostained for TGF-β1 expression in the TA. Positive areas for TGF-β1 were negligible in the Control and PD+Cur groups, but severe staining was observed in the PD+Ps group (**Figure 4**).

Discussion

PD was once considered a rare entity but is now known to be more common. Although the etiology of the disease is not fully understood, it is thought to be related to trauma resulting in abnormal wound healing [1].

Various different therapeutic modalities are recommended for PD, including both conservative (oral, topical, and intralesional treatments) and invasive (surgical) measures [1]. Surgical repair is usually performed in the form of penile plication, penile prosthesis, penile plate incision, or excision in men with significant stable penile curvature after the

failure of conservative treatment approaches. Risk factors for these procedures typically include penile shortening, erectile dysfunction, and penile numbness. If the primary goal in the treatment of the disease is to correct the curvature, surgery continues to represent the gold standard [1,13]. Surgery should be avoided in the acute inflammatory phase of PD due to the risk of disease progression and recurrence of the curvature [3,14].

Conservative approaches in the treatment of PD include oral agents such as vitamin E, tamoxifen, colchicine, procarbazine, omega-3 fatty acids, potassium para-aminobenzoate (potaba), nonsteroidal anti-inflammatory drugs, L-carnitine, phosphodiesterase type 5 inhibitors, and pentoxifylline. Topical therapies include extracorporeal shockwave treatment (ESWT), topical verapamil, H-100 gel and intralesional treatments such as verapamil, nicardipine, interferon α2B, collagenase clostridium histolyticum (CCH), and hyaluronic acid and botulinum toxin. However, except for intralesional CCH, none has demonstrated a reliable and definitive clinical benefit [1].

CCH is the first Food and Drug Administration (FDA)-approved injectable drug and can be considered a reasonable alternative for patients who are unwilling to undergo surgical treatment [15]. Intralesional collagenase injection has been reported to significantly reduce plaque size and penile curvature. However, there is no evidence that it improves penile pain or erectile dysfunction. Side effects reported in the literature include ecchymosis, swelling, corporal rupture and hematoma related to the use of collagenase [16].

Stem cell and platelet-rich plasma applications are recently developed non-invasive therapeutic options, and promising results have been reported. However, despite their promising potential, their clinical efficacy has not yet been proven. Numerous randomized clinical studies investigating their long-term effects are therefore needed [17-19].

Plant-derived products have become increasingly popular in recent years as an alternative to traditional medicines. Phytochemicals isolated from plants are characterized by numerous biological activities, primarily anti-inflammatory in nature. Curcumin, also known as diferuloylmethane, is a lipophilic polyphenol derived from the roots of Curcuma longa (turmeric). It has been widely used in traditional Asian medicine for thousands of years for its anti-inflammatory and wound-healing properties [20]. Curcumin is a compound considered "generally safe" by the FDA. The source of the pharmacological effects of turmeric is mainly bioactive curcuminoids, which include curcumin, demetoxycurcumin, and bisdemethoxycurcumin [21,22].

Curcumin is known to exhibit numerous properties, such as antioxidant, anti-inflammatory, anti-diabetic, anti-apoptotic and anti-fibrotic activities. Recent studies suggest that curcumin modulates different molecular pathways by acting on various cytokines, transcription factors, growth factors and their associated receptors, thus playing a protective role against cardiac fibrosis [7,23,24]. Curcumin treatment has been reported to reduce inflammatory cells and improve collagen deposition in animal models [25,26]. It has also been observed to be capable of ameliorating pulmonary fibrosis, characterized by infiltration of inflammatory cells, fibrotic tissue deposition and increased collagen content [27].

The normal histological structure of the TA surrounding the penile corpora cavernosa consists of an inner circular and an outer longitudinally arranged elastin and collagen network. In the pathophysiology of PD, tissue healing is impaired leading to scarring through collagen deposition and decreased elastin, possibly due to acute or repetitive penile trauma [1,28]. In the healing process of impaired tissue, repetitive traumas to the TA cause an increase in pro-fibrotic factors such as TGF-β1 and platelet-derived growth factor and a decrease in anti-fibrotic factors [29]. TGF-β1 plays a role in soft tissue fibrosis and erectile dysfunction. It is synthesized as an inactive peptide by various cell types including platelets, macrophages, and fibroblasts. When activated, it binds to specific cell surface receptors, resulting in increased connective tissue synthesis and inhibition of collagenases [29,30].

Stereological analyses in the present study revealed that the numerical data for fibrous plaque areas in the control and PD+Cur groups were close to one another, although there was a significant difference between them and the PD+Ps group. Electron microscopic evaluation of the tissues taken from the groups supported the stereological analysis, since few number of plaque structures in the PD+Cur group in comparison of the PD+Ps group. Immunohistochemical analyses revealed intense TGF-β1 expression in the PD+Ps group. In contrast, a small amount of positive staining was observed in the TA in the PD+Cur group. In light of all these data, it may be concluded that curcumin may play a potential role in the treatment of PD by exhibiting anti-fibrotic activity.

Conclusion

Pharmacotherapeutic approaches are not yet effective or widely accepted in the treatment of PD. Surgical removal of plaque or the installation of penile prostheses continues to be considered the mainstay of treatment. Curcumin, a plant-derived compound, reverses the effect of pro-fibrotic factors by affecting the expression and activation of various intracellular molecules. Curcumin treatment in this study reduced TA fibrosis in an experimentally induced rat PD model. Our results suggest that curcumin may represent a new oral therapeutic option in the treatment of PD. Although our findings are promising and suggest a possible oral medical treatment for PD, further studies are needed on the subject.

Acknowledgements: We would like to thank to our lab technician who is Huseyin Saricaoglu for his helps during tissue processing. We also thank native English speaker Carl Nino Rossini for his excellent language revision.

Ethics Committee Approval: The experimental protocol adopted in the current study was approved by the Ondokuz Mayıs University, Animal Care and Ethics Committee (HADYEK no. 2018-29-dated 25.05.2018).

Informed Consent: An informed consent was obtained from all the patients.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – M.U., A.K.; Design – M.U., A.K.; Supervision – M.U., A.K.; Resources – A.A.K., K.K.T., E.A.; Materials – A.A.K., K.K.T., E.A.; Data Collection and/or Processing – A.A.K., K.K.T., E.A.; Analysis and/or Interpretation

– M.U., A.K.; Literature Search – A.A.K., K.K.T., E.A.; Writing Manuscript – M.U., A.K.; Critical Review – M.U., S.K.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declare that this study received no financial support.

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