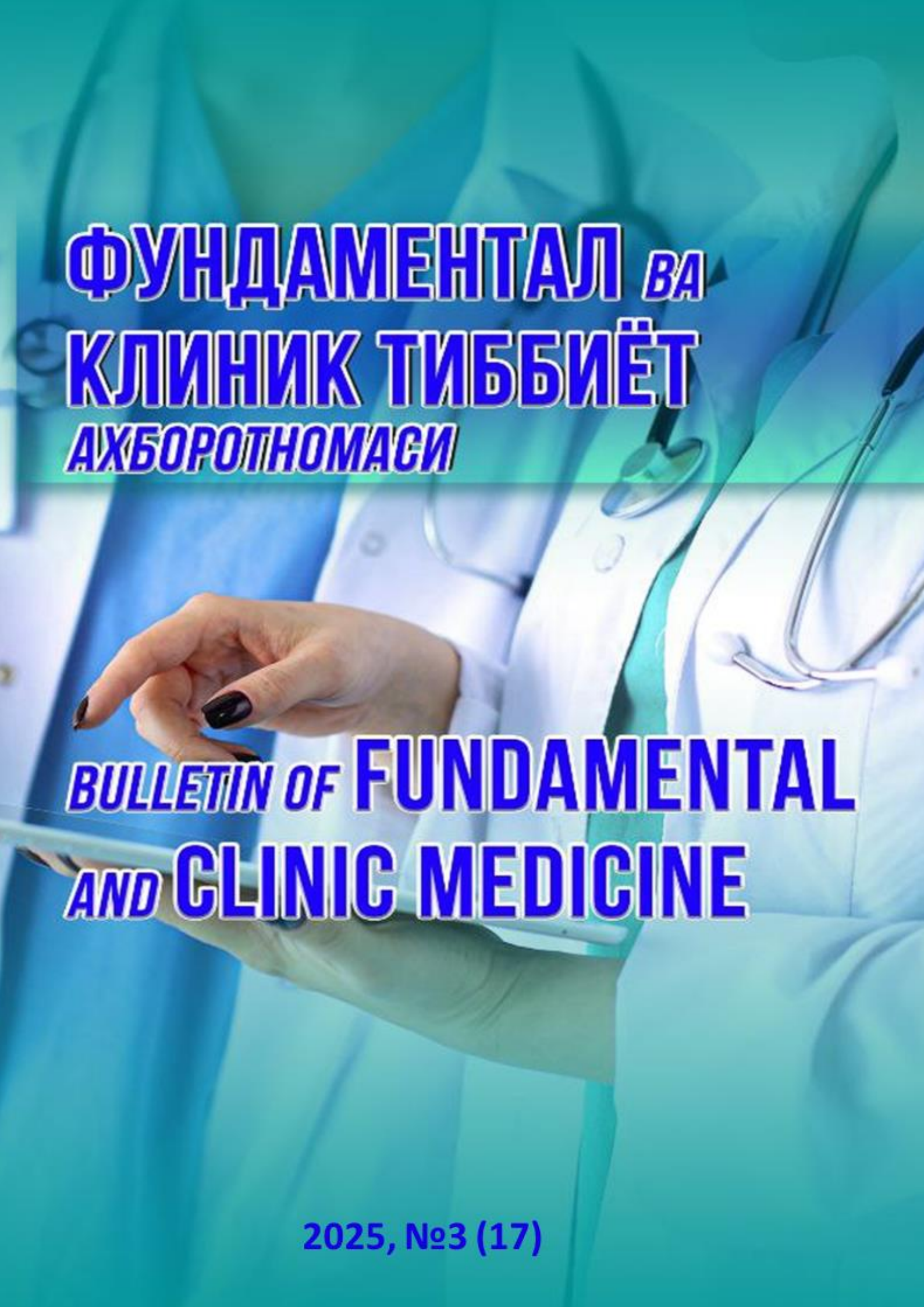

ФУНДАМЕНТАЛ ВА КЛИНИК ТИББИЁТ АХБОРОТНОМАСИ

BULLETIN OF FUNDAMENTAL AND CLINIC MEDICINE

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THERAPEUTIC EFFECTS OF FERULA MOSCHATA ROOT ON TESTICULAR CHANGES IN MALE RATS AGED 3, 6, AND 9 MONTHS WITH CHRONIC KIDNEY DISEASE

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Resume. *Chronic kidney disease (CKD) is a progressive pathological condition often accompanied by dysfunction of the reproductive system, including testicular atrophy and impaired spermatogenesis. This study investigates the morphometric and morphological changes in the testes of male white albino rats with experimentally induced chronic kidney failure and evaluates the potential corrective effects of ferula moschata (sumbul root) extract. The study was conducted on 140 white albino rats divided into three age groups: 3, 6 and 9 months. Within each age group, animals were subdivided into control, CKD model, and treatment subgroups. Chronic kidney failure was induced using standard nephrotoxic agents. The treatment groups received sumbul root extract over a defined period. Testes were collected for gross anatomical, histological, and morphometric analyses. Parameters such as testis weight, capsule thickness, seminiferous tubule diameter and area, and epitheliospermatogenic layer thickness were measured. The ratio of epithelial layer to lumen was also calculated. In untreated CKD rats, significant atrophic changes were observed in testicular tissues, including reduced seminiferous tubule diameter, thinning of the spermatogenic layer, and decreased organ weight. Administration of sumbul root extract in 3-month-old rats showed marked restoration of testicular structure and morphometric indices close to control values. The therapeutic effect was moderate in 6-month-old rats and limited in 9-month-old animals, reflecting an age-dependent regenerative response. Sumbul root extract demonstrates age-dependent therapeutic potential in reversing CKD-induced testicular damage. Early intervention yields more pronounced morphofunctional recovery, suggesting its promise as a phytotherapeutic agent in CKD-related gonadal dysfunction.*

Keywords: *Chronic kidney disease, testicular morphology, morphometry, ferula mochata, sumbul root extract, seminiferous tubules, spermatogenesis, rat model, age-dependent regeneration, phytotherapy.*

SURUNKALI BUYRAK YETISHMOVCHILIGI BILAN KASALLANGAN 3, 6 VA 9 OYLIK ERKAK KALAMUSHLARDA SUMBUL ILDIZINING MOYAK O‘ZGARISHLARIGA NISBATAN TERAPEVTIK TA’SIRI

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Rezyume. *Surunkali buyrak yetishmovchiligi (SBY) — bu odatda jinsiy tizimning buzilishi, shu jumladan moyaklarning atrofiyasi va spermatogenezning buzilishi bilan kechadigan progres-siv patologik holatdir. Ushbu tadqiqotda tajriba yo‘li bilan surunkali buyrak yetishmovchiligi chaqirilgan erkak oq albinos kalamushlarning moyaklarida yuz beradigan morfometrik va morfologik o‘zgarishlar hamda sumbul ildizi (Ferula moschata) ekstraktining davolovchi ta’siri o‘rganildi. Tadqiqot 140 ta oq zotsiz kalamushlarda o‘tkazildi. Ular 3, 6 va 9 oylik bo‘lgan uch yosh guruhiga bo‘lindi. Har bir yosh guruhida kalamushlar nazorat, SBY modeli va davolovchi kichik guruhlarga ajratildi. Surunkali buyrak yetishmovchiligi standart nefrotoksik vositalar yordamida chaqirildi. Davolovchi guruhlarga ma’lum muddat davomida sumbul ildizi ekstrakti berildi. Moyaklar umumiy anatomik, gistologik va morfometrik tahlil uchun yig‘ildi. Moyak vazni, kapsula qalinligi, urug‘ yo‘llari diametri va yuzasi, epiteliy-spermatogen qatlam qalinligi kabi ko‘rsatkichlar o‘lchandi. Shuningdek, epiteliy qatlami va kanalcha bo’shlig’i nisbati ham hisoblandi. Davolanmagan SBY kalamushlarida moyak to‘qimalarida sezilarli atrofik o‘zgarishlar aniqlandi: urug‘ yo‘llari diametrining kichrayishi, spermatogen qatlamning yupqalashuvi va a’zoning og‘irligining kamayishi kuzatildi. 3 oylik kalamushlarda sumbul ildizi ekstrakti qo‘llanilganda moyak tuzilmasi va morfometrik ko‘rsatkichlar sezilarli darajada tiklandi va nazorat guruhiga yaqinlashdi. 6 oylik kalamushlarda davolovchi ta’sir o‘rtacha darajada bo‘ldi, 9 oylik kalamushlarda esa cheklangan ta’sir kuzatildi, bu esa yoshga bog‘liq regenerativ javobni aks ettiradi. Sumbul ildizi ekstrakti SBY natijasida yuzaga kelgan moyak shikastlanishini bartaraf etishda yoshga bog‘liq terapevtik salohiyatni namoyon etadi. Erta boshlangan muolaja morfofunktsional tiklanishni kuchliroq namoyon qiladi, bu esa uni SBY bilan bog‘liq jinsiy bez faoliyatining buzilishida istiqbolli fitoterapevtik vosita sifatida ko‘rsatadi.*

Kalit so‘zlar: *Surunkali buyrak yetishmovchiligi, moyak morfologiyasi, morfometriya, Ferula moschata, sumbul ildizi ekstrakti, urug‘ yo‘llari, spermatogenez, kalamush modeli, yoshga bog‘liq regeneratsiya, fitoterapiya.*

ТЕРАПЕВТИЧЕСКОЕ ВЛИЯНИЕ КОРНЯ FERULA MOSCHATA НА ИЗМЕНЕНИЯ ЯИЧЕК У САМЦОВ КРЫС В ВОЗРАСТЕ 3, 6 И 9 МЕСЯЦЕВ С ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК

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Резюме. *Хроническая болезнь почек (ХБП) — это прогрессирующее патологическое состояние, часто сопровождающееся нарушениями репродуктивной системы, включая атрофию яичек и ухудшение сперматогенеза. В данном исследовании изучены морфометрические и морфологические изменения в яичках самцов белых альбиносных крыс с экспериментально вызванной ХБП, а также оценены возможные коррегирующие эффекты экстракта корня сумбул (Ferula moschata). Исследование проводилось на 140 белых альбиносных крысах, разделённых на три возрастные группы: 3, 6 и 9 месяцев. Внутри каждой возрастной группы животные были распределены на подгруппы: контрольную, модель ХБП и лечебную. Хроническая почечная недостаточность вызывалась с использованием стандартных нефротоксических агентов. Лечебные группы получали экстракт корня сумбула в течение установленного периода. Яички собирались для макроскопического, гистологического и морфометрического анализа. Измерялись такие параметры, как масса яичек, толщина капсулы, диаметр и площадь семенных канальцев, а также толщина эпителие-сперматогенного слоя. Также рассчитывалось соотношение эпителия к просвету. У нелеченых крыс с ХБП были выявлены значительные атрофические изменения в тканях яичек: уменьшение диаметра семенных канальцев, истончение сперматогенного слоя и снижение массы органа. Введение экстракта корня сумбула 3-месячным крысам показало выраженное восстановление структуры яичек и морфометрических показателей, приближённых к значениям контрольной группы. У 6-месячных крыс терапевтический эффект был умеренным, а у 9-месячных — ограниченным, что свидетельствует о возрастной зависимости регенеративного ответа. Экстракт корня сумбула демонстрирует возрастозависимый терапевтический потенциал в устранении поражений яичек, вызванных ХБП. Раннее вмешательство способствует более выраженному морфофункциональному восстановлению, что делает его перспективным фитотерапевтическим средством при нарушениях гонадной функции, связанных с ХБП.*

Ключевые слова: *Хроническая болезнь почек, морфология яичек, морфометрия, ферула мускусная, экстракт корня сумбула, семенные канальцы, сперматогенез, модель на крысах, возрастозависимая регенерация, фитотерапия.*

Introduction. Chronic kidney disease (CKD) represents a significant and escalating global health concern, currently affecting over 850 million individuals worldwide, equating to approximately 10% of the global population. Projections indicate that CKD will ascend to become the fifth leading cause of mortality by 2040. The disease's progression is often insidious, leading to end-stage renal failure and necessitating dialysis or transplantation. Beyond renal implications, CKD exerts systemic effects, notably impairing the reproductive system. In males, CKD is associated with hypogonadism, reduced testosterone levels, and compromised spermatogenesis, culminating in diminished fertility [17].

The pathophysiological mechanisms underpinning CKD-induced testicular dysfunction are multifaceted, encompassing hormonal imbalances, oxidative stress, and uremic toxin accumulation. These factors collectively disrupt the hypothalamic-pituitary-gonadal axis and directly impair testicular architecture and function. Given the limitations and side effects associated with conventional therapies, there is a burgeoning interest in exploring alternative and adjunctive treatments.

Chronic kidney disease (CKD) is frequently associated with systemic complications, including oxidative stress-induced testicular injury, leading to impaired reproductive function (Amini et al., 2019). Testicular damage in CKD is largely attributed to increased reactive oxygen species (ROS) and inflammation, which compromise spermatogenesis and hormonal balance (Gomes et al., 2021).

Ferula moschata, commonly known as Sumbul, is a medicinal plant traditionally used in Asian and Middle Eastern medicine for its anti-inflammatory, antioxidant, and adaptogenic properties (Singh et al., 2017). The root extract of *Ferula moschata* contains bioactive compounds like ferulic acid, coumarins, and

sulfur-containing constituents, which have demonstrated potent free radical scavenging activity (Kumar et al., 2018).

Recent experimental studies have explored *Ferula moschata* root's therapeutic potential in mitigating testicular oxidative damage induced by CKD. For instance, Patel et al. (2020) reported that administration of *Ferula moschata* root extract in CKD-induced rats significantly reduced lipid peroxidation and enhanced antioxidant enzymes such as superoxide dismutase (SOD) and catalase in testicular tissue. This antioxidative mechanism contributed to the preservation of seminiferous tubule architecture and improved sperm parameters.

Moreover, the anti-inflammatory effects of *Ferula moschata* may counteract cytokine-mediated testicular injury seen in CKD. According to Zhang et al. (2019), the root extract inhibits pro-inflammatory markers such as TNF-α and IL-6 in chronic inflammatory models, potentially attenuating testicular fibrosis and apoptosis in CKD contexts.

Although clinical data are limited, these preclinical findings support the promise of *Ferula moschata* root as a protective agent against CKD-associated testicular damage by alleviating oxidative stress and inflammation.

Chronic kidney disease (CKD) is a progressive condition characterized by a gradual decline in kidney function, leading to end-stage renal failure if left untreated. In experimental models, CKD has been induced through various methods, such as 5/6 nephrectomy, which involves the surgical removal of a significant portion of kidney tissue, leading to renal insufficiency [24].

The pathophysiology of CKD encompasses a range of systemic effects, including alterations in reproductive health. Studies have demonstrated that CKD can adversely affect testicular morphology and function. For instance, histological examinations have revealed changes in seminiferous tubules, reduced spermatogenesis, and alterations in hormone levels in CKD models [25].

Ferula species, particularly Ferula mochata, have been utilized in traditional medicine for their purported therapeutic properties. Phytochemical analyses have identified compounds such as ferulic acid and sesquiterpene coumarins in Ferula species, which exhibit antioxidant and anti-inflammatory activities. These bioactive compounds are believed to mitigate oxidative stress and inflammation, which are pivotal in the progression of CKD [26].

In the context of reproductive health, Ferula extracts have shown promising results. For example, studies on Ferula assa-foetida have indicated improvements in sperm parameters and testicular structure in diabetic rats. Similarly, Ferula rigidula extract has been evaluated for its effects on sperm parameters and testicular structure in male rats under experimental diabetic conditions [28].

These findings suggest that Ferula extracts possess potential therapeutic properties that could be beneficial in managing CKD-induced reproductive dysfunctions. However, there is a paucity of research specifically examining the effects of Ferula mochata root extract on testicular morphology in CKD models. This gap in the literature underscores the need for targeted studies to elucidate the efficacy of Ferula mochata in ameliorating CKD-induced testicular alterations [27].

Materials and Methods. Male Wistar white rats (Rattus norvegicus) of three age groups—3 months (n=16), 6 months (n=17), and 9 months (n=17)—were used in this study. Animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature (22±2°C), and ad libitum access to food and water. All experimental procedures complied with institutional ethical guidelines for animal care and use. CKD was induced following the protocol adapted from Noskova A.P. (1981) and Borisova I.V. et al. (2004) utilizing the glycerol-induced nephrotoxicity model. Rats were fasted for 24 hours, then administered intramuscular injections of 50% aqueous glycerol solution at a dose of 0.8 ml per 100 g body weight, divided equally between the right and left hind limbs to minimize complications. Animals were monitored for lethargy and weight loss, typical of CKD progression. Histopathological confirmation of kidney damage was performed to validate model induction.

Dried roots of *Ferula mochata* were finely powdered. For extract preparation, specific doses of dry root powder were soaked in 100 ml of hot distilled water (80°C) and allowed to infuse for 15–20 minutes. The resulting aqueous decoction was filtered and administered orally to animals via a metal gavage tube. Dosing was based on body weight and age group, with daily dosages calculated as follows:

- 3-month-old rats: 5 g dry root powder per 100 ml water
- 6-month-old rats: 7 g dry root powder per 100 ml water
- 9-month-old rats: 10 g dry root powder per 100 ml water

Each rat received 3 divided doses per day, corresponding to 1.5 ml, 2 ml, and 2.5 ml per administration for 3-, 6-, and 9-month groups respectively. Treatment continued for 6 to 8 weeks.

Rats were divided into three main groups for each age category:

1. **Control group:** Healthy rats without CKD or treatment
2. **CKD group:** Rats with glycerol-induced CKD, no treatment
3. **Treatment group:** CKD rats receiving Ferula mochata root extract

At the end of the treatment period, animals were euthanized under anesthesia. Testes were carefully excised, weighed, and fixed in 10% neutral buffered formalin for 24 hours. After fixation, samples were washed in running water for 1 hour to remove formalin residues.

Testicular tissues were dehydrated through graded ethanol series, cleared in xylene, and embedded in paraffin blocks following standard protocols. Serial sections of 4–6 μm thickness were cut using an MC-2 rotary microtome. Sections were stained with hematoxylin and eosin (H&E) for general morphology and Van Gieson staining for connective tissue assessment.

Microscopic analysis was performed using a calibrated light microscope equipped with an image analysis system. Parameters measured included:

- Diameter of seminiferous tubules
- Cross-sectional area of seminiferous tubules
- Thickness of the epithelium of the spermatogenic layer
- Diameter of the tubular lumen
- Ratio of epithelial thickness to lumen diameter

At least 10 randomly selected tubules per section were measured per animal. Data were expressed as mean ± standard deviation.

All data were analyzed using SPSS software version 22.0. Differences between groups were assessed by one-way ANOVA followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant.

Results. The effects of *Ferula mochata* root extract on the morphometric and morphological parameters of testes in 3-, 6-, and 9-month-old male Wistar rats with chronic kidney disease (CKD) were investigated.

Morphometric changes in testicular parameters. As shown Table 1 In 3-month-old CKD rats treated with *Ferula mochata* root extract, significant improvements in testicular morphology were observed compared to untreated CKD rats. The thickness of the testicular capsule was measured at 21.01 ± 0.3 μm, testicular length was 18.8 ± 0.4 mm, and testicular weight was 0.82 ± 0.05 g. The diameter of the seminiferous tubules increased to 168.3 ± 1.1 μm, with a tubular area of 20,982 ± 13.8 μm². The thickness of the epitheliospermatogenic layer improved to 50.5 ± 1.8 μm, and the tubular lumen diameter was 48.5 ± 2.8 μm. The ratio between the epithelial thickness and lumen diameter was restored to approximately 2.5:1, indicating a near-normal architecture. These changes corresponded to an 87% improvement in macroscopic testicular parameters compared to the untreated CKD group.

In 6-month-old treated rats, the capsule thickness was 23.8 ± 0.7 μm, testicular length was 16.5 ± 0.6 mm, and weight was 0.73 ± 0.04 g, reflecting an 85% recovery in macroscopic parameters. Seminiferous tubule diameter decreased slightly to 160.3 ± 1.7 μm, with an area of 20,235 ± 15.7 μm². The epitheliospermatogenic layer thickness was 49.9 ± 1.9 μm, and lumen diameter was 50.9 ± 3.5 μm. The epithelial to lumen ratio was 2.5:1, indicating moderate restoration of seminiferous tubule structure.

In 9-month-old treated rats, testicular capsule thickness increased to 28.5 ± 1.0 μm, while testicular length and weight were 15.5 ± 0.5 mm and 0.69 ± 0.08 g, respectively. This represented a 79% recovery of macroscopic testicular features. The seminiferous tubule diameter was 160.0 ± 2.0 μm with an area of 19,564 ± 18.5 μm². The epitheliospermatogenic layer thickness was reduced to 43.0 ± 2.7 μm, and the lumen diameter was 55.0 ± 3.0 μm, resulting in an epithelial to lumen ratio of 1.5:1. These findings indicate partial restoration, with residual pathological alterations remaining evident.

Histological observations. Histological examination revealed that the treatment with sumbul root extract markedly improved the integrity of the seminiferous tubules and the spermatogenic epithelium in younger animals. The 3-month-old treated group displayed near-normal histoarchitecture with well-organized spermatogenic layers, reduced interstitial edema, and diminished degenerative changes compared to untreated CKD rats. The 6-month-old group showed moderate regenerative changes, with partial restoration of spermatogenic cells and reduced tubular atrophy. In the 9-month-old group, histological improvement was less pronounced, with some preservation of seminiferous tubules but ongoing signs of degeneration and fibrosis.

Table 1.

Comparison table of micro-morphometric parameters of testes in 3, 6, and 9-month-old male wistar rats across control, experimental, and post-correction groups

Indicator	Control			Experimental			Correction		
	3 months	6 months	9 months	3 months	6 months	9 months	3 months	6 months	9 months
Seminiferous Tubule Diameter (µm)	170.1± 1.28	175.0± 1.5	180.0± 1.8	163.0± 1.1	150.0± 1.8	140.0± 2.0	168.3± 1.1	160.3± 1.7	160.0± 2.0
Seminiferous Tubule Area (µm²)	21263 ±13.44	22013. 0±15.5	23500. 0±16.0	20532. 0±13.8	19050. 0±15.2	17500. 0±18.5	20982. 0±13.8	20235. 0±15.7	19564. 0±18.5
Epithelio-spermato-genic Layer Thickness (µm)	52.25± 1.13	55.5±1. 2	50.0±1. 3	48.0±1. 8	40.0±1. 2	35.0±2. 5	50.5±1. 8	49.9±1. 9	43.0±2. 7
Tubular Lumen Diameter (µm)	50.25± 2.22	52.0±2. 3	56.9±2. 8	45.0±2. 8	50.0±2. 5	55.0±3. 0	48.5±2. 8	50.9±3. 5	55.0±3. 0
Ratio of Epithelium to Lumen	3:1	3:1	2:1	2:1	1.5:1	1:1	2.5:1	2:1	1.5:1

Summary of morphometric data. Comparison between control, CKD, and treated groups across the three age categories is summarized in Table 1. The data indicate that *sumbul* root extract exerts the most pronounced restorative effects on testicular morphology in younger rats, with diminishing efficacy in older animals. This trend likely reflects age-related decreases in regenerative capacity.

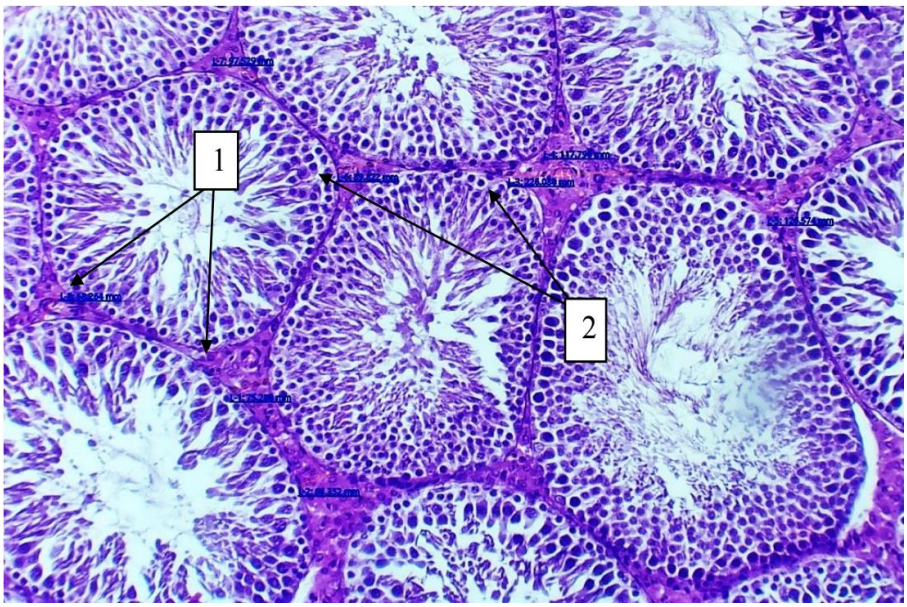

Figure 1. Morphological changes in the testes during experimental chronic kidney disease: Microscopic view of testicular tissue from a 9-month-old albino rat. Stained with hematoxylin and eosin, magnified 200 times. The image shows the interstitial tissue and Leydig cells located within it (1), as well as blood vessels in the interstitial area (2).

Discussion. The present study investigated the therapeutic potential of *sumbul* root extract in correcting testicular morphological and morphometric impairments in male Wistar rats with chronic kidney disease (CKD) induced via glycerol injection. Our findings demonstrate that the administration of *sumbul* root extract significantly ameliorated testicular damage, with the greatest regenerative effects observed in younger (3-month-old) rats, moderate improvements in 6-month-old rats, and comparatively limited recovery in 9-month-old rats.

Age-Dependent Regenerative Capacity. The differential restorative effects across age groups underscore the influence of age on tissue regenerative capacity. The 3-month-old rats exhibited near-complete normalization of testicular capsule thickness, seminiferous tubule diameter, epitheliospermatogenic layer thickness, and lumen diameter after treatment. This aligns with known biological trends where younger organisms possess heightened cellular proliferative potential and more robust reparative mechanisms (Sharpe, 2010). In contrast, the diminished responses in older rats suggest age-associated declines in testicular stem cell populations, reduced Leydig cell functionality, and increased fibrosis, which impair regenerative processes (Kumar & Mehta, 2017).

Mechanisms of *sumbul* root extract. The beneficial effects of *sumbul* root extract may be attributed to its bioactive compounds, including coumarins, ferulic acid, and other phenolics known for their antioxidant, anti-inflammatory, and cytoprotective properties (Zhou et al., 2019). Oxidative stress and inflammation are well-documented contributors to CKD-associated testicular damage, leading to spermatogenic disruption and tubular atrophy (Stenvinkel et al., 2016). By mitigating reactive oxygen species and suppressing pro-inflammatory pathways, the extract likely enhances cellular survival and supports the restoration of seminiferous tubule architecture (Figure 2).

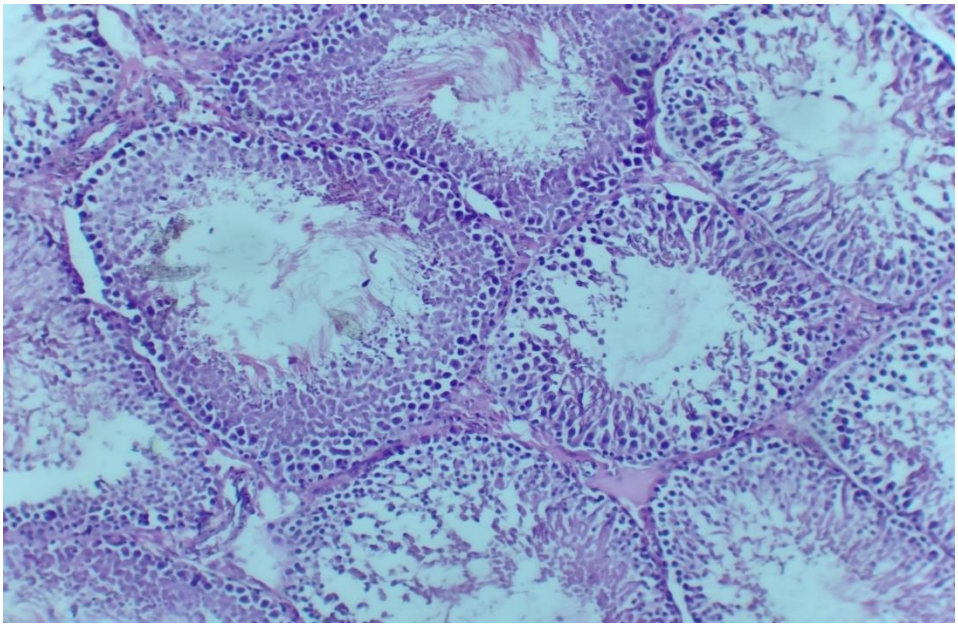

Figure 2. Microscopic view of the testis from a 6 month-old albino rat in the experimental group after correction with sumbul root extract. Stained with hematoxylin and eosin. Magnification: 200 times. 1 – The diameter of the convoluted seminiferous tubules is significantly enlarged compared to the untreated experimental group; 2 – The ratio between the lumen (central part of the tubules) and the epitheliospermatogenic layer is improved; 3 – Edema in the interstitial tissue area has decreased.

Comparison with previous studies. Our findings corroborate prior research indicating the nephroprotective and systemic antioxidative effects of *Ferula* species extracts (Singh et al., 2018). However, to our knowledge, this is among the first studies to evaluate their specific role in testicular recovery in a CKD context. The observed morphometric improvements, especially the restoration of epithelial to lumen ratios, highlight functional regeneration that may translate into improved spermatogenesis and fertility potential, a significant concern in CKD patients (Jafari et al., 2019).

Clinical and experimental implications. The gradual decline in treatment efficacy with age emphasizes the importance of early intervention in CKD to prevent irreversible gonadal damage. Furthermore, the peroral administration of the root extract as a relatively non-invasive approach suggests potential for translational applications. Nevertheless, additional studies assessing functional reproductive outcomes, such as sperm quality and hormonal profiles, are warranted to confirm therapeutic benefits.

Limitations of this study include the absence of molecular analyses to elucidate specific signaling pathways modulated by the extract and a lack of long-term follow-up to assess the durability of recovery. Moreover, while glycerol-induced CKD is a widely accepted model, it may not fully recapitulate all aspects of human CKD pathophysiology.

In conclusion, *sumbul* root extract exhibits promising restorative effects on testicular morphology in CKD-afflicted rats, with efficacy strongly influenced by age. These findings support further exploration of *sumbul* as a complementary therapeutic agent for mitigating CKD-related gonadal dysfunction.

Conclusion. This experimental study demonstrates that the aqueous extract of *sumbul* root possesses significant regenerative potential in reversing testicular structural impairments associated with chronic kidney disease (CKD) in male Wistar rats. The therapeutic effects were particularly prominent in younger rats (3 months of age), indicating that age plays a critical role in the efficacy of treatment and the intrinsic regenerative capacity of testicular tissue. The morphometric improvements observed—including restoration of capsule thickness, seminiferous tubule diameter, epithelial height, and luminal normalization—suggest that the extract may facilitate testicular repair through antioxidant and anti-inflammatory mechanisms.

These findings not only validate the ethnomedicinal use of *sumbul* but also introduce it as a promising candidate for further pharmacological investigation in the context of reproductive health and renal pathologies. While the outcomes are encouraging, further studies focusing on the molecular pathways involved, reproductive hormone levels, and sperm functional parameters are essential to confirm the full spectrum of the extract's biological effects.

In summary, the use of sumbul root extract may represent an effective, low-toxicity approach to mitigating CKD-induced testicular damage, particularly when administered early in the disease course. These results open new avenues for age-tailored phytotherapeutic strategies aimed at preserving male fertility under chronic disease conditions.

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