RESEARCH ARTICLE

Polydatin ameliorates spermatogenic dysfunction in cryptorchid mice by upregulating testicular protein O-GlcNAcylation

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Male infertility is a major global health issue with spermatogenic dysfunction caused by localized heat stress such as that associated with cryptorchidism being a primary contributing factor. O-GlcNAcylation is a dynamic and reversible post-translational modification critically involved in cellular stress responses and signal transduction. This research investigated the protective effects of the natural flavonoid polydatin (PD) against spermatogenic damage in a surgical mouse model of cryptorchidism and its underlying mechanism. The cryptorchid mice were treated with daily oral gavage of PD at 25, 50, 100 mg/kg or vehicle for 35 days. Testicular coefficient, sperm count, and testicular histopathology were assessed. Total testicular protein O-GlcNAcylation levels were analyzed by Western blot, and serum testosterone, luteinizing hormone, follicle-stimulating hormone, and oxidative stress markers of malondialdehyde, superoxide dismutase, glutathione were measured using enzyme-linked immunosorbent assay (ELISA). Compared with sham-operated mice, cryptorchid mice showed significantly reduced testicular index, severely disrupted seminiferous tubule architecture, and complete absence of sperm. PD treatment, particularly at medium to high doses of 50 - 100 mg/kg, dose-dependently ameliorated testicular atrophy, restored tubular structure, and increased sperm count. Testicular protein O-GlcNAcylation was significantly decreased by cryptorchid surgery and effectively reversed by PD treatment. In contrast, serum hormone levels and systemic oxidative stress markers remained largely unchanged. The results indicated that polydatin effectively mitigated testicular damage and spermatogenic dysfunction in cryptorchid mice, an effect likely attributed to the upregulation of local testicular protein O-GlcNAcylation. This research provided novel evidence supporting PD as a potential adjunctive therapy for male infertility and highlighted O-GlcNAcylation as a promising therapeutic target.

Keywords: cryptorchidism; male infertility; O-GlcNAcylation; polydatin; spermatogenesis.

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Introduction

Infertility affects approximately 15% of couples globally with male factors contributing to about 40 – 60% of cases [1]. The etiology of male infertility is complex and multifactorial, encompassing genetic defects, endocrine disorders, anatomical abnormalities, infections, environmental exposures, and idiopathic factors [2]. Clinically, common causes of male reproductive dysfunction include varicocele, orchitis, and prostatitis [2]. Regarding abnormal sperm parameters, idiopathic oligospermia, asthenospermia, and azoospermia represent the core diagnostic categories and are among the most common clinical manifestations of male infertility [2]. Therefore, identifying effective interventions to ameliorate spermatogenic dysfunction is of significant clinical importance.

In the search for potential therapeutic agents, natural products have garnered attention due to their multi-target effects and relatively favorable safety profiles [3]. Polydatin (PD), also known as piceid, is a natural flavonoid (3,4',5-trihydroxy-stilbene-3-β-D-glucoside, $C_{20}H_{22}O_8$). It is a glucoside derivative of resveratrol and the main active component of the traditional Chinese medicine *Polygonum cuspidatum*. PD is widely distributed in grapes, nuts, vegetables, fruits, hops, as well as in cocoa and chocolate products [4]. The conjugated double bonds in its molecular structure confer substantial antioxidant capacity, enabling PD to effectively scavenge free radicals and inhibit lipid peroxidation [5]. Studies have demonstrated that PD exerts broad protective effects across various disease models including cancers [4], neurodegenerative diseases [6], liver diseases [7], cardiovascular diseases [8], diabetes [9], respiratory diseases [10], endometritis [11], gastrointestinal diseases [12], infectious diseases [13], rheumatic diseases [14], and bone diseases [15]. These multifaceted activities underscore the therapeutic potential of PD as a multi-target natural product. Notably, accumulating evidence suggests a protective role for PD in the male reproductive system. PD can alleviate testicular oxidative stress, apoptosis, and inflammatory damage induced by radiation or chemical toxins such as arsenic and cyclophosphamide [16-18]. However, whether PD confers protection against spermatogenic dysfunction induced by the specific pathological condition of cryptorchidism, primarily mediated through local heat stress, remains unexplored. Meanwhile, protein O-GlcNAcylation is a dynamic and reversible post-translational modification that plays a key role in cellular stress responses, signal transduction, and survival [19]. Studies indicate that this modification participates in adaptive cellular responses to various injuries including heat stress.

Based on the previous research background and existing evidence, it is hypothesized that the testicular protective effect of PD against cryptorchidism induced heat stress injury may be closely associated with the regulation of testicular protein O-GlcNAcylation levels. This study systematically evaluated the effects of PD intervention on testicular morphology and spermatogenic function in a surgical mouse model of cryptorchidism and preliminarily investigated whether its action was associated with the modulation of testicular protein O-GlcNAcylation levels. The findings of this study provided novel experimental evidence and mechanistic insights to support the development of natural product-based adjunctive therapies for male infertility.

Materials and methods

Experimental animals

A total of 25 male Kunming mice (10 – 15 days old, weighing 10 – 15 g) were used in this study. All mice were of specific pathogen-free (SPF) grade and were purchased from the Huaxing Experimental Animal Breeding Farm (Zhengzhou, Henan, China). Prior to experimentation, all mice were acclimatized for 3 days in a controlled environment. The housing conditions were maintained at a temperature of 21 – 25°C, a relative humidity of 50 – 65%, and a 12 h/12 h light/dark cycle. Throughout the study, mice had

ad libitum access to standard laboratory chow and water, and the housing environment was kept quiet. The experimental protocol was approved by the Animal Ethics Committee of Huanghuai University (Zhumadian, Henan, China) with the approval No. of 2023030706.

Model establishment and grouping

25 mice were randomly assigned to five groups with 5 mice in each group, which included sham-operated group (BO), cryptorchid model group (CO), and three polydatin treatment groups of P25 (25 mg/kg), P50 (50 mg/kg), and P100 (100 mg/kg). Mice were housed separately by group. BO group underwent a sham operation under ether anesthesia and subsequently received daily oral gavage of saline for 35 days. CO and polydatin treatment groups underwent surgical induction of cryptorchidism. Briefly, after anesthesia with ether, mice were placed in a supine position, and the surgical area was disinfected with 75% ethanol. A 1 cm midline abdominal incision was made. The testis and epididymis were then sutured and fixed within the abdominal cavity. The incision was sutured and disinfected. Starting 24 h post-surgery, CO group received daily saline gavage for 35 days, while P25, P50, and P100 groups received daily gavage of polydatin at the doses of 25, 50, and 100 mg/kg (dissolved in saline), respectively, for 35 days. Body weights were recorded weekly. Twenty-four hours after the final gavage, mice were euthanized. Major organs including testes, brain, cerebellum, liver, kidneys, lungs, pancreas, colon, heart, spleen, stomach, and seminal vesicles were collected and weighed. The organ coefficient was calculated as follows.

Organ coefficient (mg/g) = Organ weight (mg) / Body weight (g)

Sperm count analysis

The epididymis was dissected, minced, and placed in a centrifuge tube containing 200 µL of pre-warmed phosphate-buffered saline (PBS). A 10 µL aliquot of the supernatant was then loaded onto a sperm counting chamber (Mailang, Nanning, Guangxi, China) for sperm counting.

Testicular histopathology

The right testis was fixed in Bouin's solution for 10 h followed by standard processing for dehydration, clearing, paraffin embedding, and sectioning. Sections were then stained with hematoxylin and eosin (H&E). Pathological changes in the testicular tissue were observed and evaluated under a light microscope at 200× magnification.

Serum hormone and oxidative stress marker analysis

Collected blood samples were aliquoted into 1.5 mL microcentrifuge tubes, kept at 4°C overnight, and then centrifuged at 2,000 × g for 20 min to obtain serum. Serum concentrations of estradiol (E), testosterone (T), follicle-stimulating hormone (FSH), luteinizing hormone (LH), gonadotropin-releasing hormone (GnRH), total superoxide dismutase (T-SOD), and malondialdehyde (MDA) were measured by using commercial enzyme-linked immunosorbent assay (ELISA) kits (UpingBio, Hangzhou, Zhejiang, China) according to the manufacturers' instructions.

Analysis of protein O-GlcNAcylation

Left testicular tissues (three samples per group) were homogenized in ice-cold lysis buffer containing 50 mM Tris (pH 7.4), 150 mM NaCl, 1% NP-40, 0.5% sodium deoxycholate, 1 mM EDTA. The homogenates were centrifuged at 13,000 × g for 20 min at 4°C to collect the supernatants. The total protein concentration in the supernatant was determined by using a bicinchoninic acid (BCA) protein assay kit (Jiangsu Cowin Biotech Co., Ltd., Taizhou, Jiangsu, China). Proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and subsequently transferred onto a nitrocellulose membrane. Protein O-GlcNAcylation levels were assessed by Western blotting using the primary antibodies RL2 and CTD110.6 (Invitrogen) (Thermo Fisher Scientific, Waltham, MA, USA) and horseradish peroxidase (HRP)-conjugated secondary antibodies. Immunoreactive bands were visualized using enhanced chemiluminescence and imaged with a

Bio-Rad ChemiDoc MP system. β-Actin was used as the control. Band intensities were quantified by measuring the integrated optical density (IOD) using Image-Pro Plus 6.0 software (Media Cybernetics, Rockville, MD, USA).

Statistical analysis

All data were presented as the mean ± standard deviation (SD). Statistical analyses were performed using GraphPad Prism software (version 8.04) (https://www.graphpad.com/). Intergroup comparisons were performed using Student's t-test. *P* value less than 0.05 was considered statistically significant, while *P* value less than 0.01 was considered highly significant.

Results

Polydatin ameliorates testicular damage and spermatogenic dysfunction in cryptorchid mice

PD administration did not adversely affect the general health or systemic organ development of the mice. All groups showed a progressive increase in body weight over the 35-day period with no significant differences among groups at any time point (Figure 1).

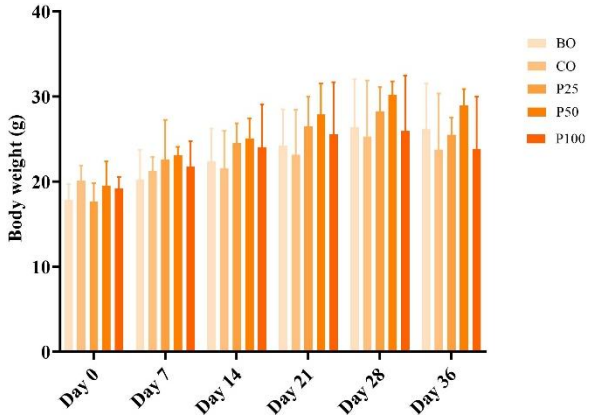


Figure 1. Body weight changes in cryptorchid mice treated with different doses of polydatin.

Similarly, the organ index (organ-to-body weight ratios) for most examined organs including brain, cerebellum, liver, kidneys, lungs, pancreas, colon, heart, spleen, and stomach showed no significant alterations in response to cryptorchid surgery or PD treatment compared to the sham-operated (BO) group (Figure 2C–2N). In contrast, both left and right testicular index were significantly reduced in the cryptorchid model (CO) group compared to the sham-operated (BO) group with left testis showing $P < 0.01$ and right testis showing $P < 0.05$. Treatment with PD at doses of 50 and 100 mg/kg partially reversed the decrease in the left testicular coefficient compared with CO group ($P < 0.01$) (Figure 2A). For the right testis, PD treatment at 25, 50, and 100 mg/kg showed a restorative effect. The recovery in the P25 group reached statistical significance compared to the CO group ($P < 0.05$) (Figure 2B). These data indicated that PD specifically alleviated cryptorchidism induced testicular atrophy without affecting overall growth or the development of other major organs.

Polydatin restores testicular histoarchitecture and spermatogenesis in cryptorchid mice

Compared with the normal control group (BO), H&E staining revealed severe pathological damage to the seminiferous tubules in the CO group (Figure 3A, 3B). The tubules exhibited atrophy, a disorganized and sparse arrangement of spermatogenic cells, and thinning of the seminiferous epithelium. Mature sperm were absent from the lumen, and interstitial cells showed signs of degeneration (Figure 3B). In contrast, PD treatment significantly ameliorated these pathological alterations (Figure 3C-3E). The seminiferous tubule boundaries became more distinct, the seminiferous epithelium thickened, spermatogenic cell numbers recovered, and mature sperm reappeared in the lumen. These restorative effects were most evident in the P50 and P100 groups (Figure 3D, 3E). Furthermore, sperm count analysis corroborated the histological findings. No spermatozoa were detected in the CO group. In contrast, PD treatment significantly increased sperm density in a dose-dependent manner compared with CO group for all doses ($P < 0.01$). The sperm densities in the P25, P50, and P100 groups were 0.12 ± 0.06, 0.56 ± 0.27, and 0.28 ± 0.15 ($\times 10^8$/mL),

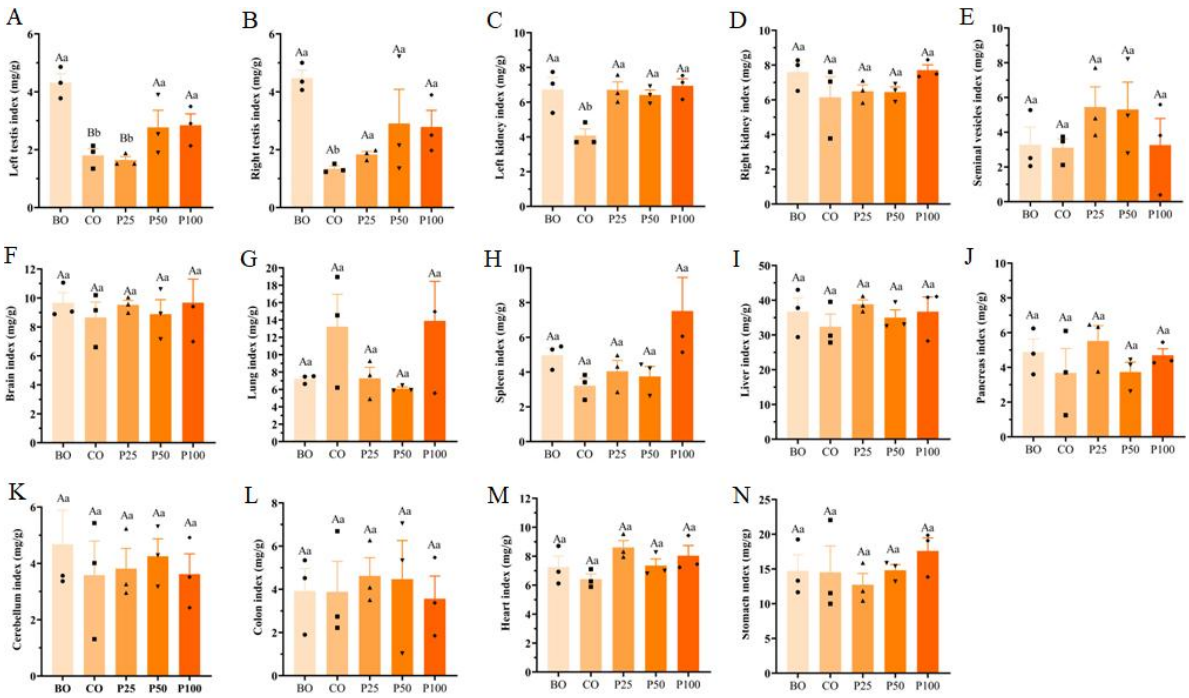


Figure 2. Effects of polydatin on organ index in cryptorchid mice. **A.** left testis. **B.** right testis. **C.** seminal vesicle. **D.** left kidney. **E.** right kidney. **F.** brain. **G.** cerebellum. **H.** pancreas. **I.** heart. **J.** lung. **K.** colon. **L.** spleen. **M.** liver. **N.** stomach. Columns marked with different lowercase letters indicated highly significant differences ($P < 0.01$), uppercase letters the same and lowercase letters different indicated significant differences ($P < 0.05$), and identical letters indicated no significant differences ($P > 0.05$).

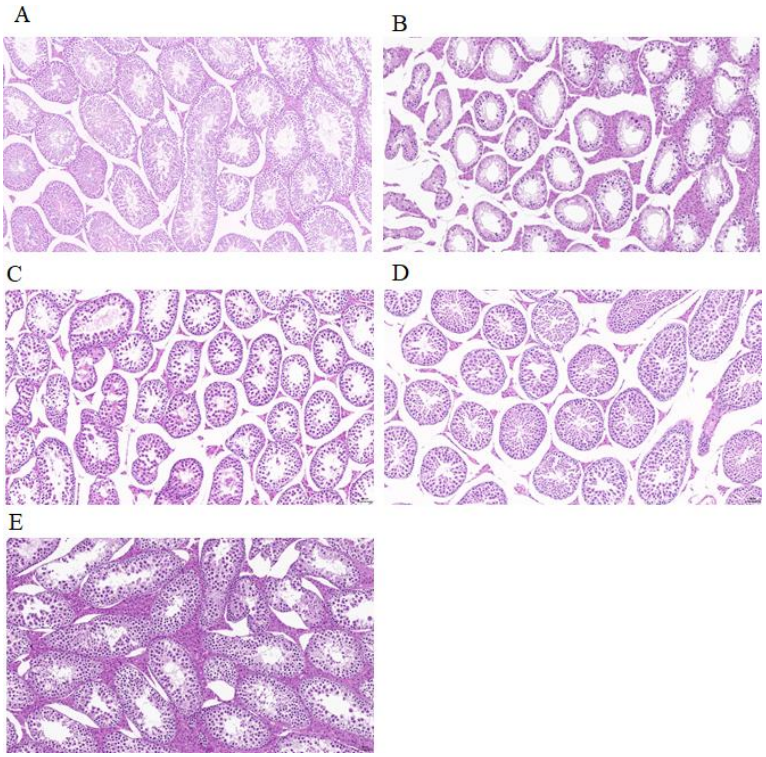


Figure 3. Representative photomicrographs of testicular histopathology (H&E staining). **A.** Sham-operated (BO) group. **B.** Cryptorchid model (CO) group. **C.** P25 group. **D.** P50 group. **E.** P100 group.

respectively (Figure 4). Pairwise comparisons among the PD-treated groups revealed that the P50 group had a significantly higher sperm count than the P25 group ($P < 0.01$), but no significant differences were found between P50 and P100 ($P > 0.05$) or between P25 and P100 ($P > 0.05$). Although all PD-treated groups still exhibited lower sperm counts than the BO group, these results collectively confirmed successful induction of the cryptorchid model and indicated that PD promoted recovery of spermatogenic function.

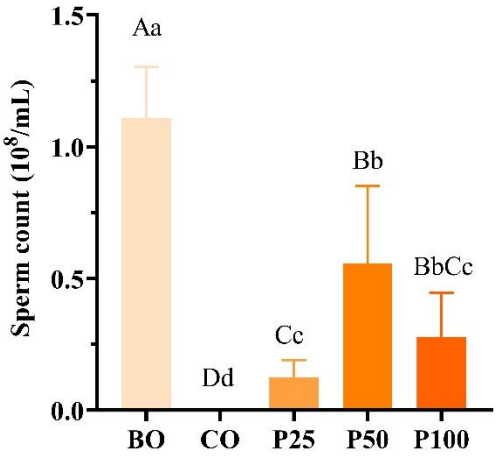


Figure 4. Sperm counts in cryptorchid mice treated with polydatin. Columns marked with different lowercase letters indicated highly significant differences ($P < 0.01$), uppercase letters the same and lowercase letters different indicated significant differences ($P < 0.05$), and identical letters indicated no significant differences ($P > 0.05$).

Polydatin upregulates testicular protein O-GlcNAcylation levels

To investigate the potential mechanism underlying PD's protective effects, testicular protein O-GlcNAcylation levels were measured. Western blot analysis using two distinct O-GlcNAc-specific antibodies (CTD110.6 and RL2) revealed that cryptorchid surgery significantly reduced testicular protein O-GlcNAcylation levels compared to the BO group. PD treatment, particularly at doses of 50 and 100 mg/kg, significantly restored O-GlcNAcylation levels (Figure 5A, 5B). These findings suggested that the protective effects of PD might be mediated through the upregulation of testicular protein O-GlcNAcylation in cryptorchid mice.

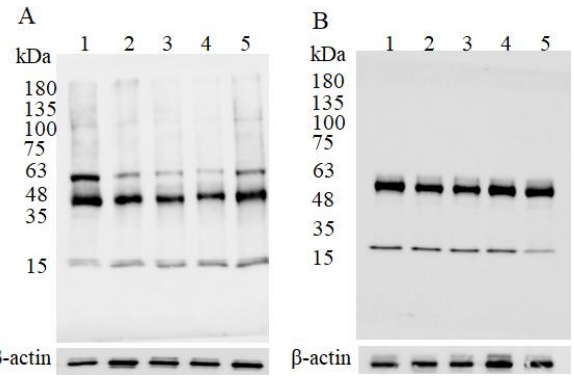


Figure 5. Western blot analysis of testicular protein O-GlcNAcylation levels. Blots were probed with O-GlcNAc-specific antibodies RL2 (**A**) and CTD110.6 (**B**). β-Actin served as the control. Lanes 1: Sham-operated (BO) group; 2: Cryptorchid model (CO) group; 3: P25 group; 4: P50 group; 5: P100 group.

Serum hormone and oxidative stress marker levels

ELISA analysis of serum testosterone, FSH, LH, GnRH, estradiol, and oxidative stress markers of SOD, MDA revealed no significant differences among the groups. A statistically significant difference in GnRH levels was observed only between the P25 and P50 groups ($P < 0.05$) (Figure 6).

Discussion

This study evaluated the protective effects of the natural flavonoid polydatin (PD) against spermatogenic damage in a surgical mouse model of cryptorchidism and explored its underlying mechanisms. The results showed that PD specifically alleviated cryptorchidism induced testicular atrophy, significantly improved seminiferous tubule architecture, and promoted the recovery of spermatogenesis in a dose-dependent manner. Further, PD treatment reversed the cryptorchidism induced decrease in testicular protein O-GlcNAcylation levels. Furthermore, under current experimental conditions, PD did not significantly alter serum

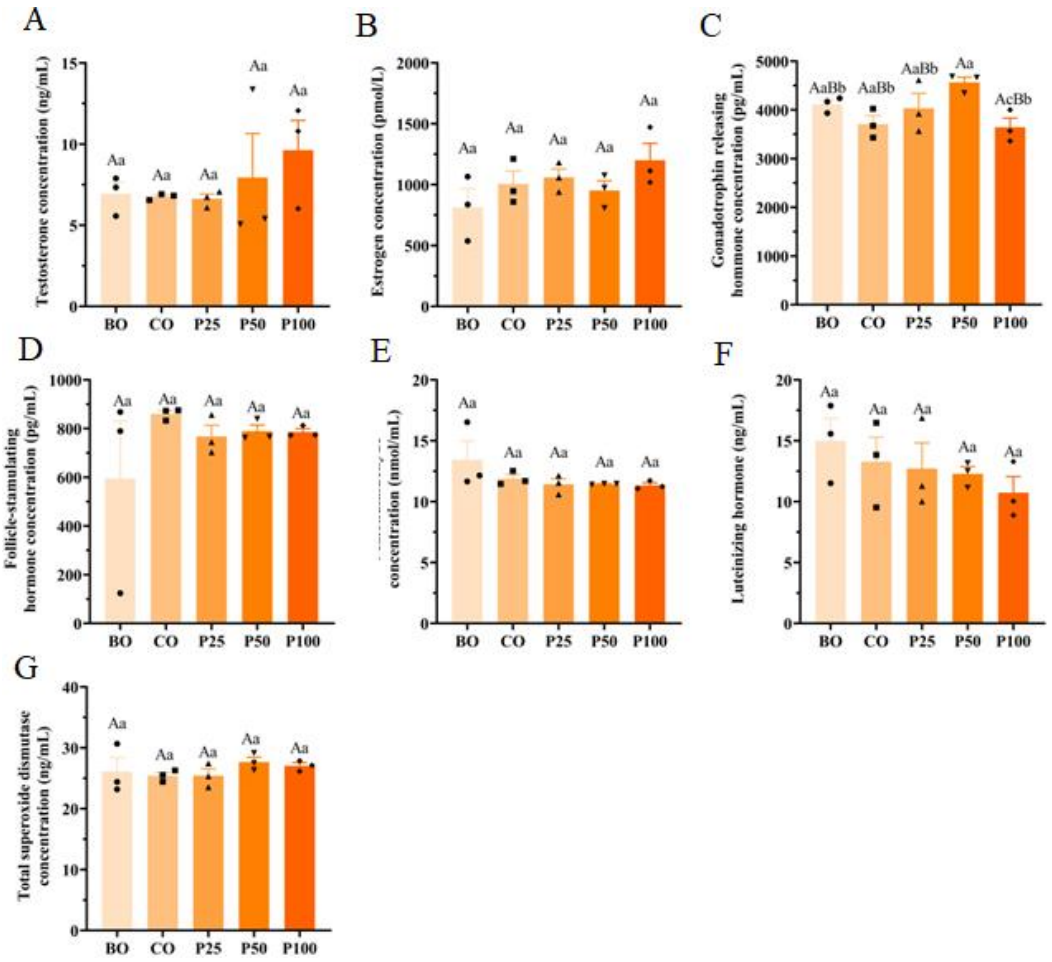


Figure 6. Serum levels of reproductive hormones and oxidative stress markers in cryptorchid mice treated with polydatin. **A.** Testosterone. **B.** Estradiol. **C.** Gonadotropin-releasing hormone (GnRH). **D.** Malondialdehyde (MDA). **E.** Follicle-stimulating hormone (FSH). **F.** Luteinizing hormone (LH). G. Total superoxide dismutase (T-SOD). Columns marked with different lowercase letters indicated highly significant differences ($P < 0.01$), uppercase letters the same and lowercase letters different indicated significant differences ($P < 0.05$), and identical letters indicate no significant differences ($P > 0.05$).

profiles of reproductive hormones or systemic oxidative stress markers. These results indicated that PD exerted a clear local protective effect against cryptorchidism induced testicular damage, and its mechanism might be closely associated with the regulation of testicular protein O-GlcNAcylation, a key post-translational modification.

This study confirmed the efficacy of PD in the specific pathological context of cryptorchidism. Cryptorchidism, characterized by elevated intrascrotal temperature and a disrupted testicular microenvironment, induces persistent oxidative stress and inflammation, thereby serving as a classic model for studying spermatogenic epithelial damage [3, 5]. The study successfully recapitulated the typical phenotype of this model including reduced testicular weight, severe seminiferous tubule damage, loss of spermatogenic cells, and azoospermia. PD treatment, particularly at medium to high doses of 50 – 100 mg/kg, effectively reversed these pathological changes as evidenced by increased seminiferous epithelial thickness, orderly spermatogenic cell arrangement, and the reappearance of mature sperm in the lumen. This finding aligned with previous reports that PD protected the testis from radiation or chemical toxin induced damage

via antioxidant and antiapoptotic pathways and clearly extended the protective repertoire of PD to spermatogenic dysfunction induced by local heat stress [18]. Importantly, while ameliorating testicular specific damage, PD did not affect the overall growth or the weight of other major organs. This suggested an organ-selective action with potentially low systemic toxicity, providing preliminary safety evidence for its development as a protector of the male reproductive system. Further, this study proposed a novel mechanistic perspective, namely that PD might exert its protective effects by upregulating testicular protein O-GlcNAcylation levels. O-GlcNAcylation is a dynamic, reversible post-translational modification widely involved in cellular stress responses, signal transduction, and transcriptional regulation [19]. Studies indicate that upregulation of O-GlcNAcylation under conditions such as heat and oxidative stress helps stabilize protein function and inhibit apoptosis, thereby playing a cytoprotective role [19]. The results showed that cryptorchid surgery significantly reduced testicular O-GlcNAcylation levels, possibly reflecting a disruption of cellular stress responses within the high temperature microenvironment. PD treatment, particularly at medium to high doses, significantly restored this modification, which strongly suggested that the protective effects of PD might partly stem from its ability to maintain or enhance the homeostasis of testicular protein O-GlcNAcylation. A reasonable hypothesis was that PD increased the availability of uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), possibly by modulating cellular metabolism such as the hexosamine biosynthesis pathway, which would provide more substrate for O-GlcNAc transferase (OGT) to modify key survival and functional proteins within spermatogenic or supporting cells, ultimately enhancing testicular tolerance to the adverse cryptorchid environment. This finding opened a new avenue for understanding PD's mechanism of action. Furthermore, analysis of these largely negative results supported the concept of a local site of action for PD. This study did not detect significant effects of PD on serum levels of key reproductive hormones (LH, FSH, testosterone) or systemic oxidative stress markers (SOD, MDA). The potential explanations might be that PD might act directly on local testicular tissues such as spermatogenic epithelium and Leydig cells, rather than *via* neuroendocrine modulation of the hypothalamic–pituitary–gonadal axis. In the cryptorchid model, direct damage from local heat stress and microcirculatory disturbance might outweigh secondary systemic hormonal alterations, and the antioxidant effects of PD might be confined to the testicular compartment without significant systemic diffusion. This result, together with the lack of effect on other organ weights, collectively underscored the organ-specific nature of PD's protection and highlighted the importance of focusing on local mechanisms such as O-GlcNAcylation in future research.

This study has several limitations. While it revealed a correlation between PD and altered O-GlcNAcylation, the specific upstream regulatory targets and downstream effector proteins remained unidentified. Future studies should employ techniques such as O-GlcNAc glycoproteomics to identify key PD-regulated target proteins and verify their functional necessity through gain- and loss-of-function experiments. Further, this study relied primarily on histomorphological and biochemical endpoints. Future work could incorporate more refined analyses such as TUNEL assay for apoptosis, quantification of inflammatory factors, and assessment of sperm functional parameters such as motility and morphology to provide a more comprehensive evaluation of PD's therapeutic effects. This study employed a surgical cryptorchid model. Future studies should investigate whether the protective effects of PD extend to other models of spermatogenic impairment such as those induced by chemotherapy or autoimmune orchitis.

This study demonstrated that polydatin effectively ameliorated testicular damage and spermatogenic dysfunction in a cryptorchid mouse model. Its protective effects might be mediated through the upregulation of testicular

protein O-GlcNAcylation and were less associated with systemic alterations in reproductive hormones or oxidative stress markers. These findings not only provided novel experimental evidence supporting the potential of polydatin as an adjunctive therapy for male infertility but also proposed testicular protein O-GlcNAcylation as a promising therapeutic target for spermatogenic dysfunction. Future research should aim to clarify the specific molecular targets of PD within the O-GlcNAcylation network and validate its efficacy in a broader range of spermatogenic impairment models to facilitate its clinical translation.

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