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Improvement of postoperative health in prostate cancer patients by puerarin combined with prostatectomy

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Abstract: This work analyzed the effect of Puerarin (PUE) combined with prostatectomy in the treatment of prostate cancer (PCa). All 122 patients with PCa received radical PCa treatment. Among them, 58 patients received PUE treatment (study group) and 64 patients did not receive PUE (control group). The inflammatory response and stress injury before and after treatment were compared and the levels of sex hormones and nutritional proteins were detected. In addition, the psychological status of the patients was assessed. Finally, carried on the prognosis of 1 year follow-up, the survival situation and erectile dysfunction. The inflammatory response and stress injury in the research group were lower than those in the control group ($P<0.05$). At the same time, the research group of sex hormones and nutritional protein levels were higher ($P<0.05$). In addition, the psychological state of the research group was also better. There was no significant difference in the overall survival rate between the two groups ($P>0.05$), However the erectile function of the research group was better than that of the control group. PUE combined with prostatectomy is effective in the treatment of PCa and is recommended for clinical use.

Keywords: Organizational health; Prostate cancer; Prostatectomy; Puerarin

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INTRODUCTION

Prostate cancer (PCa) arises from the malignant hyperplasia of prostate epithelial cells. Although it is not contagious, there is a significant genetic predisposition associated with its development (Vietri *et al.*, 2021). PCa is the most common malignancy of the male genitourinary system, with an increasing prevalence with age (Siegel *et al.*, 2020). Currently, the average 5-year survival rate of PCa patients is about 24.7% (Tan *et al.*, 2024). Radical PCa surgery is the most direct way to treat PCa (Williams *et al.*, 2022). However, the mechanically invasive operation of PCa radical surgery inevitably causes serious injuries to patients (e.g., urethral sphincter injury, genital nerve damage, anastomotic fistula, etc.) and how to minimize these injuries becomes the key to improving the outcome of PCa radical surgery (Nabavizadeh & Karnes, 2023).

Up to now, many natural products have been used in the adjuvant treatment of tumors because of their excellent anticancer effects and low cytotoxicity (Sflakidou *et al.*, 2022). Puerarin (PUE), a well-known isoflavone-C-glycoside, is the major bioactive component of *Pueraria lobata*, a traditional Chinese medicine, which has a wide range of biological activities, including cardioprotection, neuroprotection, analgesia and inhibition of alcohol intake (Choi *et al.*, 2023). Currently, Jeon YD *et al*. have confirmed that PUE can effectively improve the inflammatory response and oxidative stress in colitis (Jeon *et al.*, 2020) and Yang M *et al*. have confirmed that PUE can help to regulate the metabolic function of the human body and improve the immunity of the human body (Yang *et al.*, 2023). It is well known that postoperative inflammatory response and stress injury are the main causes of complications in patients and the improvement of these functions by PUE suggests to us that PUE will probably help to improve the safety of PCa surgery. Recently, the study of Liu H *et al*. even showed that the metabolites of PUE have significant implications for prostate health (Liu *et al.*, 2022), laying a reliable foundation for the therapeutic application of PUE in PCa.

However, there are no studies confirming the value of PUE in PCa, which limits the clinical application of PUE. In this study, we will evaluate the therapeutic effects of PUE in combination with prostatectomy on PCa to provide a more reliable and safer treatment option for PCa and to enhance patient prognosis.

MATERIALS AND METHODS

Study population

G*Power software (v3.1.9.2) was used to calculate the sample size needed for this study. Setting up 2 groups of study subjects, with Effect size=0.5, α err prob= 0.05, power = 0.8, ratio = 1:1 and Tail = one, the calculation shows that a total of 102 subjects are needed, which means a minimum of 51 subjects per group. PCa patients admitted from December, 2021 to December, 2022 were selected as the research subjects and retrospectively analyzed, all of whom underwent radical prostatectomy surgery in our hospital. Among them, patients received PUE as the research group and the other patients did not receive PUE as the control group. The hospital's Ethics Committee approved the research (2022LK041) and all the subjects

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provided written informed consent. Inclusion criteria: Age range: 18-70; with clinical manifestations of PCa (dysuria, dyspareunia, pelvic, lower back pain, etc.); prostate-specificigen (PSA) >4 ng/mL, meeting the indications for and completing radical prostatectomy (indications for surgery: clear PCa, no serious heart, lung or brain disease, no distant metastasis of tumor cells) in our hospital; confirmed diagnosis of PCa through pathological biopsy, Gleason score 2-10; sufficient cognitive and communication skills, enabling sufficient understanding of the content of this study and completion of relevant questionnaires. Exclusion criteria: The presence of other serious heart disease, kidney disease, or neurological disorders; combined with other urologic disorders; current use of hormone therapy; serious mental illnesses or emotional disorders; obvious sexual dysfunction prior to treatment; drug allergies; detachment during follow-up; expected survival <3 months.

METHODS

All patients underwent radical prostatectomy. All the operations were operated by the same group of senior surgeons, mainly including skin incision, pneumoperitoneum establishment, prostate tissue separation and resection, urethral suture and skin suture procedures. None of the patients were treated with phosphodiesterase 5(PDE5) inhibitors before the operation and any erectile function adjuvant therapy was prohibited during the postoperative follow-up period. After surgery, all patients received the anti-androgen drug carlutamide (AstraZeneca UK Limited, H20100390, 50mg/dose/d) and the gonadotropin-releasing drug goserelin (AstraZeneca UK Limited, J20120015, 3.6mg/dose, once every 4 weeks). All the above-mentioned drugs are for long-term use. 6 hours after the operation, patients were instructed to drink warm water in moderation and they could eat after the first postoperative defecation, following the principle of small meals and more protein-rich and fiber-rich foods. If the patient's pain is more intense, appropriate amount of non-steroidal anti-inflammatory drugs can be given according to the actual situation in order to reduce the pain. On this basis, the research group was given PUE injection treatment: 400 mg of PUE injection (Zhejiang Kangenbei Pharmaceutical Co., Ltd., H33020186) was mixed with 500 mL of 5% glucose injection for intravenous infusion, once a day for 20 days.

Follow-up for prognosis

Prognostic follow-up of all patients was performed for a period of 1 year. Follow-up was in the form of periodic reviews, which were defined as 1 review/month, with a termination date of January 2024 and a termination event of patient death. At the last follow-up, surviving patients were evaluated for erectile dysfunction by using the International Index of Erectile Function (IIEF) (Wang *et al.*, 2022); based on the score, the assessment was rated as barrier-free (22-30), mild impairment (17-21), or moderate/severe impairment (0-16).

Events

(1) Clinical data: Data such as age, gender and pathological stage of patients (Lowrance *et al.*, 2023) were collected. (2) Inflammation and stress injury: Fasting venous blood was collected before and after treatment to quantify tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, superoxide dismutase (SOD) and malondialdehyde (MDA) by enzyme-linked immunosorbent assay kits. (3) Sex hormones: We used an automatic electrochemiluminescence instrument to determine lutropin (LH), dihydrotestosterone (DHT), follicle-stimulating hormone (FSH) and free testosterone (FT) before and after treatment. (4) Nutritional status: Albumin (ALB), hemoglobin (HGB) and total protein (TP) were detected with an automatic biochemical analyzer before and after treatment and the malnutrition risk of patients was assessed after treatment using the Nutrition Risk Screening (NRS2002) (Wang *et al.*, 2024). (5) Psychological status: Patients' negative emotions were evaluated with the Self-Rating Anxiety/Depression Scale (SAS/SDS) (Chen *et al.*, 2023), with higher SAS/SDS scores suggesting more severe anxiety and depression. (6) Prognostic health: Prognostic health was assessed by analyzing prognostic survival and IIEF scores.

Statistical analysis

Statistical analysis was performed using SPSS24.0. The comparison of count data [(n (%)] such as gender and pathological stage of patients used the chi-square test; the comparison of measurement data like age and course of disease ($\bar{\chi}\pm s$) was conducted using independent sample t-tests and paired t-tests. The patient survival rate was calculated using the Kaplan-Meier method and compared with the Log-rank test. Results were considered statistically significant when $P<0.05$.

RESULTS

No difference was identified in clinical data between the two groups

Based on the results of sample size calculation, 122 PCa patients were selected as the research subjects. Among them, 58 patients were in the research group and the other 64 patients were in the control group. The age, sex, pathological stage and other data of patients in the two groups were statistically analyzed and no marked inter-group difference was found ($P>0.05$) (Table 1).

The research group showed milder inflammation and stress injury than the control group after treatment

The two groups had similar levels of inflammatory factors and stress injury indexes before treatment ($P>0.05$). IL-1β, IL-6, TNF-α and MDA were all decreased in the two groups after treatment, with their levels being

(86.16±11.84)pg/mL, (7.72±1.50)pg/mL, (4.21±0.54)pg/mL and (6.02±1.15)nmol/mL in the research group, respectively, lower versus the control group (P<0.05); while a rise in SOD was observed after treatment, with a level of (49.08±7.47)U/L in the research group that was higher compared to the control group (P<0.05) (Fig. 1).

The sex hormones were higher in the research group than in the control group after treatment

The two groups were also similar in pre-treatment sex hormone levels (P>0.05). After treatment, LH, DHT, FSH and FT in the research group were (7.49±1.02)U/L, (575.15±56.76)ng/L, (10.48±1.46)U/L and (0.40±0.04) nmol/L respectively, all these indicators were elevated compared to pre-treatment levels and were higher in the research group than in the control group (P<0.05) (Fig. 2).

The research group was better than the control group in psychological status

Before treatment, there was no Table inter-group difference in the results of SAS and SDS (P>0.05). Both groups had reduced SAS and SDS scores after treatment; SAS and SDS scores in the research group were (32.85±5.25) and (29.71±5.91), respectively, both of which were lower compared with the control group (P<0.05) (Fig. 3).

The nutritional status of the research group was better than that of the control group

Before treatment, there was no significant difference in the results of nutritional protein tests between the two groups (P>0.05). After treatment, the nutritional protein levels in the control group decreased (P<0.05), while ALB, HGB and TP in the research group remained unchanged (P>0.05). The post-treatment ALB, HGB and TP in the research group were (37.12±4.15)g/L, (120.07±11.89)g/L and (69.24±8.79)g/L, respectively, which were higher compared to the control group (P<0.05). Meanwhile, the NRS2002 survey results of the research group showed that there were more mild malnutrition cases and fewer severe malnutrition cases compared to the control group (P<0.05) (Table 2).

There were fewer cases of prognostic erectile dysfunction in the research group than in the control group

The difference in prognostic 1-year overall survival rate between the two groups was not statistically significant (P>0.05). After removing patients who died, we compared IIEF outcomes in the study group (n=59) and the control group (n=55), the IIEF survey results showed no difference in the number of patients with moderate/severe erectile dysfunction between the two groups (P>0.05), but the research group had more people without erectile dysfunction and fewer people with mild erectile dysfunction than the control group (P<0.05) (Fig. 4 and Table 3).

DISCUSSION

This study is the first to demonstrate that PUE synergizes with radical prostatectomy by concurrently attenuating systemic inflammation, improving endocrine function and enhancing nutritional status. The multimodal benefits of PUE make it a promising adjunct therapy for PCa patients undergoing surgery.

As a mechanically invasive procedure, radical resection for PCa results in significant inflammation and stress damage, which are critical factors affecting patient rehabilitation and warrant careful attention (Rosiello *et al.*, 2021). The results of this study showed that IL-1β, IL-6, TNF-α and MDA were lower in the research group than in the control group after treatment, while SOD was higher, confirming the milder inflammatory reaction and stress injury in the research group after treatment. PUE has been shown to be rich in high-quality starch, dietary fiber, proteins and other ingredients, which can facilitate the recovery of immune regulation function, improve blood circulation and promote the proliferation and differentiation of target organs (Hu *et al.*, 2023).

Meanwhile, the scavenging effect of PUE on oxygen free radicals also greatly avoids the peroxidation caused by active oxygen in microsomes, regulates the balance between oxygen free radicals and free radical scavengers in the body and thus lays a better foundation for promoting the health of patients (Yen *et al.*, 2023). In a meta-analysis of PUE for the treatment of diabetic nephropathy by Xu X *et al*, they confirmed that PUE was more effective in improving nerve function and hemodynamics in patients (Xu *et al.*, 2025), which is similar to our view. Therefore, the research group showed better alleviation in inflammatory responses and stress damage after treatment. Similarly, Zhou S *et al*. found that PUE has a positive effect on relieving stress injury in sepsis patients (Zhou *et al.*, 2023), consistent with our results.

In the subsequent comparison of sex hormones, the research group showed more significant improvements in LH, DHT, FSH and FT after treatment, indicating that PUE also has a significant effect on promoting the recovery of sex hormone levels in PCa patients. As we all know, the prostate is an important part of male reproductive organs and its structure and function are regulated by the hypothalamus-pituitary-testis axis and adrenal gland, so the occurrence of PCa may be related to hormones such as androgens, estrogen and non-androgen substances in testes (Simkova *et al.*, 2021). In pharmacological studies related to PUE, researchers found that the effective components of PUE can regulate the state of sex hormones and produce active substances that promote gonadal effects on white blood cells and sex hormone synthesis, accelerating the secretion of sex hormones (Yang *et al*., 2023).

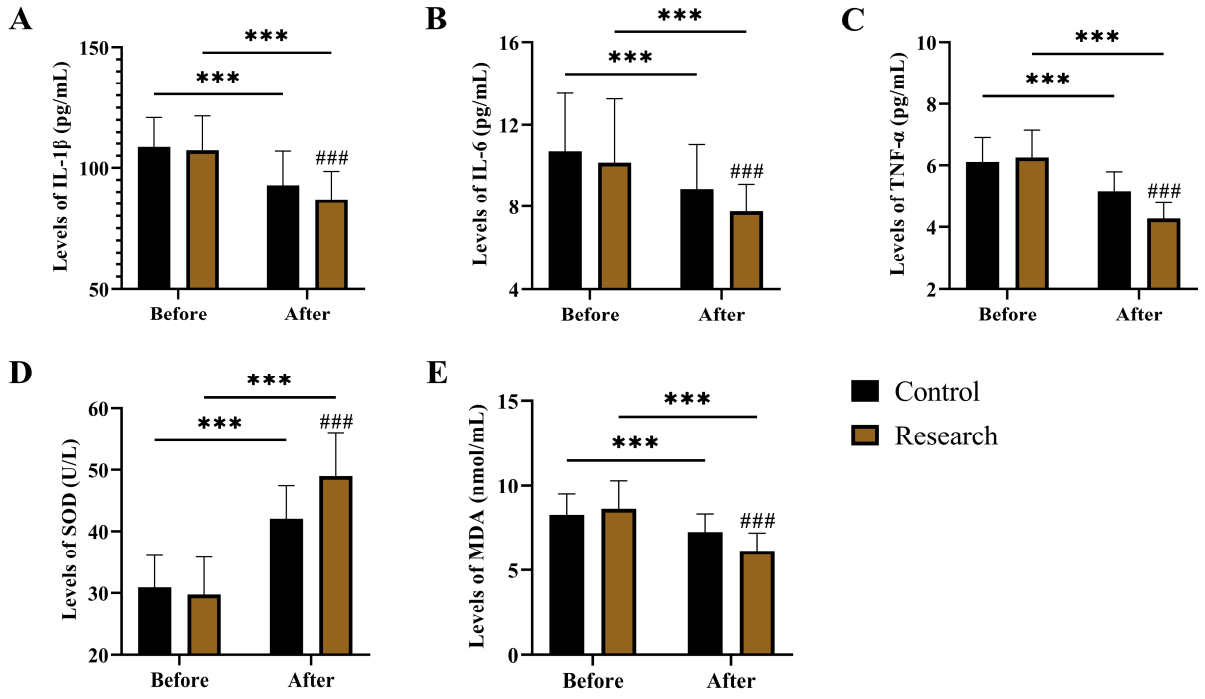

Fig. 1: Comparison of inflammatory response and oxidative stress before and after treatment. A) IL-1β, B) IL-6, C) TNF-α, D) SOD, E) MDA. Comparison with control group ###P<0.001, and comparison with before treatment ***P<0.001. Tumor necrosis factor-α, TNF-α; Interleukin, IL; Superoxide dismutase, SOD; Malondialdehyde, MDA. Tumor necrosis factor-α, TNF-α; Interleukin, IL; Superoxide dismutase, SOD; Malondialdehyde, MDA.

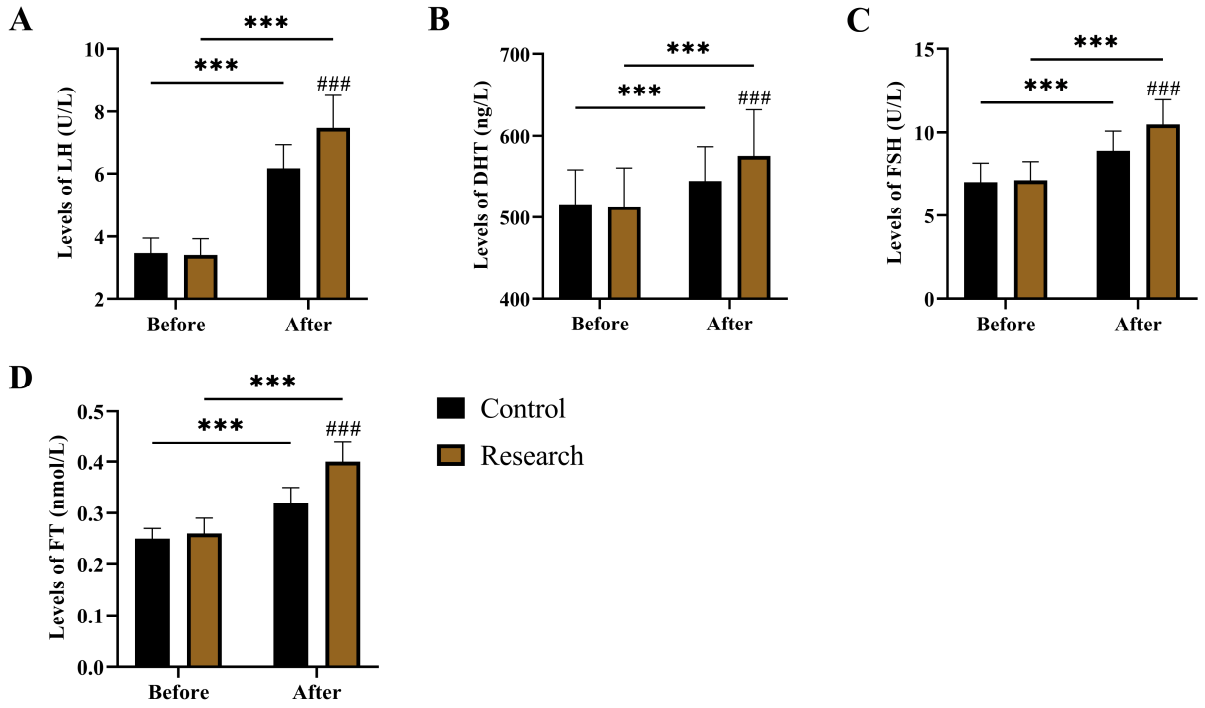

Fig. 2: Comparison of sex hormones before and after treatment. A) LH, B) DHT, C) FSH, D) FT. Comparison with control group ###P<0.001, and comparison with before treatment ***P<0.001. Lutropin, LH; Dihydrotestosterone, DHT; Follicle-stimulating hormone, FSH; Free testosterone, FT.

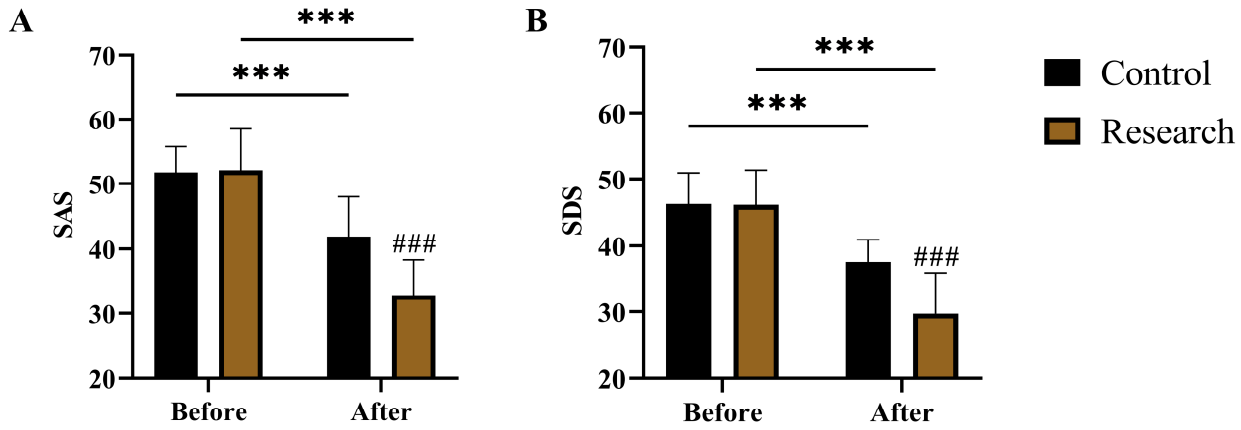

Fig. 3: Comparison of psychological status before and after treatment. A) SAS, B) SDS. Comparison with control group ###P<0.001, and comparison with before treatment ***P<0.001. Self-Rating Anxiety/Depression Scale, SAS/SDS.

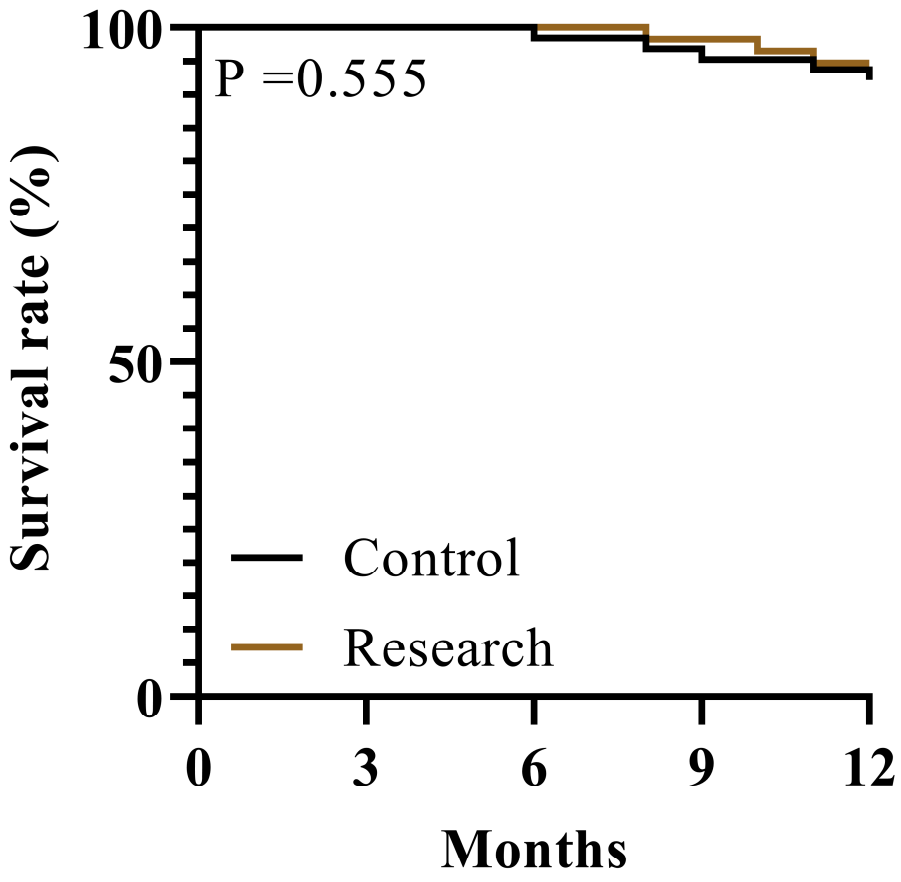

Fig. 4: Comparison of prognostic survival curve, there was no difference in the overall survival rate of prognosis between the two groups of patients (P=0.555).

Table 1: Comparison of baseline information between the two groups.

	Control group (n=64)	Research group (n=58)	t (χ^2)	P
Age (years)	58.56±5.08	59.12±5.78	0.568	0.571
Duration of disease (months)	6.39±1.99	6.05±1.75	0.994	0.322
Body mass index (kg/m^2)	23.21±1.72	23.71±1.56	1.651	0.101
Smoking (%)			0.051	0.821
yes	30 (46.88)	26 (44.83)		
no	34 (53.13)	32 (55.17)		
Drinking (%)			0.398	0.528
yes	24 (37.50)	25 (43.10)		
no	40 (62.50)	33 (56.90)		
Combined hypertension (%)			0.094	0.759
yes	17 (26.56)	14 (24.14)		
no	47 (73.44)	44 (75.86)		
Combined diabetes mellitus (%)			1.814	0.178
yes	15 (23.44)	20 (34.48)		
no	49 (76.56)	38 (65.52)		
Pathological staging (%)			0.282	0.595
I-II	47 (73.44)	45 (77.59)		
III-IV	17 (26.56)	13 (22.41)		
IIEF scores				
Barrier-free	6 (9.38)	6 (10.34)	0.032	0.857
Mild	27 (42.19)	27 (46.55)	0.235	0.628
Moderate/severe	31 (48.44)	25 (43.10)	0.349	0.555

Table 2: Comparison of nutritional status before and after treatment

		control group (n=64)	Research group (n=58)	t (χ^2)	P
ALB (g/L)	Before	37.02±3.92	36.21±5.88	0.903	0.368
	After	30.44±5.47	37.12±4.15	7.539	<0.001
	t	7.822	0.963		
	P	<0.001	0.338		
HGB (g/L)	Before	121.68±9.03	120.88±9.26	0.483	0.630
	After	112.78±12.31	120.07±11.89	3.320	0.001
	t	4.664	0.409		
	P	0.001	0.683		
TP (g/L)	Before	61.06±9.83	61.34±8.65	0.166	0.868
	After	55.12±8.06	69.24±8.79	3.356	0.001
	t	3.738	0.679		
	P	0.001	0.498		
NRS2002 (%)	None	18 (28.13)	17 (29.31)	0.021	0.885
	Mildly	18 (28.13)	27 (46.55)	4.438	0.035
	Moderate	12 (18.75)	8 (13.79)	0.546	0.460
	Severe	16 (25.00)	6 (10.34)	4.421	0.036

Note: Albumin, ALB; Hemoglobin, HGB; Total protein, TP; Nutrition Risk Screening, NRS2002.

Table 3: Comparison of prognostic erectile dysfunction

	control group (n=59)	Research group (n=55)	t (χ^2)	P
Barrier-free (%)	8 (12.50)	21 (36.21)	9.437	0.002
Mild (%)	41 (64.06)	27 (46.55)	3.782	0.052
Moderate/severe (%)	10 (15.63)	7 (12.07)	0.321	0.571

However, some studies have suggested that the long-term use of PUE has a more significant effect on estrogen activation, which in turn inhibits the secretion of androgens (Pham *et al.*, 2022). Although PCa treatment usually requires the suppression of androgen levels, the moderate rebound of sex hormone levels in the PUE group in this study may be related to the recovery of endocrine function after surgery. PUE may promote the anabolic metabolism of sex hormones by regulating the function of the hypothalamic-pituitary-gonadal axis, rather than simply inhibiting their secretion. This discovery suggests that PUE may play a unique role in maintaining postoperative gonadal homeostasis, but its dose-dependent effect needs to be further explored.

As far as the psychological status is concerned, the SAS and SDS scores in the research group were improved more obviously than those in the control group after treatment, which also shows that the use of PUE has a positive impact on mitigating the negative psychological status of patients. It is due to the fact that the main chemical component of puerarin is flavonoids, which can inhibit the central nervous system and are commonly used in traditional Chinese medicine for soothing the nerves and sedation (Liu *et al.*, 2021), helping to alleviate patients' negative emotions caused by diseases and surgical procedures. In a meta-analysis by Li Z *et al*, they stated that PUE appeared to be safer and more effective than conventional drug therapy alone in improving overall clinical efficacy and left ventricular ejection fraction in patients with acute heart failure (Li *et al.*, 2022). In addition, clinical studies suggest that postoperative nutritional status is one of the keys to ensuring patients' rehabilitation quality and maintaining a good nutritional status of patients can help avoid the risk of various complications (Sanchez Leon *et al.*, 2023). The prostate, as one of the most important reproductive organs of men, has a direct impact on the synthesis, absorption and metabolism of nutrients in the human body through its regulation of endocrine function (Matsushita *et al.*, 2020). Therefore, after prostatectomy, patients generally experience a significant loss of nutritional proteins and a significant decline in their overall health status.

PUE contains a large amount of dietary fiber, which not only promotes gastrointestinal peristalsis and strengthens the spleen and stomach, but also prevents bacteria from eroding intestinal epithelium, reduces damage to epithelial integrity and changes the composition of mucin-utilizing bacteria, thus affecting the permeability of mucus (Wong *et al.*, 2015). Short-chain fatty acids are a direct energy source for epithelial and goblet cell proliferation and PUE supplementation can increase the level of short-chain fatty acids, which plays an important role in maintaining the nutritional status of patients. The study of Xu DX *et al*. also indicated that PUE improves hepatic glucose and lipid homeostasis in vitro and in vivo by modulating the AMPK pathway (Xu *et al.*, 2021), which undoubtedly lays a more reliable foundation for ensuring the health of patients and improving their nutritional status. Given the significant impact of PUE discussed above, the milder erectile dysfunction observed in the research group compared to the control group is also predictable. This finding underscores the importance of PUE for the prognosis and overall health of patients with PCa.

However, no marked inter-group difference was found in prognostic survival, which we speculated might be due to the small number of cases included in this study, which may lead to chance results. At the same time, there are other prostatectomy adjuvants currently available in the clinic (e.g., flutamide, bicalutamide, enzalutamide, etc.), but it is not clear to us that PUE still has an advantage when comparing it to these drugs. In the follow-up, it is necessary to increase the number of cases and extend the follow-up period to further evaluate the influence of PUE on the long-term prognosis of PCa patients. In addition, we also need to consider whether there is an impact on recovery in PCa patients between different doses of PUE. In the meantime, we also need to conduct in vitro experiments should be carried out as soon as possible to confirm the mechanism of PUE on PCa, so as to provide a more comprehensive reference for clinical practice.

CONCLUSION

PUE combined with prostatectomy can reduce postoperative inflammation and stress injury in PCa patients, mitigate their negative emotions and improve sex hormone secretion and nutritional status to provide patients with a more reliable guarantee for their prognosis and health physiologically and psychologically. We suggest that in the future, clinics should popularize the use of PUE when performing prostatectomy treatment for patients with PCa, which can provide more reliable prognostic recovery for patients.

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Author contributions
Guoyong Wang conceived and designed the project, and wrote the paper. Guoyong Wang and Liping Shang generated the data. Guoyong Wang analyzed the data. Liping Shang modified the manuscript. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Data availability statement
Original data in this study are available from the corresponding author on reasonable requests.

Ethical approval
This study was approved by the Ethics Committee of Dongying Zhongyi Hospital (Approval NO: 2022LK041)

and was performed in accordance with the principles of the Declaration of Helsinki. All eligible participants signed an informed consent form.

Conflict of interest

The authors declare no conflict of interest.

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