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BACTRIAN CAMEL WHEY PROTEIN POWDER ALLEVIATES ACUTE HEAT STRESS-INDUCED KIDNEY INJURY AND APOPTOSIS IN RATS

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ABSTRACT

This study was aimed to evaluate the protective effects of Bactrian camel whey protein (CWP) powder on acute heat stress (HS)-induced kidney injury and apoptosis in rats and to compare its efficacy with bovine whey protein (BWP). An acute heat stress rat model was constructed by randomly dividing SD rats into seven groups: control group, HS model group, CWP treatment group (low dose: 100 mg/kg, medium dose: 200 mg/kg and high dose: 400 mg/kg), BWP group (400 mg/kg) and N-acetylcysteine (NAC) positive control group. The key assessment parameters included core body temperature (Tc), serum urea nitrogen (BUN) and creatinine (S-cr) levels, histopathological changes in the kidneys, immunohistochemistry of NGAL expression and apoptosis assay using TUNEL assay. Exposure of rats to a temperature of 40°C ± 0.5°C and relative humidity of 60% ± 5% for 3 h induced heat stress and caused kidney injury and apoptosis, with the most severe damage occurring at 9 h of rewarming. Histopathological examination revealed glomerular congestion, inflammatory infiltrate and renal apoptosis.CWP treatment significantly reduced kidney injury markers and apoptosis rates, with the high dose (400 mg/kg) showing effect comparable to or superior to NAC and BWP. Immunohistochemical analysis showed that CWP effectively inhibited NGAL expression and promoted renal repair. CWP significantly mitigated acute HS-induced kidney injury in rats through its antioxidant and anti-apoptotic effects. Its efficacy exceeded that of BWP, highlighting its potential as a natural protective agent.

Key words: Acute heat stress, apoptosis, camel whey protein, kidney injury

In recent years, global warming has emerged as a critical issue that cannot be overlooked. As temperatures rise, heat stress, resulting from the exposure of organisms to high temperatures and humidity, has posed a significant threat to animal welfare. This has become a major impediment to livestock reproduction and productivity. Kidney damage is one of the common complications associated with heat stress (HS), often accompanied by apoptosis (Wang, 2019; Jing, 2024). Heat stress can be categorised into acute and chronic types, depending on the duration and frequency of exposure to elevated temperatures. Acute heat stress is typically characterised by rapid, short-term exposure to high temperatures, lasting for several hours. In contrast, chronic heat stress involves prolonged exposure over weeks or months, or exposure to cyclical temperature patterns (Yin, 2021). Both forms of heat stress have the potential to undermine the sustainability of the livestock industry.

Heat stress induces oxidative stress, which leads to the activation of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the organism (Yang *et al,* 2010). This results in an imbalance between the oxidative and antioxidant systems, contributing to tissue damage and metabolic disorders. Apoptosis plays a crucial role in tissue damage and oxidative stress can trigger apoptosis through multiple pathways, including the mitochondrial pathway, death receptor pathway and endoplasmic reticulum (ER) stress pathway (Destaw *et al,* 2023). Enhancing the body's antioxidant capacity is an effective strategy to mitigate tissue damage. However, long-term use of certain antioxidant drugs may lead to toxic side effects and antioxidants such as vitamin C are prone to oxidation, which complicates their prolonged use. Therefore, the identification of a natural antioxidant that can be used long-term without side effects, while maintaining efficacy and cost-effectiveness, is the central objective of this study.

Recent research on camel milk has confirmed its potential in significantly alleviating kidney damage in diabetic rats and inhibiting apoptosis (Adelakun

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et al, 2024). Camel whey protein contains bioactive peptides that scavenge free radicals, helping to prevent diseases associated with oxidative stress. Among these, lactoferrin is identified as the primary antioxidant component in camel whey protein, with its total antioxidant capacity comparable to that of vitamin C, making it a promising natural antioxidant (Zhang *et al,* 2005). Consequently, this study employed camel whey protein as an intervention in a rat model of acute heat stress, administering it to assess its effects on kidney injury and apoptosis induced by acute heat stress.

Materials and Methods

Main reagents and instruments

4% paraformaldehyde universal tissue fixative (Servicebio-G1101-500mL); Haematoxylin and Eosin (H&E) high-definition constant dyeing kit (Servicebio-G1076); Urease method detection kit for urea nitrogen (Nanjing Built Institute of Biological Engineering -C013-2-1); Creatinine sarcosine oxidase method detection kit (Nanjing Built Institute of Biological Engineering -C011-2-1); high-speed freezing centrifuge (Sigma, Germany); Artificial climate box (Jiangsu Jintan Liangyou Experimental Instrument Factory, China); Multifunctional Enzyme Labeler (Bio-Tex, USA, ELX800); EDTA(pH8.0) (Biofroxx-1340GR); Vitamin C (VC)/Ascorbic Acid (ASA) Assay Kit (Nanjing Built Institute of Biological Engineering -A009-1-1); NAC Antioxidant (Biyun Tian-S0077)

Ethics Statement and Animal Welfare

The study was conducted using six-week-old Specific Pathogen Free (SPF) healthy SD rats, with equal representation of males and females, each weighing 220 ± 20 g. The rats were randomly housed in standard cages, provided with free access to food and water and kept in a controlled environment with a temperature of 25 ± 2°C and humidity of 50 ± 5%. A 12-hour light-dark cycle was maintained and the animals were allowed a 10-day acclimatisation period. The experiment was approved by the Scientific Research and Ethics Committee of Inner Mongolia Agricultural University (GB/T 35892-2018).

Collection and Preparation of Camel Whey Protein

Fresh camel milk was aseptically collected from 20 healthy Bactrian camels in Alxa. The milk was then pooled in equal proportions, followed by centrifugation to remove the fat. The resulting skim milk was pasteurised and purified through acid precipitation of casein and ammonium sulfate. The protein fraction was dialysed overnight at 4°C using dialysis bags with a molecular weight cut-off of 3500. The dialysed camel whey was subsequently freeze-dried using a lyophiliser and stored at -20°C (Hao, 2020; Du, 2022).

Construction of Acute Heat Stress Model

To investigate the effects of different rewarming durations on kidney injury in SD rats after heat stress (HS), 36 SD rats (18 male and 18 female) were randomly assigned to either the control group or the HS model group, which included subgroups with rewarming times of 0 h, 3 h, 6 h, 9 h and 12 h (n=6). After a 10-day acclimatisation period, the rats were exposed to HS by placing them in an artificial climatic chamber maintained at 40°C±0.5°C and 60%±5% relative humidity for 3 hours (Zhang, 2022; Geng *et al,* 2015). Following heat stress, the rats were transferred to a standard rearing environment to undergo rewarming. Rectal temperatures were recorded at 3-hour intervals and at each time point (0 h, 3 h, 6 h, 9 h and 12 h), rats were anaesthetised to collect blood for serum separation and to harvest kidneys for histological examination. The kidney tissues were fixed in 4% paraformaldehyde for H&E staining to evaluate renal damage associated with HS.

Assessment of Nephrotoxicity Markers (BUN, S-Cr)

Serum samples were centrifuged at 3000 rpm for 10 minutes and analysed according to the manufacturer's instructions. The absorbance of serum creatinine (S-Cr) was measured at 546 nm and blood urea nitrogen (BUN) was measured at 640 nm.

Histopathological Analysis of Kidney Tissues

Kidney tissue blocks were fixed in 4% paraformaldehyde overnight at room temperature. After fixation, the tissues were processed, embedded in paraffin and sectioned into 4 μm slices using a microtome. The sections were dewaxed, rehydrated, stained with haematoxylin and eosin (H&E) and mounted with neutral gum. Histological images were captured using a standard light microscope.

Experimental Design

Six-week-old rats were acclimatised in the laboratory for 1 week and then randomly assigned to one of seven groups:

Control Group: Received saline via gavage at a dose of 1 mL/day for 10 days.

Model Group: Received saline via gavage at a dose of 1 mL/day for 10 days, followed by acute heat

stress (temperature: 40 ± 0.5°C; humidity: 60 ± 5%; duration: 3 h).

CWP Groups: Divided into low, medium and high dose groups, receiving CWP at doses of 100, 200 and 400 mg/kg per day, respectively, for 10 days. Acute heat stress was then induced.

Bovine whey protein (BWP) Group: Received BWP at a dose of 400 mg/kg per day for 10 days, followed by acute heat stress.

NAC Positive Control Group: Received N acetylcysteine (NAC) at a dose of 100 mg/kg per day via intraperitoneal injection for 10 days, followed by acute heat stress.

Following 3 h of heat stress, the rats were returned to a room temperature environment for recovery. After 9 h of rewarming, they were anaesthetised and blood samples were collected from the heart. Kidney tissue was then harvested: a portion was fixed in 4% paraformaldehyde for pathological section analysis, while the remaining tissue was stored at −80°C for subsequent experiments.

Immunohistochemistry of Renal NGAL

Kidney tissue sections underwent antigen retrieval using citric acid buffer (pH 6.0) and were incubated in 3% BSA at room temperature for 30 minutes. The sections were then incubated overnight at 4°C with a primary antibody against NGAL (1:100) in a humidified chamber. The following day, the sections were incubated with a horseradish peroxidase (HRP)-conjugated goat anti-rabbit secondary antibody (1:200) for 50 minutes at room temperature. Colour development was achieved using diaminobenzidine (DAB), after which the sections were mounted with a sealing gel. Results were visualised and interpreted under a light microscope.

TUNEL Detection of Apoptosis in Kidney Cells

Kidney tissue sections underwent proteinase K treatment for antigen retrieval and cell nuclei were counterstained with DAPI. The sections were incubated in the dark at room temperature for 10 min, then mounted with an anti-fade mounting medium. Fluorescence microscopy was employed to visualise the sections and images were captured. DAPI was excited with a UV light (330–380 nm) and emitted a blue light (420 nm), while CY3 was excited with a green light (510–561 nm) and emitted a red light (590 nm).

Statistical Analysis

Experimental data were analysed using SPSS 26.0 software, employing independent sample t-tests and one-way ANOVA. Data are expressed as mean ± SEM. The data visualisation was accomplished using GraphPad Prism 10.

Result

Acute Heat Stress Model

Core body temperature (Tc) is a critical index for assessing the onset of heat stress (HS) in animal organisms. Rectal Tc was measured immediately after exposure to HS and at 3 h, 6 h, 9 h and 12 h during the rewarming phase. The results showed that HS significantly elevated the rectal temperature in rats, with the mean body temperature rising from 37.81°C at baseline to 41.31°C after statistical analysis. As shown in Fig 1, the Tc at the end of HS was significantly higher compared to the control group. However, with the progression of rewarming, Tc gradually returned to baseline values and no longer differed significantly from the control group after 12 hours of rewarming.

When comparing the Tc values at different rewarming times to those at 0 h, no significant difference was found between the 0 h and 3 h groups, with an average hourly decrease of only 0.11°C. However, there was a significant difference in Tc between the 0 h and 6 h groups, with the 0 h group showing significantly lower Tc values after 9 h of rewarming. The Tc values of the 0 h group remained significantly higher than those of the control group throughout the experiment.

These findings indicate that exposure to a temperature of 40°C ± 0.5°C and a relative humidity of 60% ± 5% for 3 hours is sufficient to induce HS in rats, as evidenced by the significantly elevated Tc values.

Detection of Kidney Injury Indices in Rats Following Acute Heat Stress

As illustrated in Fig 2, panel A shows the changes in blood urea nitrogen (BUN) concentration in rats. At 0 hours following the cessation of heat stress (HS), BUN levels remained relatively stable and did not differ significantly from the control group. However, after 3 hours of recovery, BUN concentration began to rise, with a highly significant increase compared to the control group. By 12 hours of rewarming, BUN levels had returned to baseline values, similar to those observed in the control group.

Panel B depicts the changes in serum creatinine (S-cr) concentration following HS. At 0 hours post-HS, there was no significant change in S-cr levels.

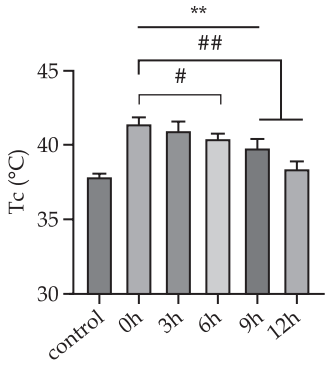

Fig 1. Effect of HS on Tc in rats. After HS, the temperature (Tc) of rectal nucleus was detected by electronic thermometer for animals. Data are expressed as mean ± SEM, "*" indicates a significant difference compared to the control group ($p < 0.05$) and "**" indicates a highly significant difference compared to the control group ($p < 0.01$);and "#" indicates a significant difference compared to the 0h group ($p < 0.05$); and "##" indicates a highly significant difference compared with the 0h group ($p < 0.01$).

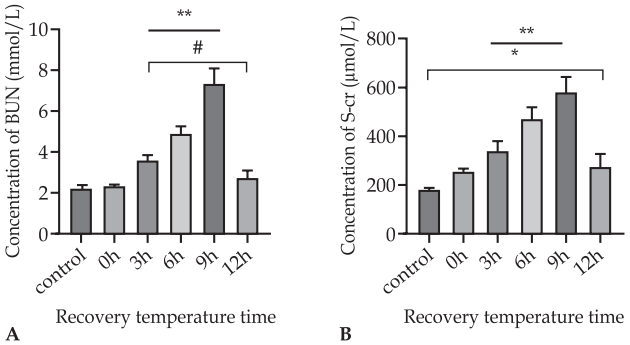

Fig 2. Effect of HS on BUN and S-cr, indicators of kidney injury in rats. A: Serum urea nitrogen (BUN) concentration in rats; B: Serum creatinine (S-cr) concentration in rats. The horizontal coordinates in the graphs indicate different rewarming times after HS. Data are expressed as mean ± SEM, "*" indicates a significant difference compared to the control group ($p < 0.05$) and "**" indicates a highly significant difference compared to the control group ($p < 0.01$);and "#" indicates a significant difference between the two groups ($p < 0.05$)

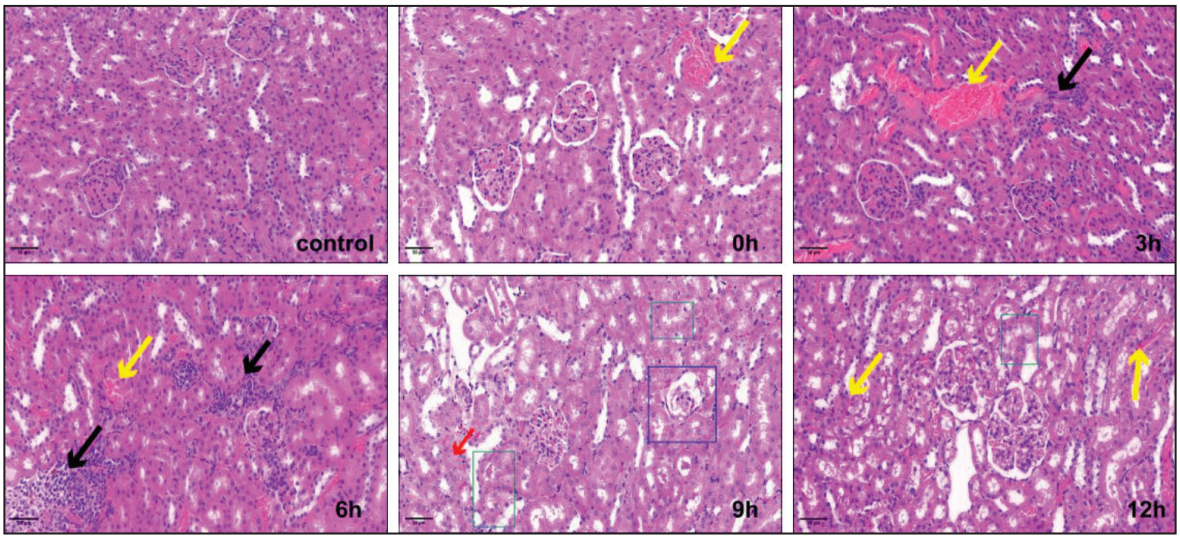

Fig 3. Histopathological changes in rat kidney at different rewarming times after HS (H&E, 200×, n=6). Rat kidneys were collected for HE staining and the intercepted field of view was 200× magnification image. The Fig is labelled with different experimental groups, i.e. different rewarming times after HS. The yellow arrows indicate renal haemorrhage, the black arrowheads point to inflammatory cell infiltration, the red arrowheads show cell nucleus fragmentation and lysis, the green box range shows granular degeneration and blistering degeneration and the blue box area shows glomerular thylakoid cells damage and loss of internal brush border structure.

After 3 hours of rewarming, S-cr concentrations rose rapidly, reaching their peak at 9 hours. The difference between the 3-hour and 9-hour time points was highly significant when compared to the control group. At 12 hours of rewarming, S-cr concentrations decreased significantly but remained notably higher than those in the control group.

The comparison of kidney injury indices further confirmed the significant increase in these biomarkers after HS, supporting the successful establishment of the acute heat stress rat model.

Histopathological Changes in Kidney Tissue of Rats After Acute Heat Stress

The histopathological alterations in the kidney tissues of rats following acute heat stress (HS) are shown in Fig 3 In the control group, which was not subjected to HS, the glomerular and tubular structures of the kidneys were intact, with cells arranged neatly and exhibiting normal cellular morphology. In contrast, at 0 hours post-HS, the glomerular capillaries were dilated and congested, accompanied by interstitial capillary dilation. Several

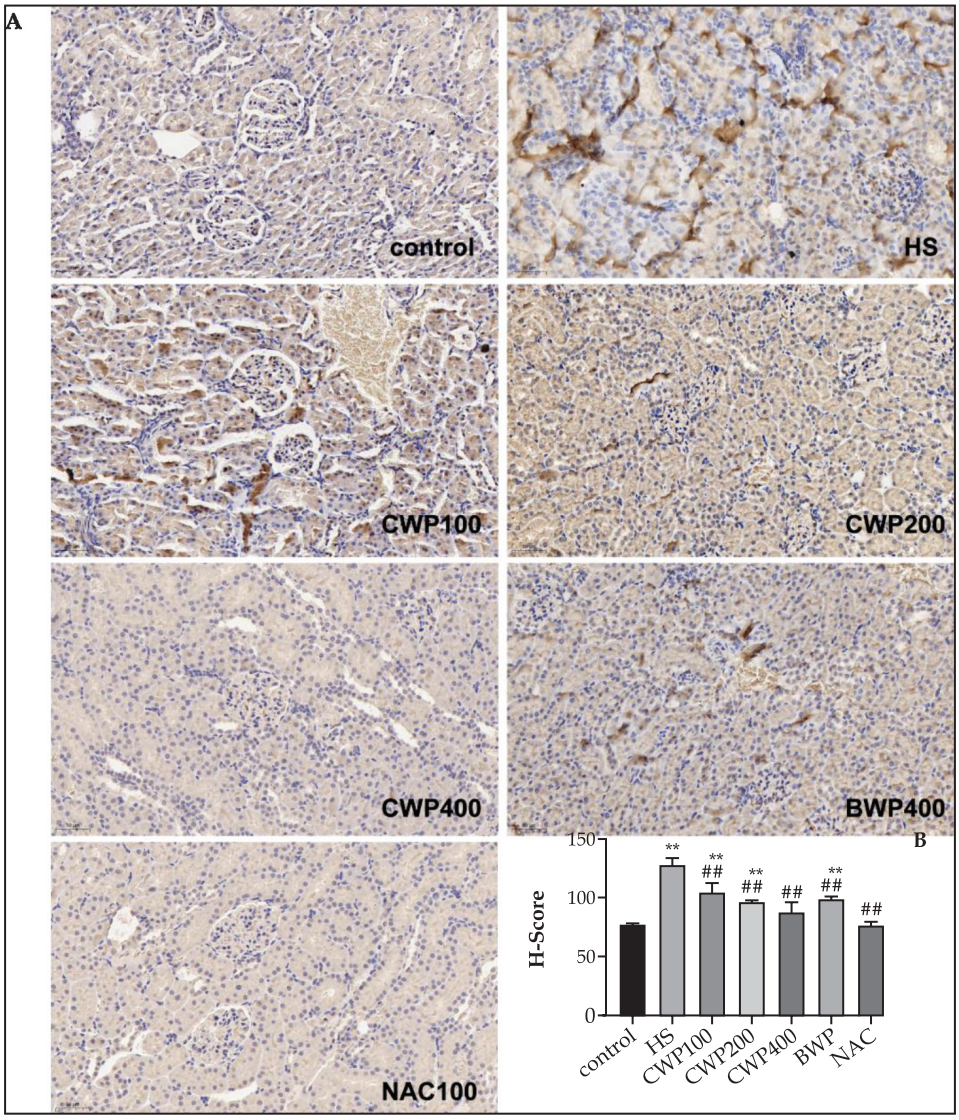

Fig 4. **A:** Immunohistochemical assay of CWP on kidney injury in acute heat stress rats (IHC, NGAL, 200×, n=6). **B:** Immunohistochemical scores. Immunohistochemical positivity scores were calculated after intelligent analysis according to Aipathwell software. Data were expressed as mean ± SEM values, "*" indicates significant difference compared to control group (P<0.05); "**" indicates highly significant difference compared to control group (P<0.01); "#" indicates a significant difference compared with the HS group (P<0.05) and "##" indicates a highly significant difference compared with the HS group (P<0.01).

areas showed distinct haemorrhagic lesions (indicated by yellow arrows).

At 3 hours of rewarming, interstitial haemorrhagic areas significantly increased, with a minor infiltration of inflammatory cells (black arrows). By 6 hours of rewarming, interstitial haemorrhages persisted, along with a substantial infiltration of inflammatory cells. At 9 hours of rewarming, structural damage to cellular tissues became evident. Notably, the renal tubular epithelial cells (highlighted by red arrows) exhibited nuclear fragmentation, lysis and granular as well as vacuolar degeneration. Urinary tubular patterns were also observed in the lumen of the renal tubules (green box) and severe damage to the glomerular capillary walls and associated cells led to cavity formation (blue box). At 12 hours of rewarming, haemorrhages remained in certain areas and vacuolar degeneration persisted in some regions.

These findings demonstrate that tissue damage did not occur immediately following HS but progressively manifested during the rewarming process. The results also confirm that exposure to a temperature of 40°C ± 0.5°C and relative humidity of 60% ± 5% for 3 hours induces kidney injury in rats, thereby establishing a successful model of acute heat stress-induced kidney injury.

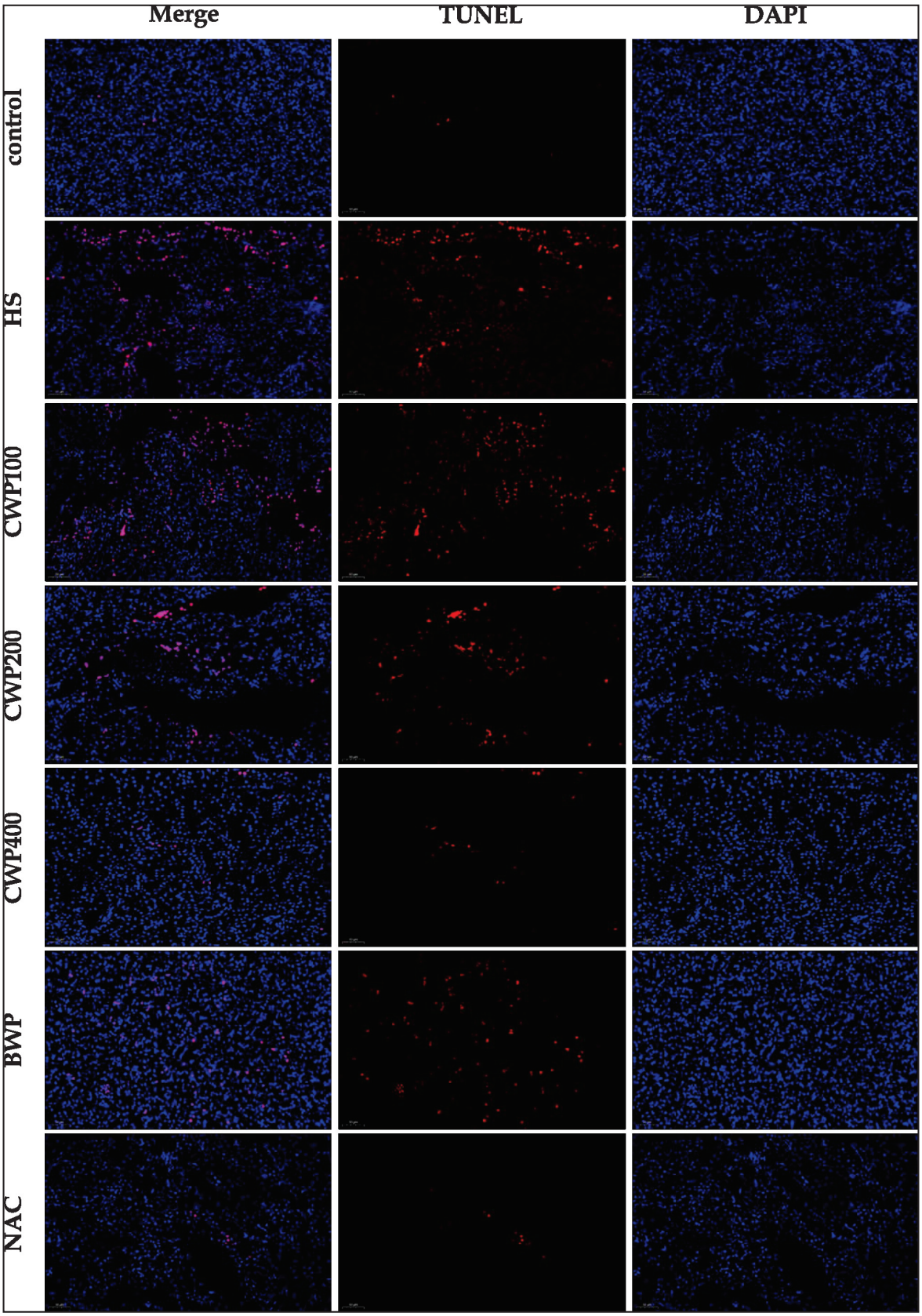

Fig 5. Apoptosis in rat kidney cells after acute heat stress (TUNEL, 200×, n=6). TUNEL assay was used to detect apoptosis in acute heat-stressed rat kidney cells under CWP intervention, 200× field of view, DAPI re-stained nuclei were blue under UV and CY3 fluorescein labelled positive apoptotic nuclei were red.

Detection of Kidney Injury in Acute Heat Stress Rats Using Immunohistochemical Methods

As shown in Figs 4, the control group exhibited minimal positivity, with a yellowish colour and almost no positive staining, while the HS model group demonstrated significantly stronger positivity, appearing brownish in colour. These differences between the two groups were highly significant. In contrast, the degree of positivity in the low, medium and high-dose CWP groups gradually decreased and significant differences were observed between these groups and the HS model group. However, no significant difference was found between the high-dose CWP400 group and the control group, suggesting that CWP400 provides better kidney protection under acute heat stress than the HS model group. Interestingly, the BWP group showed localised areas of medium-positive brownish-yellow staining, as well as areas of strong positivity.

The positive cell ratio, defined as the number of positive cells relative to the total number of cells, reflects the extent of positive cell presence. The HS model and BWP groups exhibited relatively high values in this regard. In addition, positive cell density, calculated as the number of positive cells per unit area of tissue, was denser in the HS model group, indicating a more concentrated distribution of positive cells. Meanwhile, the average optical density (AOD), representing the cumulative optical density of the positive signal per unit area, demonstrated that while BWP had the lowest AOD, its positivity distribution was uneven, with areas of intense staining and others with weak positivity. This uneven distribution led to a lower average value.

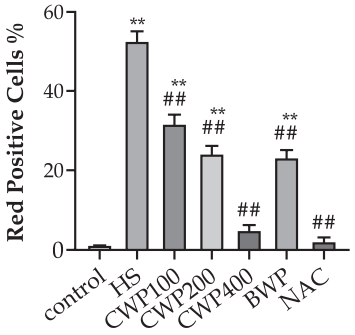

Fig 6. Apoptosis rate (Red Positive Cells %). Red light positive rate = total number of red light positive cells/total number of cells. Data are expressed as mean ± SEM values, "*" indicates significant difference compared with control group (P<0.05), "**" indicates highly significant difference compared with control group (P<0.01); "#" indicates a significant difference compared with the HS group (P<0.05) and "##" indicates a highly significant difference compared with the HS group (P<0.01).

Finally, histological scoring further corroborated these findings. The HS model group had the highest score, indicating the most intense positivity, followed by the CWP low, medium and high-dose groups. The BWP group showed positivity levels between the CWP low and medium doses, consistent with earlier conclusions. The NAC control group and the control group both exhibited the least positivity.

These results clearly indicate that as the CWP dose increases, kidney protection against injury improves significantly, outperforming BWP at equivalent doses.

Effect of CWP on Renal Cell Apoptosis in Acute Heat Stress Rats

After 3 hours of acute heat stress, the number of apoptosis-positive cells in the kidneys of rats in the HS model group increased significantly, showing a marked difference compared to the control group (Fig 5, 6). The apoptosis rate was notably reduced in the CWP medium- dose group. Additionally, no significant difference was observed between the CWP400 high-dose group and the NAC group when compared to the control group, whereas the BWP group still exhibited a more severe apoptosis response. These results suggest that the high dose of CWP effectively prevents renal cell apoptosis under acute heat stress conditions.

Discussion

Elevated body core temperature (Tc) is a hallmark of heat stress (HS), though there is no universally agreed-upon threshold Tc value for diagnosing HS. Several studies have indicated that apoptosis occurs when Tc exceeds 41.6°C for more than 45 minutes, while others report that tissue damage and apoptosis can be induced in rats by maintaining Tc at 41.5°C for 2 hours (Li *et al,* 2023). Notably, when Tc exceeds 40°C, central nervous system dysfunction and multi-organ damage, particularly to the liver and kidneys, are commonly observed (Fang *et al,* 2023). In this experiment, one rat died post-HS with a Tc of 41°C. No external trauma was observed, but foamy liquid was found in the nasal cavity, suggesting that individual susceptibility, possibly due to a weaker constitution, might have contributed to the fatal outcome.

Blood urea nitrogen (BUN) and serum creatinine (S-cr) are widely used markers for assessing renal function and monitoring kidney injury. BUN is the primary end product of protein metabolism, produced in the liver and excreted by

the kidneys. Elevated BUN levels are indicative of renal dysfunction (Hang *et al,* 2024). The urease method is commonly employed to measure BUN, where urease hydrolyses BUN, releasing ammonia and carbon dioxide. The ammonia ions then form a blue substance in an alkaline medium, with the intensity of colour being directly proportional to BUN concentration (Lui *et al,* 2022). In our study, BUN levels began to rise 3 hours after HS and peaked at 9 hours post-rewarming, indicating a delayed onset of renal damage, consistent with the findings of Faten and coworkers (Faten *et al,* 2023).

S-cr, a byproduct of muscle metabolism, is normally filtered by the kidneys. Reduced glomerular filtration, as seen in renal impairment, leads to increased S-cr levels in the blood (Acharya *et al,* 2023). The sarcosine oxidase method for S-cr detection involves a series of enzymatic reactions, ultimately forming a purplish-red compound that can be quantified colourimetrically (Cevallos *et al,* 2024). Similar to BUN, S-cr levels in this study peaked 9 hours after rewarming, corresponding with the highest degree of kidney injury following HS.

To further assess kidney injury following acute heat stress, histopathological analysis was conducted on kidney tissues collected at different rewarming times. At 0 hours post-HS, only localised blood cells were observed and tissue structure remained largely intact, with no significant difference from the control group. However, by 3 hours post-HS, haemorrhaging, inflammatory infiltration, cellular blistering and nuclear fragmentation were evident, suggesting that the body initiated an inflammatory response to mitigate HS-induced damage, which progressively worsened over time (Jing *et al,* 2024). This finding supports the successful establishment of an acute heat stress-induced kidney injury model.

Immunohistochemical analysis revealed that the BWP group exhibited a more complex positive reaction compared to the CWP group. The BWP group showed moderate to strong brownish-yellow staining, indicating a weaker repair effect on kidney injury, particularly when compared to the CWP group. This could be attributed to the composition or bioavailability of BWP, suggesting it may not provide sufficient protection against acute heat stress-induced kidney injury (Szumilas *et al,* 2024).

In this study, CWP was shown to significantly alleviate HS-induced kidney injury in rats, improving renal function and inhibiting renal cell apoptosis. CWP, rich in lactoferrin, immunoglobulins and bioactive peptides, appears to enhance immune responses, counteract oxidative stress and reduce apoptosis (Gamal *et al,* 2017), thus demonstrating its potential as a natural bioactive agent in protecting against HS-induced kidney injury.

Despite these promising findings, several issues remain to be addressed. First, the precise mechanisms of CWP, particularly its effects on cellular signaling and gene expression, are not fully understood. Further molecular biological investigations are needed to elucidate these pathways. Second, optimal dosages and timing of CWP administration require further refinement, as different dosing regimens may yield varying therapeutic outcomes. Additionally, while CWP has shown efficacy in animal models, its safety and clinical applicability need to be rigorously evaluated in clinical trials.

In conclusion, CWP offers significant protective effects against acute heat stress-induced kidney injury and apoptosis in rats. Through its antioxidant and anti-apoptotic actions, CWP holds promise as a novel natural agent for mitigating heat stress-related kidney injury. Future studies are essential to explore the mechanisms of action, determine the optimal application and assess the clinical potential of CWP, providing valuable insights into the treatment of heat stress-associated diseases.

Conclusion

An acute heat stress rat model was successfully established under conditions of 40°C ± 0.5°C ambient temperature and 60% ± 5% relative humidity for a duration of 3 hours. This model induced kidney injury, with the most pronounced damage observed at 9 hours post-rewarming. CWP demonstrated a significant protective effect in reducing kidney injury and apoptosis induced by acute heat stress in rats, with the effect being more pronounced at higher doses. At equivalent doses, BWP exhibited a less pronounced protective effect compared to CWP.

Funding

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