

Platelet-rich plasma alleviates skin photoaging and oxidative stress in rats by regulating autophagy and inhibiting the NLRP3 inflammasome pathway

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ABSTRACT

Background: Background: Ultraviolet radiation is the main cause of photoaging, which can induce oxidative stress and cellular senescence in the skin. It has been demonstrated that platelet-rich plasma (PRP) can significantly improve skin photoaging. However, the mechanism by which PRP improves photoaging remains unclear. **Materials and Methods:** In this study, UVA-induced SD rats were used as a skin photoaging model and administered with PRP treatment, aiming to elucidate the potential mechanism of its protection against photoaging. **Results:** They showed that PRP injection on the back of rats improved skin photoaging, oxidative stress, and inflammation, and inhibited skin cell apoptosis. In addition, PRP activated autophagy to inhibit NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome signaling pathway-related proteins. **Conclusion:** Our experimental results suggest that PRP plays an anti-UVA photoaging role by inhibiting autophagy and NLRP3 signaling pathways. Our study is the first to suggest that PRP anti-skin photoaging is associated with autophagy and NLRP3, providing a potential therapeutic approach for skin photoaging.

INTRODUCTION

There are two types of skin ageing: endogenous ageing, influenced by hormones, and exogenous ageing, caused by the environment. For this reason, exogenous ageing is also known as photoaging ⁽¹⁾, as exposure to ultraviolet rays is the primary environmental factor influencing skin ageing. Premature ageing of the skin due to the harmful effects of Ultraviolet (UV) irradiation is known as photoaging. Rough and dry skin texture, pigmentation, augmented wrinkles, and telangiectasia are some of the most noticeable clinical symptoms of photoaging ⁽²⁾. Photoaging is characterised histopathologically by a marked reduction in skin collagen and an aberrant buildup of elastin fibres ⁽³⁾. Matrix metalloproteinase (MMP) is also thought to have a significant role in photoaging, according to similar research ^(4,5).

Autophagy is a kind of evolutionary conservative cell process, through the degradation of damaged or dysfunctional organelles and protein to ensure cell survival ⁽⁶⁾. Neurodegenerative illnesses, infections,

cancers, and senescence are all related with altered autophagy levels or abnormalities ⁽⁷⁾. In recent years, the study found that cell autophagy may participate in the skin photoaging process. Previous studies have confirmed that activating autophagy can promote the clearance of oxidized phospholipids and protein multimers in keratinocytes induced by long-wave ultraviolet (UVA) to play an anti-apoptotic role ⁽⁸⁾. Lim *et al.* ⁽⁹⁾ confirmed that α -neoeendorphin can alleviate skin photoaging induced by ultraviolet irradiation by activating autophagy in human skin fibroblasts. Bai *et al.* ⁽¹⁰⁾ found that rapamycin could significantly improve the level of autophagy in human skin fibroblasts to treat skin photoaging induced by ultraviolet irradiation; Chen *et al.* found that Metformin could attenuate UVA-induced skin photoaging by inhibiting mitophagy ⁽¹¹⁾.

Platelet-rich plasma (PRP) is plasma containing a high concentration of platelets extracted from autologous venous blood by centrifugation. In addition to platelets, PRP contains high concentrations of growth factors and fibrin, such as platelet-derived growth factor (PDGF), transforming

growth factor (TGF- α , TGF- β), vascular endothelial cell growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor-I (IGF-I), and others⁽¹²⁾, these growth factors can bind the corresponding receptors on the cell membrane and activate a variety of downstream signaling pathways. Promote the proliferation of skin keratinocytes and fibroblasts, and increase collagen and elastin synthesis, blood vessel formation, and fat regeneration, thereby improving wrinkles and restoring skin elasticity^(13,14). PRP injection has been shown to be a safe anti-aging therapy that may dramatically enhance the skin's look and texture on the face⁽¹⁵⁾. Moussa *et al.*⁽¹⁶⁾ confirmed that PRP could significantly promote autophagy and the secretion of anti-inflammatory factors in chondrocytes, suggesting that PRP could promote autophagy and anti-inflammatory effects. Therefore, PRP may have a broad application prospect in the treatment of skin photoaging, but its specific mechanism still needs to be further verified.

The effects of PRP on skin photoaging, oxidative stress, NLRP3, and the autophagy pathway were studied in this work by using the UVA-induced photoaging paradigm in rats. PRP therapy offers promise as a method for treating skin ageing.

MATERIALS AND METHODS

The preparation of platelet-rich plasma

The rats were anesthetized and the cardiac arterial blood was drawn with a syringe. After the serum was separated, all the supernatant was absorbed and transferred to another centrifuge tube. After the serum was balanced, the tube was centrifuged for 10min at 2000 r/min. At this time, obvious stratification appeared in the centrifuge tube, the supernatant was the platelet-poor plasma of the patient, and the supernatant was platelet concentrate. Three-quarters of the supernatant in the centrifuge tube was absorbed and discarded, and the remaining slurry in the centrifuge tube was shaken to complete the preparation of platelet-rich plasma. This experimental study was approved by the Ethics Committee of Dongshan Hospital in December 2022 (No. 20221211)

Laboratory animals and treatment protocols

Six-week-old SPF SD rats (Half male and half female) were housed in a controlled environment with a constant temperature (22°C), a 12-hour light/dark cycle, and access to food and water. After adaptive feeding for 1 week, the dorsal skin area was irradiated with UVA (20 mJ/cm), and UV irradiation was applied once every other day for 30 min, and the irradiation time was extended by 10 min every 2 weeks to 80 min at 12 weeks. The irradiation was terminated at 14 weeks (cumulative UVA exposure

was 148.5 J/cm² and cumulative UVB exposure was 21.38 J/cm²). A control group (Ctrl), B a UVA group, C a UVA group with normal saline, and D a UVA group plus platelet-rich plasma (PRP). Each group consisted of six animals (n=6). 1ml of PRP and normal saline were drawn by insulin syringe and punctured into the dermis of each mouse and injected evenly into 20 spots, 0.05ml for each spot. Once a week for four weeks.

Western blot

RIPA buffer containing protease inhibitors (Beyotime Biotech Inc., China) was used to extract the skin tissue protein of rats in each group. Cracking on ice for 15min. The concentration was measured by BCA protein quantification kit (Beyotime Biotech Inc., China) after centrifugation at 4°C for 15 minutes. Total protein (30-50g) was denatured at a high temperature, then electrophoresed in SDS-PAGE gel, and the film was transferred in a moist environment. After blocking the skim milk powder at room temperature for 1 hour, the main antibody was added to the shaker at 4 degrees Celsius and left there overnight to react. The membranes were incubated with a diluted secondary antibody at room temperature for 1-1.5 hours after being rinsed three times with TBST the following day. Three rounds of TBST washing, followed by ECL (Beyotime Biotech Inc., China) luminescence and development exposure, were used on the membranes. Proteins such as matrix metalloproteinase 1 (MMP-1), collagen-1, elastin, BCL-2-associated X protein (Bax), B-cell lymphoma-2 (Bcl-2), caspase-3, Beclin1, P62, Autophagy-Related Protein LC3B (LC3B), NLRP3, pro-caspase-1, and apoptotic signaling complexes (ASCs) were examined for their relative expression levels. All antibodies were purchased from abcam (UK). The grayscale analysis was performed in Image J (NIH, USA).

Determination of superoxide dismutase (SOD), malondialdehyde (MDA), and catalase (CAT)

We measured the weight of skin samples taken from the backs of the rats. To create a 10% homogenate, skin samples were diluted with saline and sonicated twice at 4°C. Ten minutes were spent centrifuging the homogenate at 3,000 RPM. Experiments continued using aliquots of the supernatant. The BCA technique was used to count the number of protein molecules. Skin samples were analysed using MDA (Beyotime Biotech Inc., China), CAT (sigma aldrich, USA), and SOD (Beyotime Biotech Inc., China) detection kits, as per the guidelines provided by the respective manufacturers.

ELISA

Blood samples were collected from orbit and centrifuged at room temperature to collect rat serum. Interleukin 6 (IL-6), Interleukin 1b (IL-1 β), and

Tumor necrosis factor α (TNF α) were detected in each group according to the kit instructions (BOSTER, China). And statistical analysis.

Statistical

The information was analysed using SPSS (version 26.0, USA) and GraphPad 8.0 (USA) One-way analysis of variance (ANOVA) and t-tests were used to compare data from each group to the others. A significant difference is indicated by a *P value 0.05 and a very significant difference by a **P value 0.01.

RESULT

PRP can improve UVA-induced skin photoaging in rats

We irradiated rats with UVA for 8 weeks to establish a rat photoaging model. After treatment with PRP, the skin tissue of the back of rats was collected for relevant detection. The levels of MMP-1, Collagen 1, and Elastin expression in rat skin were determined using Western blotting as a proxy for photoaging. Results demonstrated that UVA-exposed rats had lower expression of Collagen 1 and Elastin and higher expression of MMP1 protein compared to untreated rats (figure 1, A-D). In contrast, PRP dramatically reduced MMP-1 in the skin of UVA-exposed rats compared to the saline group. However, levels of Collagen 1 and elastin rose dramatically (figure 1A-D). These findings provide further evidence that RPR can reduce age-related protein expression in rat skin ageing caused by UVA.

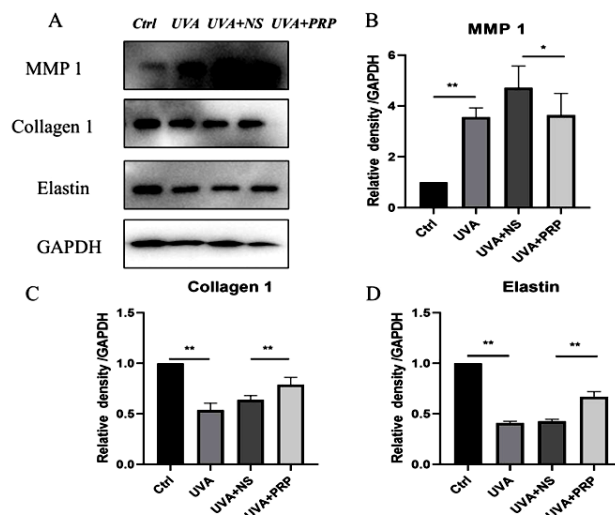


Figure 1. UVA helps the photoaging process in rat skin. **A.** RPR was used as a therapy after irradiation and protein collection. Western blotting was used to measure MMP-1, Collagen-1, and Elastin protein expression levels. **B-D;** the grayscale was evaluated with Image J. Ctrl: Positive control, UVA: UVA model irradiated rats, UVA+NS: group with normal saline, UVA+PRP: UVA model group was given PRP treatment. (n=6) * P < 0.05, ** P < 0.01.

PRP can improve UVA-induced apoptosis of skin cells

Uva-induced photoaging can lead to DNA and cell damage, and cells gradually undergo apoptosis. Western blotting was used to identify the apoptosis-related proteins Bax, Bcl 2, and caspase 3 in rat skin tissue in order to assess the impact of PRP on apoptosis of skin cells in rats.

Rats exposed to UVA had considerably higher levels of the pro-apoptotic protein Bax and lower levels of the anti-apoptotic proteins Bcl-2 and caspase 3 compared to untreated rats (figure 2, A-D). In rats subjected to UVA light, PRP therapy reduced the amount of the pro-apoptotic protein Bax in the skin relative to the saline group. At the same time, Bcl 2 and caspase 3 levels were significantly increased (figure 2A-D). These results indicated that PRP could alleviate UVA-induced apoptosis in the skin tissue of photoaging rats.

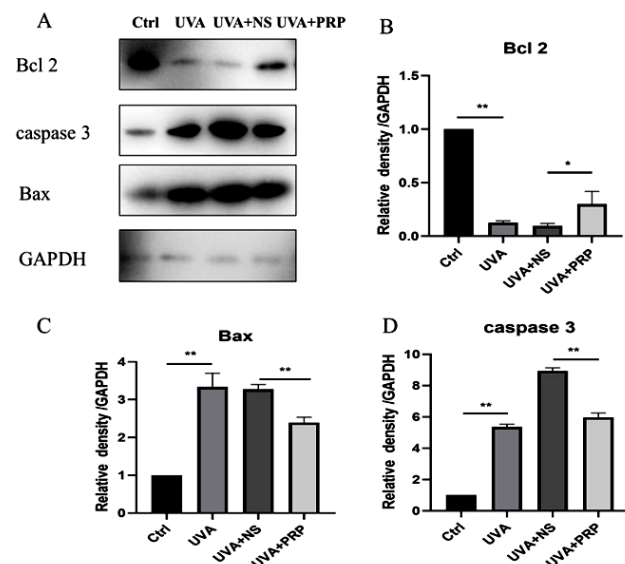


Figure 2. RPR improves UVA-induced apoptosis of skin cells. **A.** After irradiation, RPR was given for treatment and protein collection. Bax, Bcl 2, and caspase 3 protein expression levels were determined using Western blotting. **B-D:** The grayscale was evaluated with Image J. Ctrl: Positive control, UVA:UVA model irradiated rats, UVA+NS: group with normal saline, UVA+PRP: UVA model group was given PRP treatment. (n=6). * P < 0.05, ** P < 0.01.

PRP improves UVA-induced inflammation and oxidative stress

Photoaging can cause severe oxidative stress. Serum inflammatory factors and indices of oxidative stress were measured in rat skin homogenates using ELISA to assess the impact of PRP on oxidative stress in photoaging rats. The results indicated that MDA and serum inflammatory markers IL-1, IL-6, and TNF were dramatically raised, while SOD and CAT levels in the skin of UVA-exposed rats were significantly reduced. Meanwhile, PRP therapy under UVA exposure raised the contents of SOD and CAT in the skin, and decreased the contents of MDA and

inflammatory factors in the serum, compared to the saline injection group (figure 3A-F). These results suggest that PRP can alleviate UVA-induced oxidative stress and inflammation.

RPR alleviates photoaging by regulating autophagy and NLRP3 signaling pathways in rat skin tissue

To investigate the mechanism of PRP alleviating photoaging in rats, we detected the proteins related to autophagy and the NLRP3 signaling pathway in rat skin tissue by Western blot. The expressions of Beclin 1 and LC3B, two proteins involved in autophagy,

were found to be reduced in the skin tissues of UVA-induced photoaging rats, whereas the expression of P62 was found to be elevated. The expression levels of NLRP3, pro-caspaseE1, and ASC, all of which are involved in the NLRP3 signalling pathway, rose. Beclin 1 and LC3 expressions were found to be considerably higher in the PRP treatment group than in the normal saline group after UVA exposure, while the expressions of P62, NLRP3, pro-caspase-1, and ASC were decreased in the PRP treatment group. These results indicated that PRP significantly promoted autophagy and inhibited NLRP3 signaling pathway activation.

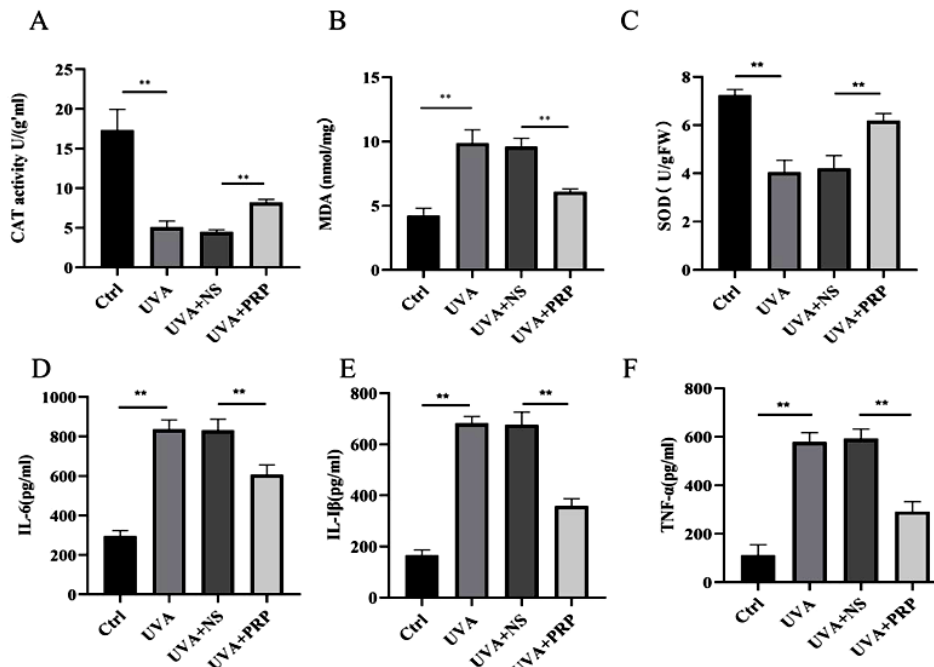


Figure 3. PRP alleviates UVA-induced oxidative stress and inflammation in rats. **A-C**, the kit colorimetric method to measure the contents of CAT, SOD, and MDA in skin homogenate. **D-F**, Elisa was used to determine the levels of IL-6, IL-1β, and TNF-α in the sera of each group's rat (n=6) Ctrl: Positive control, UVA:UVA model irradiated rats, UVA+NS: group with normal saline, UVA+PRP: UVA model group was given PRP treatment.(n=6) * P < 0.05, ** P < 0.01.

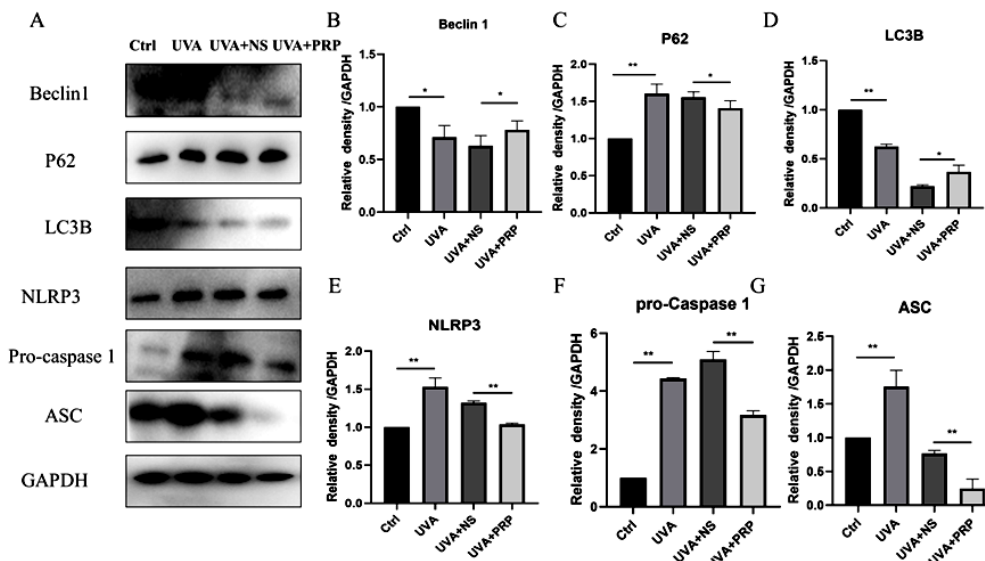


Figure 3. PRP alleviates UVA-induced oxidative stress and inflammation in rats. **A-C**, the kit colorimetric method to measure the contents of CAT, SOD, and MDA in skin homogenate. **D-F**, Elisa was used to determine the levels of IL-6, IL-1β, and TNF-α in the sera of each group's rat (n=6) Ctrl: Positive control, UVA:UVA model irradiated rats, UVA+NS: group with normal saline, UVA+PRP: UVA model group was given PRP treatment.(n=6) * P < 0.05, ** P < 0.01.

DISCUSSION

Long-term exposure to UVA will cause skin photoaging, making it the most significant kind of UV radiation at the earth's surface⁽¹⁷⁾. UV exposure can hinder cell renewal, reduce tissue regeneration and repair ability, and lead to skin aging. Wrinkle deepening and enlargement, hyperpigmentation, and cancer in severe cases^(18, 19). Therefore, it is very important to prevent and treat UVA-induced photoaging. Histologically, photoaging is characterized by the reduction of dermal collagen fibers, degeneration, and deposition of elastic fibers, etc.⁽²⁰⁾. Skin connective tissue damage is a characteristic of skin during photoaging, and collagen and MMP are most closely related to skin connective tissue homeostasis. Injecting PRP into mice's backs led to a reduction in MMP-1 protein expression and an increase in Elastin and Collagen-1 protein expression, according to our research. This data demonstrates that PRP can reduce the skin photoaging caused by UVA exposure.

Studies have shown that the occurrence of skin photoaging may also be caused by oxidative stress caused by prolonged UV irradiation⁽²¹⁾. Excessive ROS in tissues is the main manifestation of oxidative stress⁽²²⁾. ROS mainly causes serious damage to the body by oxidizing various biological macromolecules in tissues, such as DNA, proteins, and lipid membranes, while MDA, as the final product of lipid peroxidation, will have adverse effects on the respiratory chain of mitochondria^(21, 23). Under normal physiological conditions, endogenous antioxidant enzymes SOD and CAT are fully released and catalyze the reduction of ROS to oxygen and water⁽²⁴⁻²⁵⁾. This study showed that when UVA irradiation induced the increase of MDA in rat skin, the antioxidant enzyme defense activity decreased. However, treatment with PRP inhibited the reduction of antioxidant enzyme activity. Based on these findings, it appears that PRP's protective impact against oxidases may be responsible for its beneficial effect on skin photoaging.

Sensor (NLRP3), adapter (ASC), and effector (caspase 1) make up the NLRP3 inflammasome, a multiprotein platform⁽²⁶⁾. There are two stages to inflammasome activation: the detection of NLRP3 activators and the subsequent overexpression of NLRP3, ASC, and caspase-1. Infection by microorganisms and sterile inflammation triggered by damage-associated molecular patterns (DAMPs)^(27, 28) both activate NLRP3. Conjugator P62, when activated by the NLRP3 inflammasome, may identify mitochondria and inflammasome-related proteins as organelles damaged by external stress, hence initiating the autophagy process⁽²⁹⁾. Several disease areas have turned their attention to studying the molecular dialogue between the inflammasome and autophagy. Many studies have been published

recently on the relationship between autophagy and the NLRP3 inflammasome. The apoptosis-associated spot-like protein (ASC), pro-caspase-1, and NLRP3 protein make up the NLRP3 inflammasome⁽³⁰⁾. Autophagy has been proven in several studies to drastically reduce tissue inflammatory damage by blocking the activation of the NLRP3 inflammasome. Zhang *et al.*⁽³¹⁾ demonstrated that activation of autophagy could significantly inhibit the formation of the NLRP3 inflammasome, thereby alleviating myocardial ischemia-reperfusion injury in diabetic animal models. Ahmed *et al.*⁽³²⁾ confirmed that neuroinflammation caused by NLRP3 inflammasome in Alzheimer's disease (AD) may be amplified and regulated by glial maturation factors, thereby inhibiting the clearance of A β by autophagosomes in the brain and inhibiting the therapeutic effect of autophagy on AD. In addition, some studies have found that targeting inflammasome NLRP1 and NLRP3 may be an important way to improve skin inflammation, and photoaging and reduce the risk of skin tumors⁽³⁾. We observed that RPR upregulated Beclin-1 and LC3B, two proteins involved in autophagy, and downregulated P62 expression. Injection of PRP decreased protein production of NLRP3, pro-caspase-1, and apoptosis-inducing factor (ASC), and also prevented activation of the NLRP3 inflammasome. These findings indicate that PRP may ameliorate UVA-induced photoaging in rats by inhibiting NLRP3 inflammasome activation via the induction of autophagy.

CONCLUSION

In summary, this study found that PRP significantly ameliorated UVA-induced skin photoaging in rats, inhibited apoptotic protein expression, and reduced oxidative stress and inflammatory factors in tissue homogenates or serum. It may function by activating autophagy and inhibiting the NLRP3 inflammatory vesicle pathway. This study provides potential therapeutic tools for anti-aging of the skin.

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Ethics approval and consent to participate: The study was approved by the Ethics Committee of Dongshan Hospital. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Competing interests: Declared none.

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Authors' contributions: Y.Z., participation in the

whole work; perception and design; generating plans; drafting of the article; data analysis; final approval of the version to be published. H.L., re-generating the plans and drafting the manuscript. S.L., re-generating the plans. D.Z., perception and final approval of the version to be published.

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