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Effect of freeze-dried platelet-rich plasma on FGF-2 and type I collagen expression in traumatic ulcers of diabetes mellitus: An in vivo study

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ABSTRACT

Background: *Diabetes mellitus is a chronic disease characterized by the pancreas's inadequate production of insulin or the body's impaired utilization of insulin, resulting in dysregulation of blood sugar levels. Diabetes mellitus causes prolonged wound healing due to decreased growth factors, including fibroblast growth factor 2 (FGF-2) and type I collagen.* ***Purpose:*** *This research analyzes the effect of topical administration of freeze-dried platelet-rich plasma (FD-PRP) on the healing process of traumatic ulcers in diabetic Wistar rats by increasing FGF-2 and type I collagen expression.* ***Methods:*** *Allogenic FD-PRP was obtained from the blood of 35 Wistar rats and 2% carboxymethyl cellulose (CMC) was added to make a gel formulation. Diabetes was induced in 30 Wistar rats using streptozotocin, followed by the creation of traumatic ulcers on the lower labial mucosa using a hot burnisher. The traumatic ulcers were then topically treated with FD-PRP gel in the treatment group and 2% CMC gel in the control group. Analysis of FGF-2 and type I collagen expression was performed through indirect immunohistochemical methods following treatment for 3, 5, and 7 days.* ***Results:*** *The expression of FGF-2 and type I collagen in the FD-PRP was higher than in the control group ($p < 0.05$).* ***Conclusion:*** *Topical application of FD-PRP plays an important role, especially in increasing the FGF-2 and type 1 collagen expression, in the healing process of traumatic ulcers in diabetic Wistar rats.*

Keywords: *diabetes mellitus; FGF-2; platelet rich plasma; traumatic ulcer; type I collagen*

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that causes the pancreas to produce insufficient insulin or the body to be unable to effectively utilize insulin to regulate blood sugar.[1,2] It has rapidly increased in prevalence, with a global estimate of 463 million people (aged 20–79) affected in 2019 and predicted to reach 700 million by 2045.[3,4] Diabetes can cause complications in various bodily organs.[5] One such complication is delayed wound healing, thereby increasing the risk of infection that endangers the patient's health.[6] The most common lesions that affect the oral mucosa of individuals with DM are ulcerative lesions.[7,8]

The occurrence of micro and macrovascular disorders causes a delayed healing process in DM that results in a decrease in vascularity, leading to tissue hypoxia due to the aggregation of advanced glycosylation end-products (AGEs). Increased AGEs will inhibit neutrophil chemotaxis, growth factors, angiogenesis, fibroblast proliferation, and collagen synthesis. Reduced fibroblast proliferation will cause a decrease in fibroblast growth factors-2 (FGF-2) expression and type I collagen synthesis.[9,10] Fibroblast growth factor-2 is a type of growth factor produced by fibroblast cells that plays a role in the activation, mitogenesis, migration, and differentiation of various cells.[11–13] Type I collagen is the main constituent of the extracellular matrix that restores ulcers' continuity

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and tensile strength and returns the ulcer tissue to its initial shape.[14]

One of the alternative therapies currently used for wound healing is the administration of platelet-rich plasma (PRP), a biological derivational product obtained from the patient's blood, which contains a high platelet concentration.[15] This high concentration of platelets increases growth factors that play an essential function in ulcer healing, including platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and FGF. These growth factors assist in macrophage and fibroblast aggregation, collagen synthesis, and the formation of new epithelial tissue.[16] Platelet-rich plasma has been successfully used in other avocations, including oral surgery, general surgery, spinal surgery, plastic and aesthetic surgery, and cardiac surgery.[17–19] Allogenic PRP is used because it meets the needs of PRP in large quantities and standardized procedures.[20]

Freeze-drying is used to increase the shelf life of PRP products so that they can be used in clinical practice. A study comparing freeze-dried platelet-rich plasma (FD-PRP) with fresh PRP in acute ulcer healing in experimental animal models increased PDGF-AA, VEGF, EGF, and TGF-β1, and the density of collagen compared to those of fresh PRP. For this reason, FD-PRP is recommended for accelerating oral ulcer healing.[21]

Topical administration of FD-PRP on traumatic ulcers of the oral mucosa of non-diabetic rats increased the fibroblast number and fibronectin expression related to the traumatic ulcers' healing.[22] Prior research to prove the effect of allogenic topical administration of FD-PRP on the labial mucosa of traumatic ulcers in Wistar rats with DM showed an increase in the number of fibroblast cells and fibronectin expression.[23] Due to FD-PRP's ability to increase the number of fibroblasts in diabetic conditions, this research aimed to analyze its effect in stimulating the growth factor, especially FGF-2 and type I collagen expressions, to support traumatic ulcer healing.

MATERIALS AND METHODS

This research is a laboratory experiment using a post-test-only control group design. The study's protocol was approved by the institutional ethical committee of the Faculty of Dental Medicine, Universitas Airlangga, with the number 372/HRECC.FODM/VIII/2020.

The FD-PRP was produced in Bank Cells of Dr. Soetomo General Hospital, Surabaya, Indonesia. Blood was taken from the hearts of 35 male Wistar rats, aged between 2–3 months. Approximately 7–10 ml of blood was drawn from each rat using a syringe containing 9% citric acid dextrose anticoagulant. During this procedure, all the rats were anesthetized using intramuscular ketamine injection at a dose of 50 mg/kg body weight (BW).

The blood was placed in a sterile tube and centrifuged at 4000 rpm for 10 minutes to separate the red blood cells from the plasma. The plasma was then taken from the top of the tube using a disposable syringe and transferred to a dry tube. The second centrifugation was conducted at 4000 rpm for 10 minutes to separate the PRP (bottom 1/3 of the tube) from the few platelets (top 2/3 of the tube). The PRP was processed in freeze-dried form and sterilized with UV light. The PRP freeze drying process was utilized, where the PRP sample is first frozen at −83ºC for 24 hours, then dried using a sublimation dryer, so that the allogenic FD-PRP will be lyophilized. The results of the production of allogenic FD-PRP were immediately identified with a label corresponding to its rat source.[24]

A total of 30 male Wistar rats were selected based on the following inclusion criteria: age between 60–90 weeks, weight between 150–250 grams, and healthy (characterized by active and agile movements, shiny fur, and clear eyes). Diabetes mellitus was induced in these animals by intraperitoneal injection of a freshly prepared solution of streptozotocin (STZ) in a citrate buffer (50 mg/kg BW). To prevent potentially fatal hypoglycemia post-injection, the rats received a 10% sucrose solution throughout the first night. Diabetes mellitus was verified three days after injection when the fasting blood glucose levels were found to be ≥126 mg/dL. Exclusion criteria for this study were rodents that were sick during the adaptation period and showed aggressive behavior (fighting between rats in the cage).

Traumatic ulcers were created by touching the tip of a ball burnisher number 3, heated for ± 45 seconds over a Bunsen burner, on the Wistar rats' lower labial mucosa. After 24 hours, ulcer formation was observed as a yellowish-white ulcer surrounded by a reddish area. During this procedure, all animals were under anesthesia using intramuscular ketamine injection at a dose of 50 mg/kg BW.

After the traumatic ulcer was confirmed, FD-PRP gel (with 2% carboxymethyl cellulose [CMC] added) was topically applied to the traumatic ulcer once a day for 3, 5, and 7 days.[22,23] The FD-PRP gel was applied to the traumatic ulcer until the whole ulcer area was covered. Meanwhile, the control group was topically treated using 2% CMC gel. The labial mucosa was retracted and held for 60 seconds to make sure that the drug was in contact with the ulcer. After the treatment period ended, all animals were sacrificed using intramuscular ketamine injection at a dose of 50 mg/kg BW. The lower labial mucosa was collected and fixed with 10% buffered formalin solution for subsequent tissue embedding using paraffin.

Fibroblast growth factor-2 and type 1 collagen expression were analyzed using indirect immunohistochemistry with primary antibody anti-FGF-2 (rat monoclonal antibody, dilution 1:200, sc-365106, Santa Cruz Biotechnology Inc, Germany) and type I collagen (rat monoclonal antibody, diluted 1:200, sc-136154, Santa Cruz Biotechnology Inc, Germany). The secondary antibody used was

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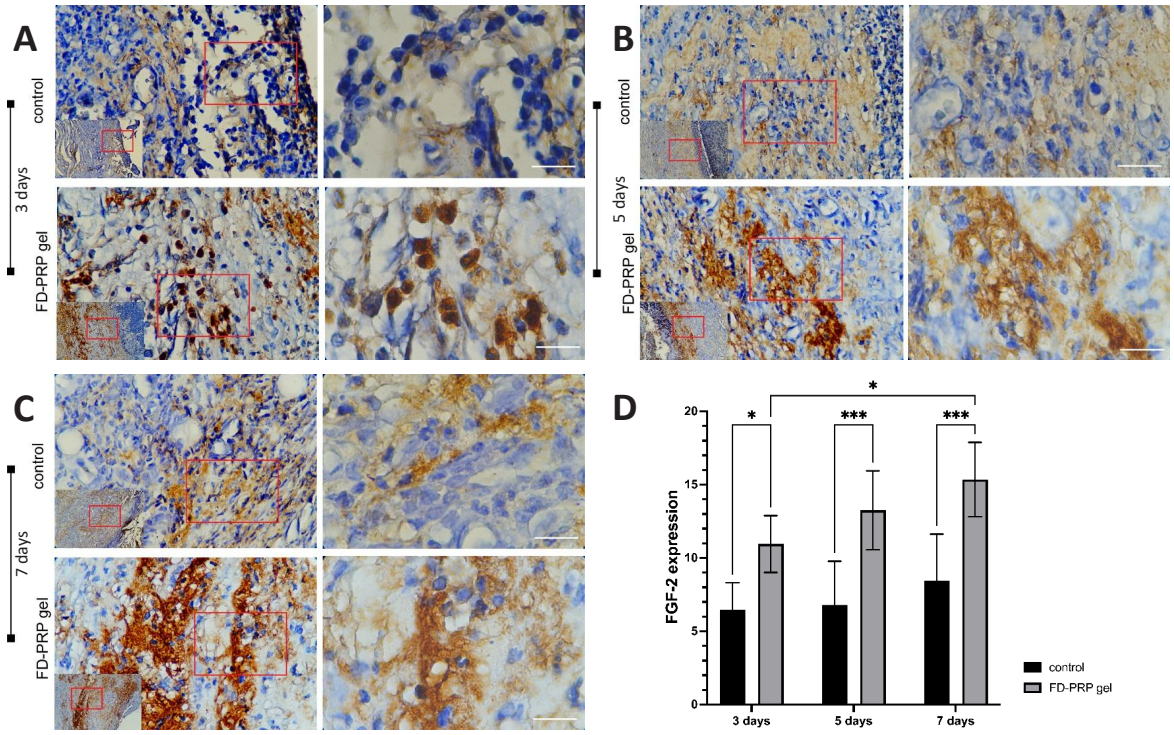

Figure 1. Immunohistochemistry analysis of FGF-2 expression in traumatic ulcer tissue after 3 days (A), 5 days (B), and 7 days (C) of treatment with FD-PRP gel or control. Cells exhibiting positive staining for FGF-2 are indicated by brown cytoplasm and observed under a light microscope at different magnifications. Scale bar 200 µm. The quantification of FGF-2 expression in traumatic ulcer tissue. The bar graph indicates the significant differences between the compared groups. The comparison was performed using two-way ANOVA and the Tukey-HSD test with *p < 0.05; ***p < 0.001.

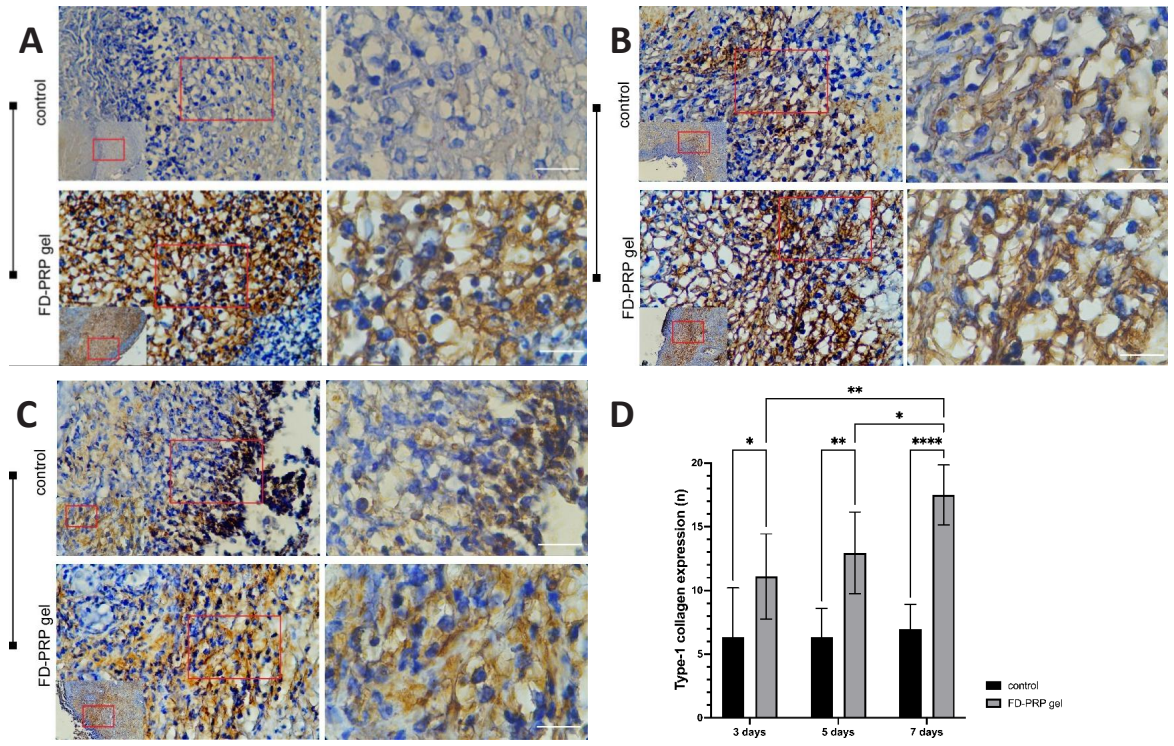

Figure 2. Immunohistochemistry analysis of collagen type-1 expression in traumatic ulcer tissue after 3 days (A), 5 days (B), and 7 days (C) of treatment with FD-PRP gel or control. Cells exhibiting positive staining for collagen type-1 are indicated by brown cytoplasm and observed under a light microscope at different magnifications. Scale bar 200 µm. The quantification of collagen type-1 expression in traumatic ulcer tissue. The bar graph indicates the significant differences between the compared groups. The comparison was performed using two-way ANOVA and the Tukey-HSD test with *p < 0.05; **p < 0.01; ****p < 0.0001.

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Goat anti-Rabbit IgG Heavy & Light Chain (HRP) and diamino benzidine. Counterstaining was performed using Hematoxylin-Mayer. Mounting was accomplished using an embedding medium and covered with a glass coverslip. The investigation was conducted using a light microscope (Nikon E-100, Sony A7) at 1000x magnification.

The data for FGF-2 and type 1 collagen expression were presented as the mean and standard deviation. Data normality and homogeneity were assessed using the Kolmogorov-Smirnov test and Levene's test. Differences in FGF-2 and type 1 collagen expression were analyzed using a two-way ANOVA and Tukey HSD post hoc test with statistical significance set at $p < 0.05$. Statistical analysis was performed using GraphPad PRISM 9 for MacBook.

RESULTS

The FGF-2 expression appears as brown staining in the cytoplasm of fibroblasts with a blue nucleus (indicated by the red box in Figure 1A-C). The FD-PRP topical treatment showed a higher FGF-2 expression than the control group at all observation time points ($p < 0.05$; $p < 0.0001$, respectively). The topical treatment of FD-PRP for 7 days showed a higher FGF-2 expression than treatment for 3 days ($p < 0.05$; Figure 1D). Topical application of FD-PRP can increase FGF-2 expression in fibroblasts during ulcer healing in diabetic rats, with expression levels increasing over time, particularly evident after 7 days of treatment.

The type I collagen expression appears as brown staining with a blue nucleus (indicated by the red box in Figure 2A-C). The topical treatment of FD-PRP showed a higher Type I collagen expression than the control group at all observation time points ($p < 0.05$; $p < 0.001$; $p < 0.0001$, respectively). The topical treatment of FD-PRP for 7 days showed a higher Type I collagen expression than treatment for 5 days and 3 days ($p < 0.05$ and $p < 0.01$, respectively; Figure 2D). Topical application of FD-PRP significantly enhances the expression of FGF-2 and type I collagen in diabetic rats' ulcer tissue. These effects were consistently higher compared to the control group at all time points, with a marked increase observed after 7 days of treatment, indicating that FD-PRP promotes and accelerates the wound healing process in a time-dependent manner.

DISCUSSION

Platelet-rich plasma was initially introduced in the 1970s and was first used in 1987 in open-heart surgery. It is also used for healing ulcers in periodontology and maxillofacial surgery.[25,26] The extraordinary utility of PRP was demonstrated in 2009 when it was used as an adjuvant for healing injuries in sports players, becoming a new treatment for sports-related injuries. Due to developments and ongoing research, PRP is now an endogenous therapeutic technology that is increasingly in demand and attracting attention in regenerative medicine because of its potential to stimulate and accelerate the ulcer healing process.[17,19] Other research on PRP found that macrophage cells produce more than 30 types of growth factors and induction factors, thus accelerating the inflammatory response beyond the wound's natural healing rate.[19]

Fresh PRP is a form of regenerative therapy that uses blood plasma rich in platelets to accelerate healing and repair tissues. Fresh PRP is stable and can be used up to 8 hours after collection. Fresh PRP can also be activated to enhance its therapeutic effects. The activation process is important because it helps release the growth factors and other bioactive substances contained within the platelets. To activate platelets and granule secretion, calcium can be added in the form of $CaCl_2$ or thrombin. Platelet-rich plasma and the activator solution are mixed in a ratio of 10:1 and must be used within 10 minutes of activation, because after this timeframe, the platelets will have released 70% of their growth factors. Platelet-rich plasma can be applied directly in an inactive form because it will become activated after entering the body. It is activated in the body through a series of biological processes triggered by its interaction with the tissue. Activation leads to the release of growth factors and cytokines that facilitate healing, tissue regeneration, and repair. The natural activation mechanism ensures that PRP only exerts its effects at the injury or treatment site, which optimizes its therapeutic benefits.[23,27] Allogenic PRP can be used as an alternative to the limitations of autologous PRP because it can be produced in compliance with international protocols that allow the manufacture of PRP on a large scale, which is cost-effective and has good quality PRP product standards.[28]

Freeze-dried platelet-rich plasma has the same platelet and growth factor concentration as fresh PRP and has the benefit of extended shelf life beyond 8 weeks. In addition, sterilized FD-PRP can be stored up to 5 years.[18,29] The application of FD-PRP was confirmed to increase the number of fibroblasts and the amount of neovascularization in the full-thickness skin wound healing process.[24] The effect of FD-PRP on the oral mucosa might be similar to its effect on the skin.

Platelet-rich plasma's mechanism of action involves platelets, which, from functioning in homeostasis, also release angiogenesis factors and tissue repair. Platelet secretory granules also contain growth factors, coagulation factors, cytokines, adhesion molecules, and integrins. The growth factors include PDGF, TGF, FGF, VEGF, platelet-derived endothelial growth factors, insulin-like growth factor, keratinocyte growth factor, and EGF.[17] Fibroblast growth factor in PRP can induce the formation of fibroblasts that produce collagen, especially collagen type I.[30] After it is applied and forms a blood clot, PRP collects in the extracellular matrix. During the matrix degradation process, growth factors are released, which interact and bind to the tyrosine kinase receptors (TKR) that are on the tissue cell membrane and extend into the cell cytoplasm. This binding triggers activation of messenger proteins in the cytoplasm,

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ultimately leading to cell division initiation through mRNA transcription. Growth factors can work through paracrine and autocrine mechanisms, where they either stimulate neighboring cells or enhance their own activity, respectively, encouraging various cells to function actively. Platelets in PRP also contain adhesion molecules, such as fibronectin, fibrin, and vitronectin, which play a crucial role in the cell migration process and increase PRP's potential biological activity.

The FD-PRP demonstrated an ability to increase the FGF-2 expression and promote the proliferation of fibroblasts.[11,12] When applied a day after ulcer formation, during the inflammatory stage, FD-PRP, which is rich in growth factors, acts as an anti-inflammatory cytokine that controls inflammation in the tissue. Growth factors in PRP, including FGF-2, will bind to TKR to further stimulate fibroblast cell augmentation and differentiation in the proliferative phase. The increased proliferation of fibroblasts will elevate the production of FGF-2, which will then be recaptured by fibroblast cells through FGF-2 receptors for additional proliferation. Further treatment using FD-PRP for 7 days showed substantially more FGF-2 expression than 5 days and 3 days of treatment because the fibroblasts only started producing FGF-2 on the third day after the trauma.[31] Investigation showed that a day after the injury, the level of FGF2 started to increase and intensified after the third day.[32] The interaction of growth factors FGF-2 with TKR will increase fibroblast proliferation, which affects the increase in FGF-2 expression after 7 days.

Type I collagen synthesis by fibroblast cells occurs in the proliferative phase, starting between days 3 to 5, and reaching its peak on day 7.[11,13] The expression of type I collagen in the control and treatment groups did not increase much on day 3. This was due to the administration of allogenic FD-PRP, which contains growth factors that do not directly increase type I collagen but first increase fibroblast proliferation. Fibroblasts will appear in the trauma area at the end of the inflammatory phase and initial proliferative phase, which is 24–48 hours after trauma. When fibroblasts arrive at the ulcer area, they attach to the fibrin clot and ulcer bed via several integrins. The fibroblasts then begin to proliferate, producing matrix metalloproteinases and proteinases, such as seperinase, to eliminate denatured proteins. These proteinases are controlled by tissue inhibitors of metalloproteinases, which also originate from fibroblasts. Furthermore, a new ECM is formed that is rich in type III collagen, fibronectin, and hyaluronic acid. Collagen III is produced rapidly and is then degraded by proteases and remodeled by fibroblasts to type I collagen, which has stronger tensile strength.[33]

The results of the observation showed that the expression of type I collagen in fibroblast cells increased more in the group treated with FD-PRP than in the control group. This might be because in diabetes, PRP has altered immune responses and prolonged inflammation. This aligns with the study that showed that the expression of type I collagen increased on days 5 and 7 after administration of the propolis extract in diabetic rats.[34] The statistical difference test in the control group did not have a significant difference ($p > 0.05$), whereas in the treatment groups it revealed a significant difference ($p=0.004$). This was due to the rapid synthesis of collagen. Growth factors will bind to specific receptors on fibroblast cells and stimulate gene activity to proliferate and stimulate fibroblast migration to ulcerated tissue, increasing the number of fibroblasts. The larger the number of fibroblasts, the more collagen type I will increase.

The results of this study must be interpreted with caution and its limitations borne in mind. We focused only on the production of type I collagen and FGF-2 expression induced by FD-PRP administration. However, PRP is rich in other growth factors, such as PDGF and VEGF, which might also influence the angiogenesis, proliferative, and remodeling process. Despite these limitations, this study has contributed notably to the current knowledge of PRP potential in the healing process.

This study concludes that the expression of FGF-2 and type I collagen in the traumatic ulcer healing process of the oral mucosa of diabetic Wistar rats increased significantly after topical application of FD-PRP. This underscores the pivotal role of allogenic FD-PRP in the ulcer healing process, particularly during the initial stages of the proliferative phase. Further research is needed to explore the effects of allogenic FD-PRP in healing traumatic ulcers of the oral mucosa of diabetic Wistar rats using other indicators, such as VEGF and PDGF. Moreover, longitudinal studies are necessary to observe the expression of FGF-2 and type I collagen as the ulcer healing process transitions into the remodeling phase.

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