Aerobic Exercise Inhibits Mitochondrial Ferroptosis in a Rat Model of Depression by Activating the SLC7A11/GPx4 Pathway

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Abstract Objective: Investigate the role of SLC7A11/GPx4-mediated ferroptosis in aerobic exercise's antidepressant effects.
Methods: 36 male SD rats were divided into Control (Con), Depression Model (Mod - CUMS), and Aerobic Exercise (AE - CUMS + 4 weeks exercise) groups (n=12 each). Post-intervention, behavioral tests (sucrose preference, OFT) were conducted. Serum ferritin (SF) and mitochondrial 8-OHdG were measured by ELISA. Prefrontal cortex (PFC) pathology was assessed via HE staining and mitochondrial ultrastructure via TEM. PFC protein levels (GPx4, SLC7A11, FPN1, FTH1) were analyzed by Western blot.Results: Compared to Con, Mod rats showed significantly reduced sucrose preference (P<0.01) and OFT crossings/rearings (P<0.05), elevated serum SF and 8-OHdG (P<0.05), neuronal damage (HE), and mitochondrial damage (swelling, cristae disruption) indicative of ferroptosis (TEM). Protein levels (SLC7A11, GPx4, FPN1, FTH1) were significantly lower in Mod (P<0.05). Compared to Mod, AE rats exhibited significantly increased sucrose preference (P<0.01) and OFT activity (P<0.05), reduced SF and 8-OHdG (P<0.05), alleviated neuronal damage (HE), and improved mitochondrial morphology (TEM). Protein levels (SLC7A11, GPx4, FPN1, FTH1) were significantly higher in AE (P<0.05).Conclusion: Aerobic exercise significantly ameliorated CUMS-induced depression in rats. The mechanism likely involves activating the SLC7A11/GPx4 pathway, inhibiting mitochondrial ferroptosis, and improving iron metabolism, suggesting a novel therapeutic target.

Keywords: Aerobic Exercise; Depression; Mitochondria; Ferroptosis

Depression is a common mental disorder characterized by persistent and recurrent core clinical symptoms including mood dysregulation, sleep disturbances, impaired concentration, anhedonia, and loss of appetite [1]. With its high disability rate, high suicide rate, and high treatment costs, depression has become the fourth leading disease worldwide [2]. Enhancing attention to and prevention of depression, reducing the socio-economic burden, and improving overall population health are urgent issues in global public health.
Hypotheses regarding the pathogenesis of depression include the monoamine hypothesis, inflammation hypothesis, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and mitochondrial dysfunction hypothesis [3]. Recent studies have found that ferroptosis—a form of programmed cell death triggered by iron-dependent accumulation of lipid peroxides—plays a key role in the progression of depression [4-5].
Solute carrier family 7 member 11 (SLC7A11) is a transmembrane protein that transports extracellular cystine into cells for the biosynthesis of cysteine and glutathione (GSH). By maintaining intracellular GSH levels, SLC7A11 provides the reactive substrate for glutathione peroxidase 4 (GPx4) to exert its antioxidant effects and inhibit ferroptosis. The SLC7A11/GPx4 pathway is a crucial pathway for maintaining redox homeostasis and inhibiting ferroptosis in the body [6-7].
Recent studies have found that aerobic exercise can activate the SLC7A11/GPx4 pathway. Treadmill training inhibits ferroptosis and alleviates cerebral ischemia/reperfusion (I/R) injury by activating the SLC7A11/GPx4 pathway [8]. Irisin, secreted by muscles in

response to exercise, stimulates the expression of GPx4 and SLC7A11, inhibiting ferroptosis in the hippocampus. Exercise activates GPx4 to inhibit ferroptosis, ameliorating myocardial injury induced by a high-fat diet [9]. Intact mitochondrial structure and proper function are essential for maintaining normal brain function and emotional health. Mitochondria are susceptible to peroxidative damage leading to structural disruption and dysfunction, exacerbating depressive symptoms [10]. However, whether exercise can inhibit mitochondrial ferroptosis via the SLC7A11/GPx4 pathway to alleviate depression remains incompletely elucidated.

This experiment will investigate the effects of aerobic exercise on brain iron status, the ferroptosis regulatory pathway, and mitochondrial structure in a CUMS rat model of depression to clarify the mechanism by which exercise ameliorates depression.

1. Materials and Methods

1.1 Experimental Animals

Thirty-six 8-week-old SPF male Sprague Dawley (SD) rats, weighing (300±20) g, were purchased from the Animal Experiment Center of Xinjiang Medical University (Animal Production License No.: SCXK (Xin) 2018-0002). After purchase, rats were housed in cages in a standard animal laboratory with an ambient temperature of (25±2)°C, humidity (50±5)%, and a 12-hour light/dark cycle, with sufficient water and food provided for one week for adaptation. Rats were randomly divided into 3 groups (n=12 per group): Control group (Con), Model group (Mod), and Aerobic Exercise group (AE). After one week of normal feeding, the Mod and AE groups underwent 28 days of CUMS modeling. The AE group received 4 weeks of moderate-intensity treadmill endurance exercise intervention (speed: 15 m/min, slope: 0°, duration: 20 min/day) after modeling completion. Behavioral assessments were performed on all groups after the experiment.

1.2 Experimental Reagents

SF and 8-OHdG ELISA kits were purchased from Shanghai Youxuan Biotechnology Co., Ltd. Antibodies against SLC7A11, GPx4, FPN1, FTH1, and GAPDH were purchased from Cell Signaling Technology, USA.

1.3 Establishment of CUMS Rat Model

Except for the Con group, rats in the other two groups underwent the classic CUMS protocol. Eight different mild stressors were applied randomly to establish the rat depression model, with the same stressor not applied consecutively, for a duration of 28 days. Specific stressors included: 24h food deprivation, 24h water deprivation, cage tilt for 24h, cage bedding soaked for 24h, tail pinch for 1min, light/dark reversal within 24h, restraint for 2h, noise disturbance for 1h.

1.4 Behavioral Observations

1.4.1 General State Observation

Weight loss and mood dysregulation are common symptoms of depression. Throughout the experiment, rat body weight, fur condition, feces, and emotional state were observed and recorded.

1.4.2 Sucrose Preference Test (SPT)

SPT was used to detect anhedonia in CUMS-induced depressed rats and is a core indicator for evaluating the CUMS model. Three days before the test, rats were adapted to 1% sucrose solution. On day 4, the formal test was conducted. On days 2 and 4, the positions of the sucrose and water bottles were swapped every 12h. On day 4, the weight of the remaining sucrose solution and pure water bottles for each rat was recorded. The intake of sucrose solution and pure water over 24h was measured, and the sucrose preference ratio (ratio of 1% sucrose solution intake to total liquid intake) was calculated.

1.4.3 Open Field Test (OFT)

OFT is a behavioral test for observing spontaneous activity, exploratory behavior, and anxiety levels. The OFT arena was a lidless wooden box measuring 100cm×100cm×45cm, with black walls and floor. Rats were transported to a dim, quiet, clean environment 3 hours beforehand. After setup, each rat was gently placed in the center of the box, and software recorded its movement path within the open field for 5 minutes. The arena was cleaned before each test. Indicators selected for this experiment were: (1) Number of horizontal crossings (2) Number of rearings.

1.5 Sample Collection and Detection Methods

1.5.1 Sample Collection and Processing

After all behavioral tests, rats were anesthetized via intraperitoneal injection of 2% sodium pentobarbital. Blood was collected from the abdominal aorta, left to stand for 30 minutes, and centrifuged at 3500 rpm for 15 minutes. The supernatant serum was collected and stored at -80°C for ELISA. Rats were decapitated, and the brains were removed. Prefrontal cortex tissue was dissected on ice and stored in liquid nitrogen for Western blot. Approximately 1mm×1mm×1mm pieces of prefrontal cortex tissue were cut and placed in 4°C pre-cooled 2.5% glutaraldehyde fixative, then stored at 4°C for electron microscopy section staining.

1.5.2 Enzyme-Linked Immunosorbent Assay (ELISA)

Rat serum was thawed, and the levels of SF and 8-OHdG in serum samples were detected according to the ELISA kit instructions.

1.5.3 HE Staining

Brain tissue was fixed, dehydrated, embedded in paraffin, sectioned, stained with hematoxylin and eosin (HE), mounted with neutral balsam, and observed under a light microscope to assess the pathological condition of SD rat brain tissue at multiple magnifications.

1.5.4 Transmission Electron Microscopy (TEM)

Prefrontal cortex tissue fixed in glutaraldehyde solution was dehydrated, infiltrated, embedded, sectioned, stained, and examined by TEM to observe the ultrastructure of prefrontal cortex neurons, the number of autophagosomes, and mitochondrial morphology.

1.5.5 Western Blot Detection of Iron Metabolism-Related Protein Expression in Prefrontal Cortex

Prefrontal cortex tissue was retrieved from liquid nitrogen. RIPA lysis buffer and grinding beads were added, followed by centrifugation to collect the supernatant. Protein concentration was quantified using the BCA method. Using the JESS automated protein analysis system (ProteinSimple), samples were prepared according to the instructions (DTT, 0.1×Sample Buffer, 5×master Mix, Ladder). Protein denaturation was performed at ≥95°C, followed by cooling, vortex mixing, brief centrifugation (5s, radius 2.5cm), and storage on ice. Primary antibodies were prepared: SLC7A11 (1:50), GPx4 (1:50), FPN1 (1:50), FTH1 (1:50), GAPDH (1:1000). Chemiluminescence reagents Lumino-S and Peroxide (200μL each) were vortexed and stored on ice. Using JESS, self-check was performed, "a bio-techne brand 12-230 kDa Separation 8×25 Capillary Cartridges" were selected, samples were loaded according to the manual, and detection was performed. Results were analyzed using ImageJ software to quantify WB band gray values.

1.6 Statistical Analysis

Data are expressed as mean ± standard deviation ($\bar{x}\pm s$). Statistical analysis was performed using SPSS 21.0. Differences between groups were analyzed by one-way analysis of variance (ANOVA), with a significance level of $P<0.05$.

2. Results

2.1 Effect of Aerobic Exercise on the General State of CUMS Rats

After 28 days of CUMS, compared with the Con group, rats in the Mod group showed varying degrees of symptoms including yellowish fur, weight loss, irritability, and aggression. Differences in body weight gain were observed among groups. Compared with the Con group, body weight gain was significantly decreased in the Mod group ($P<0.01$); compared with the Mod group, body weight gain was significantly increased in the AE group ($P<0.01$, Table 1).

Table 1. Comparison of Rat Body Mass in Each Group ($\bar{x}\pm s$) g

Group	Intervention Time(d)	N	Body Mass(g)	F-value	P-value
Blank group	0	12	222.61±37.45	94.39	＜0.01
	7	12	264.28±41.75▲▲##		
	14	12	313.36±44.66▲▲##		
	28	12	336.17±42.41▲▲##		
Model group	0	12	224.17±28.78		
	7	12	236.12±39.37**		
	14	12	251.17±36.99**##		
	28	12	272.28±39.36**##		

Aerobic exercise group	0	12	221.15±23.46		
	7	12	260.44±27.21**▲▲		
	14	12	303.61±32.84**▲▲		
	28	12	322.84±30.02▲▲		

**Note: Compared with Con group, *P<0.01; Compared with Mod group, ▲▲P<0.01; Compared with AE group, ##P<0.01.*

2.2 Effect of Aerobic Exercise on Depressive-like Behavior in CUMS Rats

Comparison of sucrose preference values among the three groups: Compared with the Con group, the sucrose consumption ratio was decreased in the Mod group (P<0.01); compared with the Mod group, the sucrose consumption ratio was increased in the AE group (P<0.01), results shown in Table 2.

Table 2. Comparison of Sucrose Preference among Groups ($\bar{x}\pm s$)

Group	n	Sucrose Consumption Ratio (%)
Blank group	12	96.26±4.22
Model group	12	81.48±3.57**
Aerobic exercise group	12	91.07±2.79##
F		24.42
P		*P<0.01*

**Note: Compared with Con group, *P<0.01; Compared with Mod group, ▲▲P<0.01; Compared with AE group, ##P<0.01.*

Comparison of OFT results among the three groups: At day 0, there were no significant differences in the number of horizontal crossings and rearings among groups (P>0.05). At days 7 and 14, the number of horizontal crossings and rearings in both the Mod and AE groups were significantly lower than in the Con group (P<0.01), indicating successful CUMS modeling. At day 28, the number of horizontal crossings and rearings in the AE group were significantly higher than in the Mod group (P<0.01). (Fig. 1 and Fig. 2 - Note: Figure captions translated based on provided text)

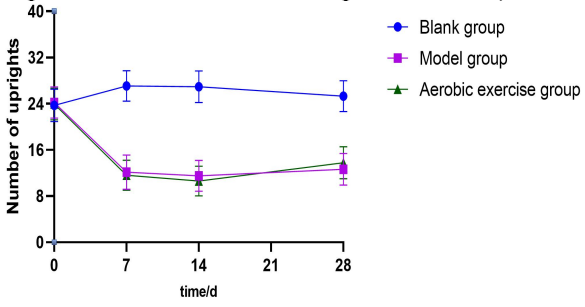

Figure 1. Comparison of Rearing Times among the Three Groups in the Open Field Test

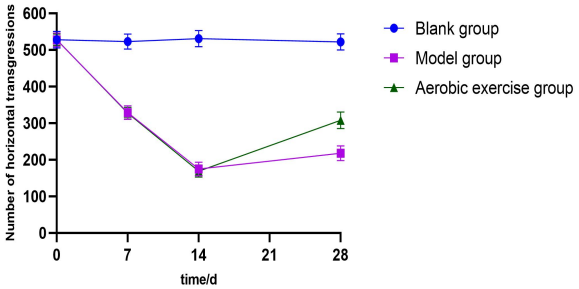

Figure 2. Comparison of Horizontal Crossing Numbers among the Three Groups in the Open Field Test

2.3 Effect of Aerobic Exercise on Pathological Damage and Mitochondrial Structure/Morphology in the Brain Tissue of CUMS Rats

HE staining of brain tissue sections observed under light microscopy (Fig. 3): In the Con group, cortical neurons showed normal morphology, intact structure, high cell density, distinct layers, large round blue nuclei with uniform staining and clear nucleoli. The Mod group showed obvious neuronal damage, with many degenerating, necrotic, and lost cells; cells were sparse, disorganized, lacking clear layers; many cells had unclear nuclear membranes, indistinct nucleoli, and pyknotic, deeply stained nuclei. Compared to the Mod group, the AE group showed significantly improved neuronal morphology; most cells had intact morphology and structure, were neatly arranged, with clear nuclear membranes and nucleoli; a few degenerated/necrotic cells were present, indicating significantly reduced damage.

TEM showed (Fig. 4): Compared with the Con group, the Mod group exhibited varying degrees of mitochondrial swelling, cristae disruption, early vacuolization, or pyknosis, showing typical ferroptosis characteristics. Compared with the Mod group, mitochondria in the AE group had regular morphology with neatly and densely arranged cristae.

2.4 Effect of Aerobic Exercise on Oxidative Stress in CUMS Rats

Comparison of ELISA results among the three

groups: Compared with the Con group, serum SF and 8-OHdG concentrations were significantly increased in the Mod group (P<0.05). Compared with the Mod group, serum SF and 8-OHdG concentrations were significantly decreased in the AE group (P<0.01, Table 3).

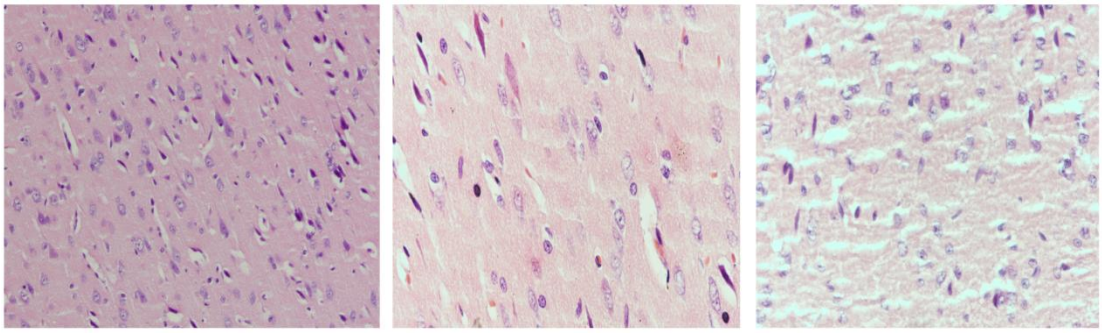

Figure 3. HE Staining of Brain Tissue (HE, ×200)

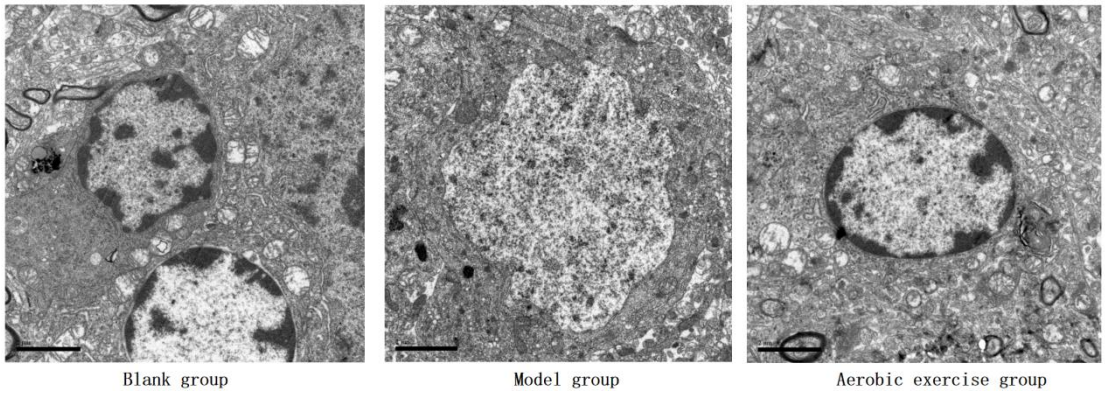

Figure 4. Transmission Electron Microscopy of Prefrontal Cortex Tissue

Table 3. Comparison of Serum Factor Levels among Groups ($\bar{x}\pm s$)

Group	n	SF	8-OHdG
Blank group	12	71.55±11.81	220.35±22.82
Model group	12	106.33±10.21*	303.16±36.44**
Aerobic exercise group	12	87.87±12.92$^{\#}$	260.99±29.75$^{\#\#}$
F		20.06	31.10
P		*P*<0.01	*P*<0.01

2.5 Effect of Aerobic Exercise on the Expression of SLC7A11/GPx4 Pathway-Related Proteins in CUMS Rats

As shown in Fig. 5, compared with the Con group, the expression levels of SLC7A11, GPx4, FPN1, and FTH1 were significantly decreased in the Mod group (P<0.05). Compared with the Mod group, the expression levels of SLC7A11, GPx4, FPN1, and FTH1 were significantly increased in the AE group (P<0.05).

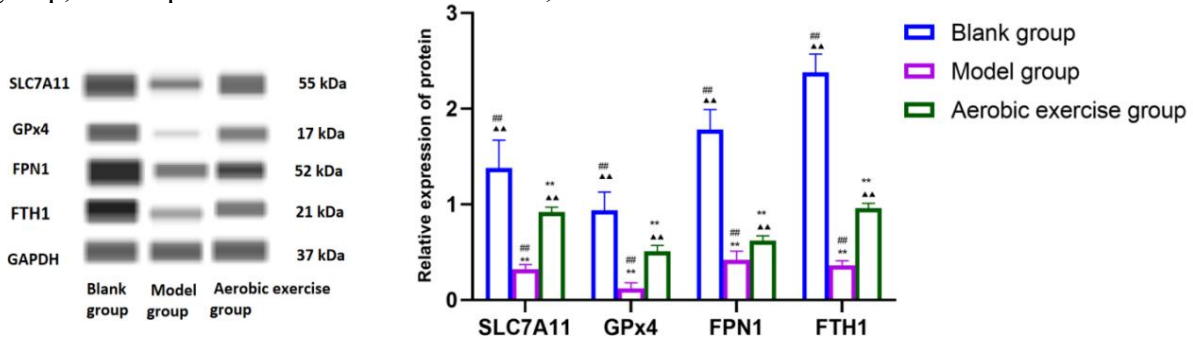

Figure 5. Expression of SLC7A11/GPx4 Pathway-Related Proteins

3. Discussion

Chronic stress can induce persistent depression-like states in humans and rodents, such as weight loss, despair, anhedonia, reduced motivation, and mild cognitive impairment. While animal models may not fully replicate all human depressive symptoms, they should exhibit key features such as anhedonia, reduced motivation, neuroanatomical changes, and neuroendocrine dysregulation. The CUMS model effectively simulates adverse events like chronic life stress and traumatic stress, inducing depressive behaviors in rodents that can persist for months [11]. In this study, rats in the depression model group exhibited slow weight gain, anhedonia, decreased activity levels, and reduced spatial exploration, manifesting behaviors similar to depression.

Recent studies have found that excess iron can generate hydroxyl radicals via the Fenton reaction, causing peroxidative damage to cell membrane phospholipids, damaging mitochondrial and microsomal membranes, reducing cytochrome c oxidase activity, hindering electron transfer, inhibiting energy production, ultimately leading to cell degeneration, loss of function, and inducing cardiovascular diseases, diabetes, neurodegenerative diseases, and mental disorders [12-13]. This iron-dependent form of non-apoptotic cell death is termed ferroptosis. The main characteristics of ferroptosis are increased reactive oxygen species (ROS) generation and accumulation of lipid peroxides [14]. It is also characterized by disruption of mitochondrial ultrastructure. In this study, TEM revealed mitochondrial swelling, cristae disruption, early vacuolization, or pyknosis in the Mod group, showing typical ferroptosis features.

Serum SF represents the body's iron storage. Serum SF was significantly lower in the AE group compared to the Mod group, indicating that aerobic exercise reduced body iron content. Reduced iron storage can prevent iron overload-induced ferroptosis, thereby reducing damage to the nervous system. 8-OHdG is a major biomarker of mitochondrial DNA damage by ROS [15]. The results of this study indicate that exercise reduced peroxidative damage to mitochondria in depressed rats, which is related to reduced body iron content. Reducing oxidative stress caused by free iron-induced Fenton reactions can effectively improve depression.

The SLC7A11/GPx4 pathway is a crucial regulatory pathway for inhibiting ferroptosis in the body. GPx4 requires GSH as a substrate to convert toxic lipid peroxides into non-toxic lipid alcohols. SLC7A11 is involved in GSH synthesis [16]. The cystine/glutamate antiporter system (System Xc-), of which SLC7A11 is a key component, is the only known cystine transmembrane transporter and plays a vital role in GSH synthesis [17]. Upregulating SLC7A11 expression promotes increased GSH levels in cardiomyocytes and neurons, inhibits ferroptosis, and protects myocardium and neurons from peroxidative damage. Downregulation of SLC7A11 can stimulate the accumulation of lipid peroxidation products, inducing ferroptosis in neurons [18]. In this study, compared to the Mod group, the expression of SLC7A11 and GPx4 in the prefrontal cortex tissue of the AE group was increased, inhibiting the accumulation of lipid peroxidation products and reducing neuronal ferroptosis. The lower iron content in the prefrontal cortex of AE group rats may be caused by three factors: ① Exercise accelerates iron mobilization and utilization. ② Some iron is released extracellularly. ③ Free iron is stored as ferritin heavy chain (FTH1) to prevent peroxidative damage. The main iron efflux protein on neuronal membranes is ferroportin 1 (FPN1) [19-21]. FPN1 is also the only known iron efflux protein on mammalian cell membranes, responsible for releasing intracellular iron into the bloodstream [22]. Higher expression of FPN1 in the prefrontal cortex of AE group rats also indicates that exercise promoted iron release from cells. Ferritin heavy chain 1 (FTH1) is an important intracellular iron storage protein. Free iron ions in the cytoplasm that are not utilized or exported can be stored in ferritin. Increased FTH1 in the prefrontal cortex of AE group rats sequesters free iron ions within the ferritin core, helping to maintain iron homeostasis within neurons.

In summary, aerobic exercise can enhance the expression of SLC7A11 protein in the prefrontal cortex of depressed rats, increasing GSH synthesis and providing sufficient substrate for GPx4 to exert its antioxidant

function. Consequently, the mitochondrial DNA oxidative damage marker 8-OHdG in the serum of exercise group rats was reduced, helping to maintain normal neuronal structure and function and alleviate depressive symptoms. Activating SLC7A11/GPx4 to inhibit ferroptosis through exercise holds promise as a new intervention pathway for depression.

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