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Extraction of ginsenoside Rg2 from stems-leaves of *Panax ginseng* and its protective effect on myocardial injury in rats with sepsis

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Abstract

This study prepared ginsenoside Rg2 (GRg2) and investigated its protective effect on myocardial injury in sepsis rats. Fifty rats were divided into sham, lipopolysaccharide (LPS), LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups. The latter three groups were treated with 20 mg/kg GRg2, 20 mg/kg GRg2 plus 5 mg/kg EX527 and 5 mg/kg EX527, respectively. Then, the LPS-induced sepsis model was made in the latter four groups. Results showed that, after 7 h from modeling, compared with LPS group, in LPS+GRg2 group, the left ventricular end-diastolic diameter and left ventricular end-systolic diameter were lowered, the left ventricular fraction shortening and left ventricular ejection fraction were elevated, the serum creatine kinase isoenzyme MB, cardiac troponin I, tumor necrosis factor α and interleukin 6 levels were decreased, the myocardial superoxide dismutase level was increased, the myocardial malondialdehyde level was significantly decreased, the myocardial B-cell lymphoma-2 expression level was increased, and the myocardial B-cell lymphoma-2 associated X level was obviously decreased, the myocardial silent information regulator 1 (SIRT1) level was increased, and the myocardial nuclear factor kappa-B (NF-κB) p65 level was decreased. In conclusion, GRg2 can alleviate myocardial injury in sepsis rats through reducing inflammatory response and oxidative stress and regulating apoptosis and SIRT1/NF-κB signaling pathways.

Keywords: ginsenoside Rg2; myocardial injury; sepsis; SIRT1; NF-κB.

Practical Application: This study may provide a reference for preparation of ginsenoside Rg2 and its clinical application to prevention of myocardial injury in sepsis.

1 Introduction

Sepsis is a systemic inflammatory response syndrome caused by the imbalance of immune response to infection. It seriously endangers the life of patients, and it is also one of the important causes of death in severe patients (Pène et al., 2008). Under the guidance of a large number of basic and clinical researches, the treatment strategy of sepsis has been standardized, which can reduce the mortality of patients to a certain extent. However, the incidence of sepsis is increasing and the cost of treatment is still high. It is found that, the cardiac function is directly related to the prognosis of sepsis patients. The majority of sepsis patients have the myocardial injury (Zang et al., 2014). The myocardial injury caused by sepsis is a pathological process involving many factors, including inflammatory response, oxidative stress, microcirculation disturbance, mitochondrial dysfunction, calcium overload and so on (Ming et al., 2000; Horton et al., 2003; Tyagi et al., 2009; Piquereau et al., 2013). Therefore, it is necessary to study the pathogenesis of myocardial injury in sepsis and explore the effective and safe drugs.

It is found that many compounds from plants have good activities in antioxidant, anti-inflammatory, anti-tumor and other aspects (Ha et al., 2022; Khan et al., 2022; Li, et al., 2022; Zhao et al., 2022). *Panax ginseng* is a traditional medicine used to enhance the immunity, which is therapeutically beneficial in terms of invigorating the *Qi*, relieving the fatigue, and strengthening the physique (Li et al., 2021). *Panax ginseng* contains saponins, flavonoids, peptides and other chemical components. Saponins are the most important active components of Ginseng. Ginsenoside Rg2 (GRg2) is a monomer of panoxatriol saponins, which has a wide range of pharmacological activities (Zhang et al., 2008)[7]. It has the effect in inhibiting inflammatory response, resisting oxidative stress, reducing apoptosis and other aspect (Cho et al., 2013; Kang et al., 2016). It is found that, the apoptosis signaling pathway and silent information regulator 1 (SIRT1)/nuclear factor kappa-B (NF-κB) signal pathways are involved in the myocardial injury (Wei et al., 2014; Zhang et al., 2017). In this study, we extracted GRg2 from stems-leaves of *Panax ginseng*, and investigated the protective effect of GRg2 on myocardial injury in sepsis rats and the related mechanisms.

2 Materials and methods

2.1 Extraction of GRg2 from stems-leaves of Panax ginseng

Stems-leaves of *Panax ginseng* were taken, and soaked in water for 1 h, followed by decocting twice, 2 h each time. After filtering for each time, the filtrates were obtained, and combined, followed by concentrating under reduced pressure. The concentrated solution was purified with macroporous resin. The target eluent was collected. After concentrating under reduced

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pressure and drying, the total saponins were obtained. The total saponins were taken, and 95% ethanol was added according to the mass volume ratio of 1: 1. After heating, the total saponins were dissolved to obtain solution A. Sodium hydroxide (1/10 of mass of total saponins) was taken, and was dissolved in an appropriate amount of water, followed by adding ethanol with volume of 300 times to water. After mixing well, the solution B was obtained. Solution B was slowly added to solution A, followed by standing for 12 h. After filtering, the filtrate was collected. After concentrating under reduced pressure, the total ginsenosides were obtained. After purifying by silica-gel column chromatography, the Grg2 product was obtained.

2.2 Animal experiment and modeling

Fifty Wistar rats (half male and half female, 250-280 g) were randomly divided into sham, LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups, 10 rats in each group. The rats in sham and LPS groups were given 10 mL/kg 0.5% CMC-Na solution by gavage, respectively. The rats in LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups were given 20 mg/kg GRg2 by gavage, 20 mg/kg GRg2 by gavage plus 5 mg/kg EX527 (SIRT1 inhibitor) by intraperitoneal injection and 5 mg/kg EX527 intraperitoneal injection, respectively. The treatment was performed once a day, for three consecutive days. On the fourth day, the rats in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 group were intraperitoneally injected with 10 mg/kg LPS. The rats in sham group were intraperitoneally injected with the same amount of normal saline. During the treatment and modeling process, no rat died in each group (Figure 1).

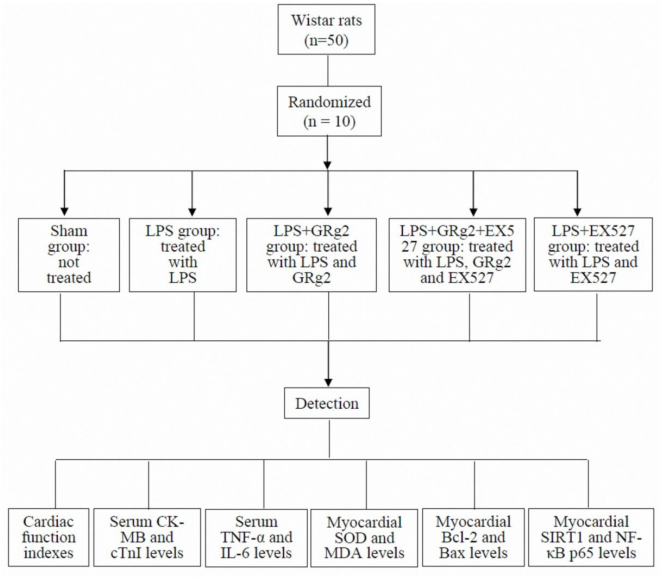

Figure 1. Flow chart of the randomization and treatment of animals. LPS, lipopolysaccharide. CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I, TNF-α, tumor necrosis factor α; IL-6, interleukin 6; SOD, superoxide dismutase; MDA, malondialdehyde; Bcl-2, B-cell lymphoma-2; Bax, B-cell lymphoma-2 associated X; SIRT1, silent information regulator 1; NF-κB, nuclear factor kappa-B.

2.3 Echocardiography

After 7 h from LPS injection, the cardiac function of rats was evaluated by echocardiography. The rats were anesthetized by intraperitoneal injection of 10% chloral hydrate and were fixed. Then, the left ventricular end-diastolic diameter (LVIDd), left ventricular end-systolic diameter (LVDSd), left ventricular fraction shortening (LVFS) and left ventricular ejection fraction (LVEF) were measured. Each parameter was measured for three consecutive cardiac cycles, and the average value was obtained.

2.4 Detection of serum myocardial enzymes and inflammatory factors

After echocardiography, the peripheral blood sample was taken from the rats. After centrifuging at 2000 r/min for 15 min, the serum was obtained. The myocardial enzyme indexes including creatine kinase isoenzyme MB (CK-MB) and cardiac troponin I (cTnI) and inflammatory indexes including tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) were detected by enzyme-linked immunosorbent assay. The detection procedures were according to the instruction of kits.

2.5 Detection of myocardial oxidative stress indexes

The heart of rats was taken. Partial myocardial tissues were separated, and were rinsed with pre-cooled normal saline. Under the condition of ice-water bath, the homogenate was prepared with normal saline. After centrifuging 3500 r/min for 15 min, the supernatant was obtained. The superoxide dismutase (SOD) activity was detected using hydroxylamine method. The malondialdehyde (MDA) level was detected by thiobarbituric acid method. The detection procedures were according to the instruction of kits.

2.6 Western blotting

Western blotting was performed to detect the expressions of B-cell lymphoma-2 (Bcl-2), B-cell lymphoma-2 associated X (Bax), SIRT1 and NF-κB p65 protein in myocardial tissue. Part of rat myocardial tissues were taken and weighed. The homogenate was prepared, followed by addition of tissue cell lysate. The total protein was extracted, and was quantified by bicinchoninic acid method. After sodium dodecyl sulfate polyacrylamide gel electrophoresis, membrane transfer and blocking, the membranes loading proteins were incubated with the primary antibody at 4 °C overnight. Then, the membranes were incubated with the secondary antibody conjugated with horseradish peroxidase for 30 min at room temperature. After visualization with the electrochemiluminescence system, the membranes were photographed. The intensity of bands was analyzed with Image J software. The ratio of target optical density to β-actin was calculated, which presented the expression level of target protein (the ratio value in sham group was corrected to 1).

2.7 Statistical analysis

Data were expressed as mean ± standard deviation. The statistical differences between different values were determined by analysis

of variance (ANOVA) followed by LSD-t test. Differences were considered significant at $P < 0.05$.

3 Results

3.1 Effect of GRg2 on cardiac function of sepsis rats

After 7 h from LPS injection, compared with sham group, in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups the LVIDd and LVIDs were significantly elevated ($P < 0.05$), and the LVFS and LVEF were significantly lowered ($P < 0.05$). Compared with LPS group, in LPS+GRg2 group the LVIDd and LVIDs were significantly lowered ($P < 0.05$), and the LVFS and LVEF were significantly elevated ($P < 0.05$) (Table 1).

3.2 Effect of GRg2 on serum CK-MB and cTnI levels in sepsis rats

As shown in Table 2, the serum CK-MB and cTnI levels in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups were significantly higher than those in sham group, respectively ($P < 0.05$). Compared with LPS group, in LPS+GRg2 group the serum CK-MB and cTnI levels were significantly decreased, respectively ($P < 0.05$).

3.3 Effect of GRg2 on serum TNF-α and IL-6 levels in sepsis rats

Compared with sham group, the serum TNF-α and IL-6 levels in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups were obviously increased, respectively ($P < 0.05$). However, each index in LPS+GRg2 was significantly lower than that in LPS group ($P < 0.05$) (Table 3).

3.4 Effect of GRg2 on myocardial SOD and MDA levels in sepsis rats

Table 4 showed that, the myocardial SOD level in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups was significantly lower than that in sham group, respectively ($P < 0.05$), and the MDA level in these groups was significantly higher than that in sham group, respectively ($P < 0.05$). Compared with LPS group, in LPS+GRg2 group the SOD level was significantly increased ($P < 0.05$), and the MDA level was significantly decreased ($P < 0.05$).

3.5 Effect of GRg2 on myocardial Bcl-2 and Bax expression levels in sepsis rats

Compared with sham group, in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups the myocardial Bcl-2 expression level was obviously decreased ($P < 0.05$), and the Bax expression level was obviously increased ($P < 0.05$). Compared with LPS group, in LPS+GRg2 group the Bcl-2 level was obviously increased ($P < 0.05$), and the Bax level was obviously decreased ($P < 0.05$) (Table 5).

3.6 Effect of GRg2 on myocardial SIRT1 and NF-κB p65 expression levels in sepsis rats

Table 6 showed that, vompared with sham group, in LPS, LPS+GRg2, LPS+GRg2+EX527 and LPS+EX527 groups the myocardial SIRT1 expression level was obviously decreased ($P < 0.05$), and the NF-κB p65 expression level was obviously increased ($P < 0.05$). Compared with LPS group, in LPS+GRg2 group the SIRT1 level was obviously increased ($P < 0.05$), and the NF-κB p65 level was obviously decreased ($P < 0.05$).

4 Discussion

Sepsis is a disease with high incidence and high mortality. It often occurs after infection, shock and severe trauma. Sepsis is a multiple organ dysfunction (MODS), and is one of the most common causes of death in intensive care unit. Myocardial injury is a common complication of sepsis, and also an important factor affecting the prognosis of sepsis patients. The effective prevention and treatment of myocardial injury is of great significance to

Table 1. Comparison of cardiac function index among five groups.

Group	n	LVIDd (mm)	LVIDs (mm)	LVFS (%)	LVEF (%)
Sham	10	4.98 ± 0.92	3.42 ± 0.52	43.29 ± 5.05	67.03 ± 5.05
LPS	10	7.12 ± 1.23$^{\#}$	6.25 ± 1.01$^{\#}$	32.02 ± 4.32$^{\#}$	54.33 ± 4.37$^{\#}$
LPS+GRg2	10	6.17 ± 1.02$^{\#*}$	5.17 ± 0.89$^{\#*}$	36.53 ± 4.89$^{\#*}$	60.17 ± 5.51$^{\#*}$
LPS+GRg2+EX527	10	6.34 ± 0.78$^{\#}$	5.52 ± 0.73$^{\#}$	28.77 ± 3.54$^{\#\%}$	53.04 ± 6.46$^{\#\%}$
LPS+EX527	10	7.23 ± 0.59$^{\#\%\&}$	6.34 ± 1.02$^{\#\%\&}$	30.20 ± 4.30$^{\#\%}$	52.38 ± 4.72$^{\#\%}$

$^{\#}P < 0.05$ compared with sham group. $^{*}P < 0.05$ vs. LPS group. $^{\%}P < 0.05$ vs. LPS+GRg2 group. $^{\&}P < 0.05$ vs. LPS+GRg2+EX527 group. LVIDd, left ventricular end-diastolic diameter; LVDSd, left ventricular end-systolic diameter; LVFS, left ventricular fraction shortening; LVEF, left ventricular ejection fraction.

Table 2. Comparison of serum CK-MB and cTnI levels among five groups.

Group	n	CK-MB (U/L)	cTnI (mg/L)
Sham	10	92.67 ± 15.04	0.11 ± 0.02
LPS	10	331.16 ± 56.30$^{\#}$	4.04 ± 0.56$^{\#}$
LPS+GRg2	10	215.04 ± 37.19$^{\#*}$	2.18 ± 0.18$^{\#*}$
LPS+GRg2+EX527	10	343.30 ± 48.70$^{\#\%}$	4.26 ± 0.67$^{\#\%}$
LPS+EX527	10	382.29 ± 52.11$^{\#\%}$	4.92 ± 0.43$^{\#*\%\&}$

$^{\#}P < 0.05$ compared with sham group. $^{*}P < 0.05$ vs. LPS group. $^{\%}P < 0.05$ vs. LPS+GRg2 group. $^{\&}P < 0.05$ vs. LPS+GRg2+EX527 group. CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I.

Table 3. Comparison of serum TNF-α and IL-6 levels among five groups.

Group	n	TNF-α (pg/mL)	IL-6 (pg/mL)
Sham	10	32.07 ± 5.60	24.25 ± 3.50
LPS	10	113.23 ± 16.42$^{\#}$	80.81 ± 11.27$^{\#}$
LPS+GRg2	10	71.18 ± 12.18$^{\#*}$	49.29 ± 6.32$^{\#*}$
LPS+GRg2+EX527	10	123.70 ± 20.37$^{\#\%}$	75.77 ± 9.73$^{\#\%}$
LPS+EX527	10	138.52 ± 18.05$^{\#*\%\&}$	90.30 ± 10.91$^{\#*\%\&}$

$^{\#}$P < 0.05 compared with sham group. *P < 0.05 vs. LPS group. $^{\%}$P < 0.05 vs. LPS+GRg2 group. $^{\&}$P < 0.05 vs. LPS+GRg2+EX527 group. TNF-α, tumor necrosis factor α; IL-6, interleukin 6.

Table 4. Comparison of myocardial SOD and MDA levels among five groups.

Group	n	SOD (U/mg)	MDA (mmol/mg)
Sham	10	54.80 ± 7.20	2.12 ± 0.32
LPS	10	18.14 ± 2.17$^{\#}$	7.20 ± 1.01$^{\#}$
LPS+GRg2	10	40.25 ± 5.83$^{\#*}$	4.43 ± 0.67$^{\#*}$
LPS+GRg2+EX527	10	26.36 ± 3.26$^{\#*\%}$	6.72 ± 1.06$^{\#\%}$
LPS+EX527	10	10.92 ± 1.05$^{\#*\%\&}$	11.52 ± 0.79$^{\#*\%\&}$

$^{\#}$P < 0.05 compared with sham group. *P < 0.05 vs. LPS group. $^{\%}$P < 0.05 vs. LPS+GRg2 group. $^{\&}$P < 0.05 vs. LPS+GRg2+EX527 group. SOD, superoxide dismutase; MDA, malondialdehyde.

Table 5. Comparison of myocardial Bcl-2 and Bax expression levels among five groups.

Group	n	Bcl-2/β-actin	Bax/β-actin
Sham	10	1.00 ± 0.00	1.00 ± 0.00
LPS	10	0.52 ± 0.07$^{\#}$	2.82 ± 0.43$^{\#}$
LPS+GRg2	10	0.81 ± 0.12$^{\#*}$	2.19 ± 0.31$^{\#}$
LPS+GRg2+EX527	10	0.67 ± 0.17$^{\#*\%}$	2.51 ± 0.29$^{\#*\%\&}$
LPS+EX527	10	0.45 ± 0.06$^{\#\%\&}$	3.20 ± 0.40$^{\#*\%\&}$

$^{\#}$P < 0.05 compared with sham group. *P < 0.05 vs. LPS group. $^{\%}$P < 0.05 vs. LPS+GRg2 group. $^{\&}$P < 0.05 vs. LPS+GRg2+EX527 group. Bcl-2, B-cell lymphoma-2; Bax, B-cell lymphoma-2 associated X.

Table 6. Comparison of myocardial SIRT1 and NF-κB p65 expression levels among five groups.

Group	n	SIRT1/β-actin	NF-κB p65/β-actin
Sham	10	1.00 ± 0.00	1.00 ± 0.00
LPS	10	0.42 ± 0.07$^{\#}$	3.20 ± 0.43$^{\#}$
LPS+GRg2	10	0.75 ± 0.12$^{\#*}$	1.97 ± 0.27$^{\#*}$
LPS+GRg2+EX527	10	0.52 ± 0.08$^{\#*\%}$	2.70 ± 0.43$^{\#\%}$
LPS+EX527	10	0.36 ± 0.03$^{\#\%\&}$	4.31 ± 0.68$^{\#*\%\&}$

$^{\#}$P < 0.05 compared with sham group. *P < 0.05 vs. LPS group. $^{\%}$P < 0.05 vs. LPS+GRg2 group. $^{\&}$P < 0.05 vs. SIRT1, silent information regulator 1. NF-κB, nuclear factor kappa-B.

improve the prognosis of sepsis patients. In this study, the LPS-induced sepsis model of rats was established, and the protective effect of GRg2 on myocardial injury in sepsis was investigated. Results showed that, after 7 h from LPS injection, compared with LPS group, in LPS+GRg2 group the LVIDd and LVIDs were significantly lowered, the LVFS and LVEF were significantly elevated, and the serum CK-MB and cTnI levels were significantly decreased. This reveals that, GRg2 has the protective effect on myocardial injury in rats with LPS-induced sepsis.

More and more studies have shown that the inflammatory response is an important factor leading to MODS in sepsis (Brady & Otto, 2001; Fry, 2012). The plasma lipopolysaccharide binding protein (LBP) specifically recognizes LPS and binds to it. Then LBP presents LPS to monocyte macrophages and make LPS to bind to its CD14 receptor on the surface of cell membrane. After that, CD14 transfers LPS to TLR4/MD-2 receptor complex, eventually leading to the activation of NF-κB and production of cytokines (Reinhart et al., 2012). In sepsis, the body's immune system is over activated, leading to the massive release of inflammatory factors such as TNF-α, IL-6 and IL-1β, which cause the severe and persistent inflammatory response. In this study, compared with LPS group, the serum TNF-α and IL-6 levels in LPS+GRg2 group were obviously decreased. This confirms that, GRg2 can directly reduce the inflammatory response, which may be related to its alleviation of myocardial injury in sepsis rats.

The destroyed balance of oxidation system and antioxidant system in cardiac defense system is the key factor of myocardial injury in sepsis (Víctor et al., 2009). SOD plays an important role

in regulating the production of reactive oxygen species and is an important antioxidant enzyme in body. It can combine with superoxide radicals and convert them into hydrogen peroxide which is then decomposed into oxygen and water under the action of related enzymes (Wei et al., 2016). MDA is one of the final products of membrane lipid peroxidation. When lipids such as arachidonic acid are attacked by free radicals, the lipid peroxides form and spontaneously break, resulting in the production of MDA. The amount of MDA can reflect the severity of lipid peroxidation (Yesilbursa et al., 2005). Results of this study showed that, compared with LPS group, in LPS+GRg2 group the SOD level was significantly increased, and the MDA level was significantly decreased. These results indicate that GRg2 can reduce the level of oxidative stress, thus alleviating the myocardial injury in sepsis rats.

Apoptosis is a spontaneous process of programmed death. Bcl-2 and Bax are the key regulators in mitochondrial pathway. Bcl-2 can inhibit the apoptosis, while Bax can promote the apoptosis. The dominance of Bcl-2 leads to the inhibition of apoptosis, and the dominance of Bax leads to the promotion of apoptosis. The ratio of Bcl-2 to Bax is a key factor in the regulation of cell survival, which is called the "molecular switch" of apoptosis (Leung & Wang, 1999). In the present study, compared with LPS group, in LPS+GRg2 group the Bcl-2 level was obviously increased, and the Bax level was obviously decreased. It can be concluded that GRg2 can inhibit the myocardial apoptosis in sepsis rats, thus exerting the protective effect on myocardial injury.

SIRT1 is a key signaling molecule in sepsis. It can regulate the transcriptional activity of p53, FOXO and NF-κB, thus regulating the inflammation, cell proliferation and oxidative stress (Song et al., 2019). NF-κB is an important transcription factor that mediates the inflammatory response and oxidative stress. Under normal conditions, NF-κB combines to inhibitory factor-κB (IκB). Under the stimulation of various factors, IκB is phosphorylated, and NF-κB is activated and translocated from cytoplasm to nucleus for transcription, then mediating the inflammatory reaction (Zhang et al., 2013). Activation of SIRT1 can inhibit the activity of NF-κB (Lin et al., 2012). It is found that Resolvin D1 can up-regulate the expression of SIRT1 and inhibit the phosphorylation level of NF-κB in lung tissue of septic mice, thus reducing the release of inflammatory cytokines and improving the survival rate of mice (Zhuo et al., 2018). In our study, compared with LPS group, in LPS+GRg2 group the SIRT1 level was obviously increased, and the NF-κB p65 level was obviously decreased. These results indicate that GRg2 can activate SIRT1/NF-κB signaling pathway, thus playing a protective role in myocardial injury in sepsis rats.

5 Conclusions

In conclusion, GRg2 alleviates myocardial injury in sepsis rats through reducing inflammatory response and oxidative stress and regulating apoptosis and SIRT1/NF-κB signaling pathways. The further action mechanism of GRg2 on myocardial injury in sepsis still needs to be clarified.

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