# Effect of Morin on Lipopolysaccharides-Induced Acute Kidney Injury in Mice

Original Article

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## ABSTRACT

**Introduction:** Sepsis is a serious complaint caused by a dysregulated host response to infection. It is one of the most common causes of admission to intensive care units. Acute kidney injury (AKI) is the most frequent complication of sepsis in critically ill patients and often requires renal replacement therapy. Despite decades of sepsis research, no specific therapies for sepsis emerged. Morin is a flavonoid that is abundant in the plants of the Moraceae famil, and has protective effect against many diseases that are mostly affected by inflammation and overproduction of oxidative stress, including a range of nephrotoxicity models rather than septic-induced AKI.

**Aim of the Study:** Thus, the present study was carried out to evaluate the effect of morin on the survival rate, clinical symptoms, renal histological alterations, and the immunoreactivity of the cell survival marker BCl2 in septic-induced AKI.

**Methods:** sepsis-induced AKI was induced in mice by a single intraperitoneal injection of lipopolysaccharides (LPS;5mg/kg). Treatment with morin (50 mg/kg bw) started 5 hours after LPS challenge, then for 2 more days.

**Results:** The results showed that LPS-injected mice had low survival rate (44% vs 100% in normal control) and showed several clinical signs including;hypoactivity, lethargy, loss of appetite, ruffled fur, high breathing rate, hind limb paralysis, and closed eyes. On the other hand, morin-treated animals showed significantly higher survival rate than that of the septic control group (90% vs 44%), recovery from the signs of sepsis, enhancement of the histology of kidney. In addition, morin decreased the immunoreactivity of the cell surviving marker BCl2.

**Conclusion:** these findings indicate that morin has a notable therapeutic effect against sepsis-associated AKI and may be a useful therapeutic option for increasing the survival rates of septic patients or even for preventing its associated renal complications.

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**Key Words:** Acute kidney injury, cell survival, clinical symptoms, morin, mortality rate.

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## INTRODUCTION

Sepsis is a severe illness generated by an unbalanced host reaction to an infection[1]. Increased respiration rate and decreased body weight are early signs of sepsis[2]. The symptoms of severe sepsis include irregular heartbeat, shallow breathing, and hypoactivity. Moreover, two or more organ systems, like the kidney, may fail in severe sepsis and septic shock[3,4]. Acute kidney injury (AKI) is the most common side effect of sepsis in critically sick patients, and it commonly necessitates renal replacement therapy[5]. AKI's renal tissue exhibits tubular and glomerular damage histologically in the form of tubular cell vacuolization, swelling, loss of the brush boundary, tubular atrophy, glomerulosclerosis, and glomerular atrophy[6,7]. The BCl2 protein is a member of the family that controls cellular homeostasis and is essential for several biological functions, including kidney growth, repair, and cell survival[8]. Along with contributing to apoptosis, it affects renal and mitochondrial morphogenesis[9]. The maintenance of mitochondrial integrity and cell viability is achieved through upregulation of BCl2, which also promotes the intrinsic mechanism of apoptosis in tubular injury in AKI[10,11]. Damaged tissues have a substantial rise in BCl2, an anti-apoptotic protein that promotes cell survival, in response to oxidative stress[12].

The World Health Organization views sepsis as a health priority[13] since it is one of the most frequent reasons for intensive care unit admissions[5]. Hospital mortality in septic shock approaches 60%[14]. Severe sepsis and septic shock are common in Egypt, where mortality is 47.13%[15]. Although the use of antibiotics treats the underlying cause of sepsis and somewhat lowers its mortality, antibiotic abuse brought about new difficulties as a result of the stress that antibiotics placed on the lives of bacterial pathogens,

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leading to the emergence of drug-resistant and even multi-resistant strains[16].

Natural substances like flavonoids have gained a lot of interest for the treatment of various clinical problems[17]. A bioactive compound called morin (3,5,7,2′,4′-pentahydroxyflavone) is common in the family Moraceae[18]. Morin is a crucial drug that is recommended for a number of illnesses, most of which are caused by inflammation and high ROS formation[19]. In a variety of nephrotoxicity models, morin has been shown to exhibit promising anti-inflammatory and antioxidant properties[20-26]. Morin is also readily available and has not been linked to any negative side effects from use[26]. Thus, the present study aimed to evaluate the effect of morin on the mortality rate, clinical symptoms, renal histological alterations, and the immunoreactivity of the cell survival marker BCl2 in induced AKI mice.

## Materials and methods

### *Drugs and Chemicals*

Morin hydrate and lipopolysaccharides (from Escherichia coli) were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA).

### *Experimental animals*

CD-1 male mice from the Medical Research Center at the Faculty of Medicine, Ain Shams University, (Cairo, Egypt) were purchased att the weight of six to eight weeks old and weight between 25 and 30 g. Mice were employed in the experiments for a week after getting acclimated in a lab setting. They were housed in plastic cages and given water and regular chow pellets as food.

### *Experimental design*

Four equal groups of 40 mice each were chosen at random and formed as follows: Normal mice in Group I (the negative control group) weren't given LPS or Morin injections; Group II (Morin group): Mice were treated with oral morin hydrate at a daily dose of 50 mg/kg b.wt[25,26] for 3 consecutive days; Group III (LPS group): Mice were intraperitoneally injected with 5 mg/kg LPS to create a AKI model[27]; and Group IV (LPS+ Morin group) mice were first challenged with LPS and then given oral morin hydrate treatment. Five hours after the LPS challenge, the morin treatment began, continuing for two more days.

All of the mice were regularly checked during the experiment for body weight and clinical signs of sepsis. For survival experiments, mice were monitored, and the mortality was recorded daily.

### *Histopathology*

After 24 hours, kidney samples were left to dry at room temperature in 10% neutral buffered formalin. The samples were then rinsed overnight in running tap water. They underwent an escalating series of alcohol dehydration, terpineol clearing, and paraffin wax embedding. Transverse slices were cut at a thickness of 5 microns, dewaxed, hydrated, and stained with hematoxylin and eosin or Periodic Acid-Schiff (PAS)[28].

### *Immunohistochemistry*

The cell survival marker (BCL2) was detected immunohistochemically utilising the avidin-biotin-peroxidase method. Brown coloration indicated positive reactions[29].

### *Statistical analysis*

Mean values and standard error of means were used to express numerical data. All statistical analysis were done with GraphPad Prism (CA, USA). One-way ANOVA was used to statistically evaluate the data before post hoc multiple comparisons (Tukey's test) were performed to compare the groups. The statistical significance level was set at $P<0{\cdot}05$.

## RESULTS

### *Mortality rate*

Throughout the experiment, there were no mortalities reported in the normal or morin control groups. The mortality in the AKI group was extremely high at only 56%. 10% of AKI mice survived after receiving morin treatment. Mortality rate of all groups is represented in (Figure 1).

### *Body weight*

The negative control group's body weights gradually increased during the period of experiment. Lower body weights were recorded after giving morin to normal mice compared to the negative control group. Septic mice had significantly lower body weights compared to the normal group, which were significantly improved by morin therapy. (Table 1).

### *Clinical symptoms*

Normal mice appeared healthy and active, with white and soft fur (Figure 2a). After administering morin to normal mice, the animals showed no significant change in their appearance or behavior (Figure 2b). One hour after LPS injection, all mice became hypoactive and lethargic. An hour later, they started excreting soft yellow feces and showed loss of appetite, while 80% of them had high breathing rate, which was clearly observed by naked eyes. Starting from the 4$^{th}$ hour after LPS injection, 10% of the mice showed hind limb paralysis and ruffled fur. On day 2, 60% of the surviving LPS-challenged mice appeared weak, and were still suffering from high breathing rate and hypoactivity, but their activity was slightly improved (active when provoked). 20% of them had hind limb paralysis and 30% showed closed eyes. On day 3, 40% of the mice showed closed eyes and 30% of them had hind limb paralysis (Figures 2c,d). On the other hand, septic mice treated with morin showed none of the clinical symptoms of the septic control group (Figure 2e).

### *Histological and histochemical results*

The renal tissue of the negative control mice underwent microscopic analysis and revealed normal architecture, differentiated into an outer cortex and an inner medulla. Malpighian corpuscles and proximal and distal convoluted tubules made up the cortical tissue (Figures 3a,b). The specimens from the mice treated with morin were identical to those from the control group (Figures 4a,b). On the other hand, septic mice displayed atrophied renal tubules and corpuscles as well as a disordered renal histological architecture (Figures 5a,b), while morin administration reduced these histological alterations (Figures 6a,b).

The PAS technique was used to demonstrate the membrane integrity of the tubules and glomeruli and to get further histological information. The kidney of a negative control mouse showed PAS reaction (magenta). Strong PAS reactions were seen in the tubular basement membrane and the brush border of the PCT lining cells in normal mice. The cells lining the tubules displayed a moderate to strong PAS reaction in their cytoplasm. Bowmans' glomerulus and capsule displayed an intense PAS reaction. The nuclei displayed a negative PAS reactivity (Figure 3c). Samples taken from uninfected mice treated with morin animals revealed no deviation from the kidney's normal histology (Figure 4c). The PAS technique was applied to confirm the abnormal alteration of the renal tubules and glomeruli in the infected mice. Due to vacuolation of the cytoplasm and the absence of a brush boundary, the renal tubules of this group displayed a weak PAS reaction. Tubules' basement membrane displayed a mild PAS reaction. Weak PAS reaction was present in the atrophied glomerulus and sclerotic basement membrane of Bowman's capsule. The nuclei displayed a weak PAS reactivity. (Figure 5c,d). This group's tubules and glomeruli reestablished a strong PAS reaction in the tubules' basement membrane, the lining cells of the PCT's brush border. Bowmans' capsule and glomerulus both displayed significant PAS reactions (Figure 6c).

### *Immunohistochemical results*

Normal expression of BCl2 is found in tubular cells but not glomerular cells. BCl2 was weakly expressed in the tubular cells of normal and morin-treated sections (Figures 7a,b, 8). In contrast, AKI specimens showed strong BCl2 expression in tubular cell (Figures 7c, 8). On the other hand, weak BCl2 reactivity was seen in AKI tissues treated with morin. (Figures 7d, 8).

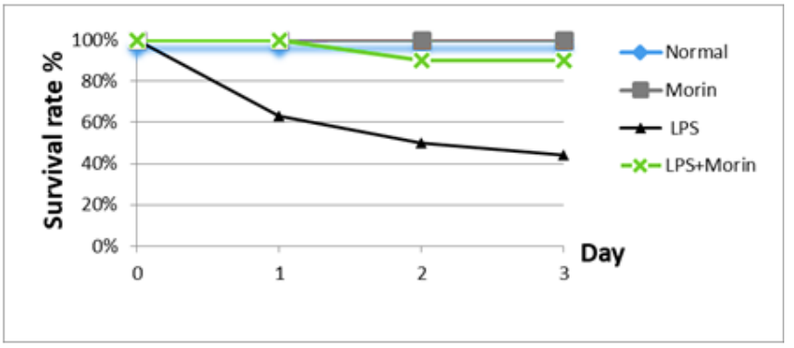


**Fig. 1:** Effect of morin on the mortality rate in normal and septic mice

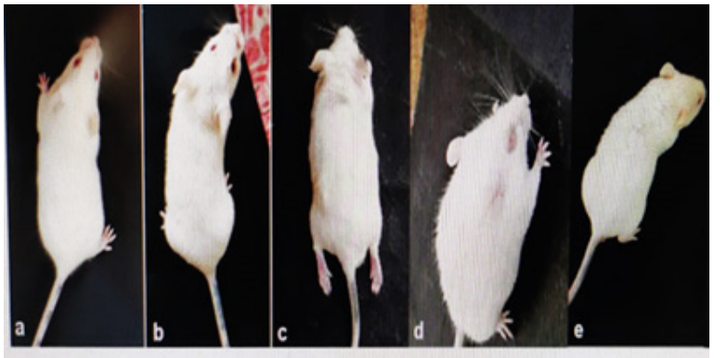


**Fig. 2:** Effect of morin on gross morphology of normal and septic mice a: normal; b: morin; c,d: septic mice; e: septic mice treated with morin

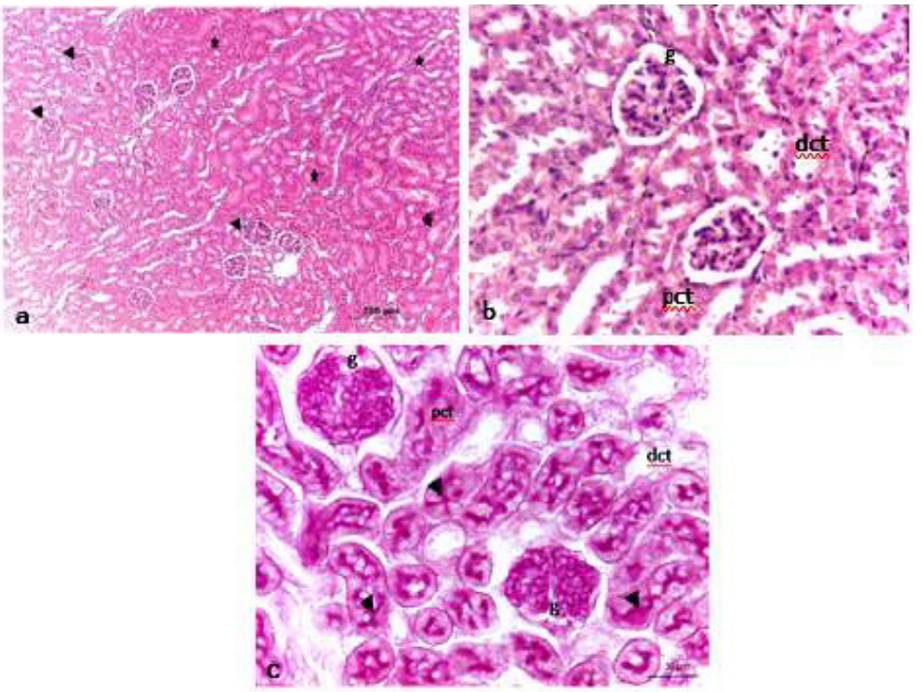


**Fig. 3:** a,b: Photomicrograph of a section of the kidney of a negative control (normal) mouse showing normal cortical architecture of closely packed tubules (asterisks), renal corpuscles (arrowheads), the proximal convoluted tubules (pct) and the distal convoluted tubules (dct). (Hx & E); c: PAS reaction (magenta) in a section of the kidney of a negative control mouse. The glomeruli (g), the tubular basement membranes and the brush borders (arrowheads) of the proximal convoluted tubules (pct) show strong PAS reaction. The cytoplasm of the tubular cells has moderate to strong PAS reaction. The nuclei show negative reactivity. (PAS technique).

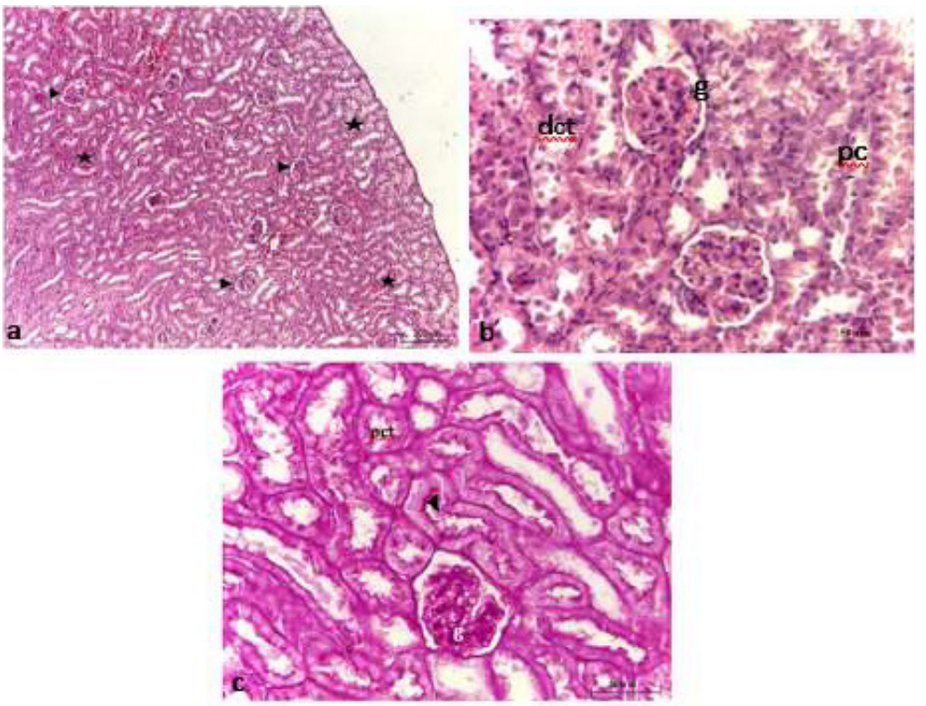


**Fig. 4:** a, b: Photomicrograph of a section of the kidney of a morin-treated mouse showing normal cortical architecture of closely packed tubules (asterisks), renal corpuscles (arrowheads), the proximal convoluted tubules (pct) and the distal convoluted tubules (dct). (Hx & E stain); c: PAS reaction in a section of the kidney of a morin-treated mouse. The glomerulus (g), the tubular basement membranes and the brush borders (arrowheads) of the proximal convoluted tubules (pct) show strong PAS reaction. The cytoplasm of the tubular cells shows moderate to strong PAS reaction. The nuclei show negative PAS reaction. (PAS technique).

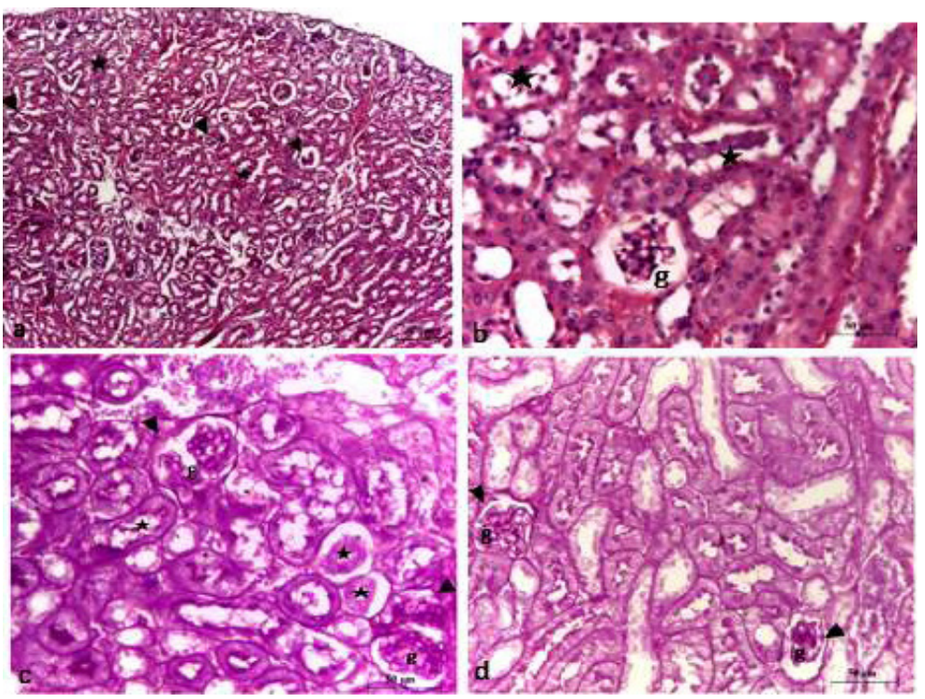


**Fig. 5:** a, b: Photomicrograph of a section of the kidney of AKI mouse showing altered renal architecture, manifested by disorganized, deformed tubules (asterisks) and atrophied glomeruli (g). Atrophied glomeruli (arrowheads) are also observed. (Hx & E stain); c, d: PAS reaction in renal section of septic mice. The vacuolated cells of renal tubules and exfoliated cells (asterisks) show moderate PAS reaction. The sclerotic Bowmans's capsule (arrowheads) and atrophied glomeruli (g) have weak to moderate PAS reaction. (PAS technique).

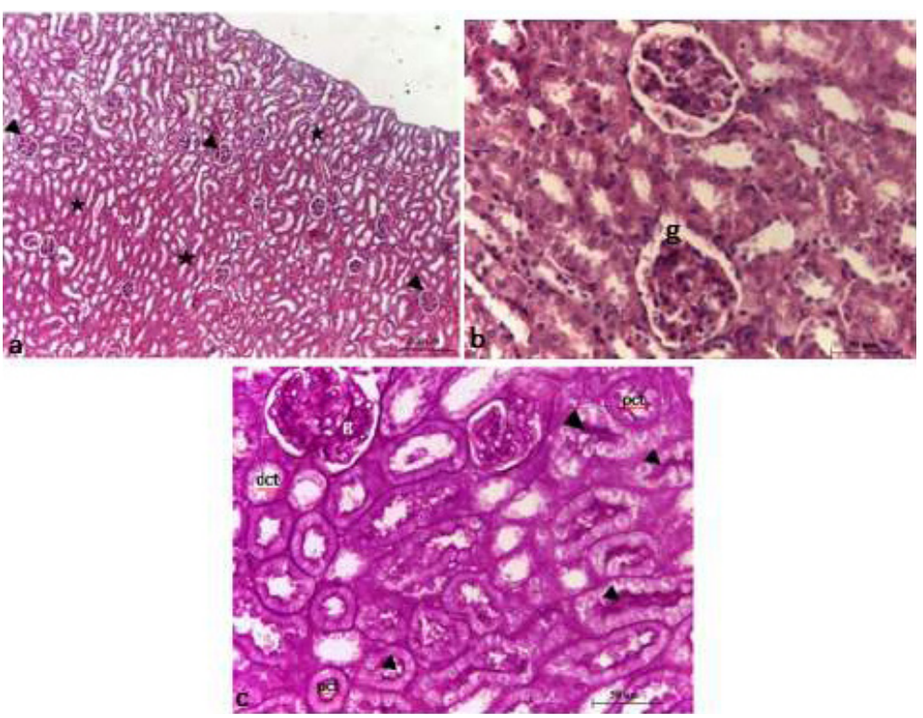


**Fig. 6:** a, b: Photomicrograph of a section of the kidney of a septic mouse treated with morin, showing restoration of normal architecture and organization of renal tubules (asterisks) and renal corpuscles (arrowheads). (Hx & E stain) c: PAS reaction in renal section of a septic mouse treated with morin. The basement membrane of renal tubules, the brush border (arrowheads) of proximal convoluted tubules (pct) and the glomeruli (g) restore strong PAS reaction. The cytoplasm has moderate to strong PAS reaction. (PAS technique).

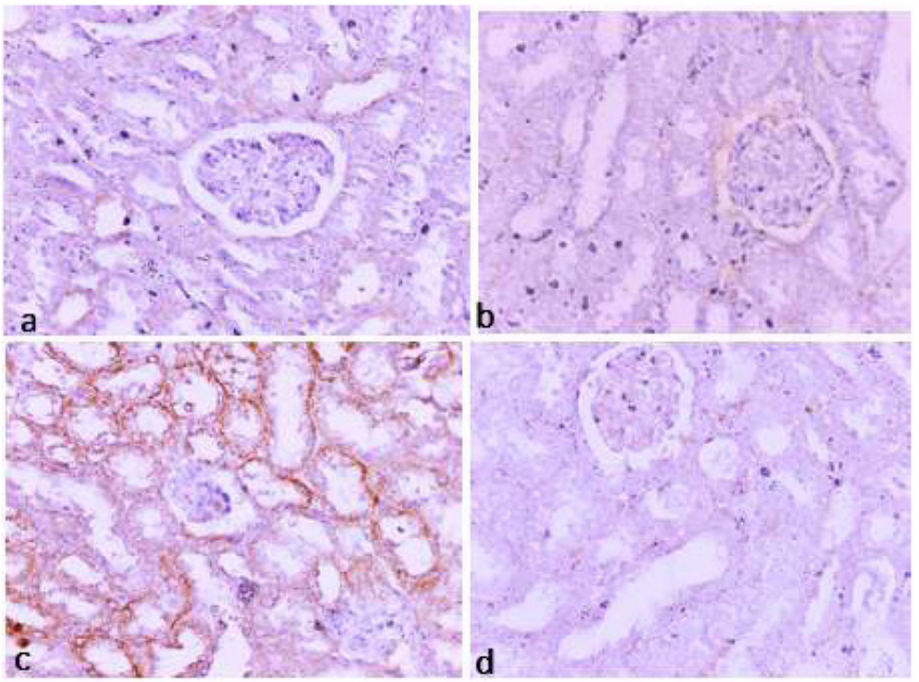


**Fig. 7:** Photomicrograph of the effect of morin on BCl2 immunoexpression in renal tissue of normal and septic mice. (a) Normal; (b) morin-treated; (c) sepsis; (d) sepsis+morin.

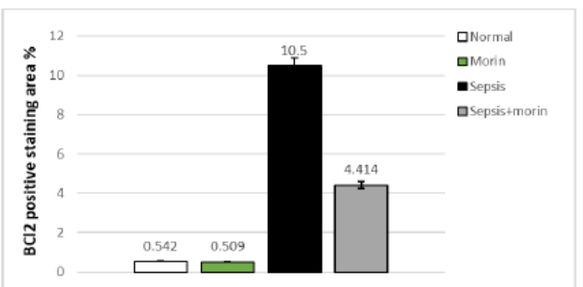


**Fig. 8:** Effect of morin on BCl2 expression in normal and septic renal tissue

**Table 1:** Effect of morin on the body weight change in normal and septic mice

| Groups | Body weight change |
|---|---|
| Normal | 15.62 ± 5.71 |
| Morin | -2.12 ± 2.35† |
| LPS | -9.75 ± 1.76†† |
| LPS + Morin | -5.4 ± 0.60* |

Data are expressed as mean ± SEM.
†Symbol represents significance compared with normal group, where †:$P$<0.05 and ††:$P$<0.001.
*Symbol represents significance compared with LPS group, where *: $P$<0.05.

## DISCUSSION

In the current study, morin significantly improved the survival rate, sepsis-related clinical symptoms, renal histological changes, and the immunoreactivity of the cell survival marker BCl2 in septic-induced AKI mice. According to Kim *et al*.[30], septic mice displayed a number of symptoms, including decreased body weight, which was explained by the mice's decreased appetite and food intake. The hypoactivity observed in septic mice is most likely caused by sepsis-related excessive inflammation, which increases energy demands and results in locomotor obstruction to help preserve energy and divert it from growth and reproduction programmes into tissue preservation and survival programmes[31]. LPS inhibits locomotor activity, which can lead to lethargy and hind limb paralysis[32]. High breathing rates, hind limb paralysis, and closed eyes may result from the bacterial LPS injection, which has been commonly used in immunological research as one of the models of neuroinflammation in rodents[33,34].

In addition to having a high mortality rate, septic mice also had decreased vasomotor tone, decreased peripheral vascular resistance, decreased blood pressure and cardiac output, hypoperfusion, and hypoxygenation of tissues and organs. These changes in inflammation may be related to sepsis-associated exacerbated inflammation that contributes to multiple organ dysfunction[33,35,36]. The renal tissue damage was confirmed microscopically, the renal specimens of septic mice showed altered renal histological architecture evidenced by disorganized, deformed renal tubules, and atrophied glomeruli. Previous septic-induced AKI models showed similar histological observations[37,38,39]. Due to constant exposure to damaging factors, degenerated tubules expressed BCl2, which could be interpreted as a self-protection mechanism[8,11]. Several instances have established the role of BCl2 in preventing oxidative stress-related cell death[8].

Compared to high mortality rate of septic control mice (56%), animals treated with morin showed signs of recovery from septic symptoms and a lower mortality rate (10%). Morin's antioxidant and anti-inflammatory properties could be mostly responsible for its ameliorative benefits[28,40,41]. In various models of nephrotoxicity treated with morin, Kuzu *et al*.[25] and Kandemir *et al*.[26] reported an improvement in structural alterations of the renal cells. The reduction in immunoexpression of the cell survival marker may be related to the improvement in the structure of septic renal tissues following morin treatment (BCl2). According to Ren *et al*.[42], flavonoids lower the level of BCl2 expression compared to that of septic mouse. As ROS act as a direct activator of BCl2 and other cellular defence mechanisms[43,44,45,46], this may be because of the pivotal relationship between BCl2 expression and oxidative stress. This is most likely because BCl2 is crucial for many biological processes, including renal cell development, repair , and survival[8].

## CONCLUSION

In conclusion, morin is suggested to be a therapeutic option for the treatment of septic-induced AKI, as it decreased the mortality rate, ameliorated the clinical symptoms, improved histological structure and restored immunoexpression of the cell survival marker (BCl2) in septic mice.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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**الملخص العربى**

# تأثير مورين على القصور الكلوي الحاد الناجمة عن عديدات السكاريد الدهنية في الفئران

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**المقدمة:** تعفن الدم هو شكوى خطيرة ناجمة عن استجابة المريض الغير منتظمة للعدوى. وهو أحد الأسباب الأكثر شيوعًا لدخول وحدات العناية المركزة. تعد الإصابة بالقصور الكلوي الحاد من أكثر المضاعفات شيوعًا لتعفن الدم لدى المرضى المصابين بأمراض خطيرة وغالبًا ما تتطلب العلاج بالغسيل الكلوي. على الرغم من كثرة الأبحاث في العقود الماضية حول تعفن الدم، لم تظهر علاجات محددة له. المورين هو فلافونويد متوفر بكثرة في نباتات عائلة Moraceae، وله تأثير وقائي ضد العديد من الأمراض التي تتأثر في الغالب بالالتهاب والإفراط في إنتاج الإجهاد التأكسدي، بما في ذلك مجموعة من نماذج السمية الكلوية غير القصور الكلوي الحاد الناجم عن تعفن الدم.

**الهدف من الدراسة:** أجريت هذه الدراسة لتقييم تأثير مورين على معدل البقاء على قيد الحياة، والأعراض الظاهرية، والتغيرات النسيجية الكلوية، والنشاط المناعي لعلامة بقاء الخلية BCl٢.

**المواد و الطرق:** تم إحداث القصور الكلوي الحاد الناجم عن تعفن الدم في الفئران عن طريق جرعة واحدة داخل الغشاء البريتوني. تم حقن عديدات السكاريد الدهنية LPS (٥ مجم/كجم) بدأ العلاج بالمورين (٥٠ ملغم/كغم من وزن الجسم) بعد ٥ ساعات من حقن ال LPS ثم لمدة يومين إضافيين.

**النتائج:** أظهرت النتائج أن الفئران المحقونة بـ LPS كان لديها معدل بقاء منخفض (٤٤٪ مقابل ١٠٠٪ في المجموعة الضابطة) وأظهرت العديد من اعراض تعفن الدم بما في ذلك؛ نقص النشاط، والخمول، وفقدان الشهية، وارتفاع معدل التنفس، وشلل الأطراف الخلفية، وانغلاق العيون. من ناحية أخرى، أظهرت الحيوانات المعالجة بالمورين معدل بقاء أعلى بكثير من المجموعة الضابطة للقصور الكلوي الحاد الناجم عن تعفن الدم (٩٠٪ مقابل ٤٤٪)، والشفاء من اعراض تعفن الدم، وتعزيز أنسجة الكلى. بالإضافة إلى ذلك، قلل مورين من النشاط المناعي لل BCl٢ في الانسجة.

**الخلاصة:** في الختام، تشير هذه النتائج إلى أن مورين له تأثير علاجي ملحوظ ضد القصور الكلوي الحاد الناجم عن تعفن الدم وقد يكون خيارًا علاجيًا مفيدًا لزيادة معدلات البقاء على قيد الحياة لمرضى تعفن الدم أو حتى لمنع المضاعفات الكلوية المرتبطة به.