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Protective Effects of Citronellol Against Rhabdomyolysis-Induced Acute Kidney Injury in Mice by Inhibiting NF-κB and IL-1β Signaling Pathway [#]

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Abstract

Acute kidney injury is a serious pathophysiological event consequent to rhabdomyolysis. Inflammatory mechanisms play a role in the development of rhabdomyolysis-induced acute kidney injury. Citronellol is a naturally occurring monoterpene in aromatic plant species' essential oils. Citronellol exists in two forms: (+)-Citronellol, which is found primarily in citronella, Amyris and eucalyptus citriodora oils, and (-)-Citronellol, which is mostly present in pelargonium and rose oils (both are colorless liquids with a rose fragrance). In this study, we explored the protective effects of Citronellol on acute kidney injury resulting from glycerol-induced rhabdomyolysis. Rhabdomyolysis was induced single IM injection of glycerol 50% (10mg/kg) in thigh caudal muscle; four groups of mice were allocated, control orally-given 0.1ml normal saline, glycerol administered mice as model rhabdomyolysis- induced acute kidney injury, glycerol plus Citronellol (50mg/kg), and glycerol plus Citronellol (100mg/kg) mice. The renal function of mice from all groups was evaluated by measuring urea and creatinine. Creatine kinase level was measured to detect rhabdomyolysis. Inflammation was evaluated by nuclear factor kappa-B (NF-κB) and interleukin one beta (IL-1β) gene expression levels. Citronellol in both doses, 50&100 mg/kg, significantly-decreased serum urea, creatinine, and creatine kinase compared to the glycerol group. In addition, citronellol resulted in significantly lower expression of both nuclear factor kappa-B (NF-κB) and interleukin-one beta (IL-1β) in the renal tissue. Prophylaxis with low and high doses of citronellol improved inflammatory responses and renal function these positive effects were achieved, by inhibiting the development of inflammatory cytokines, nuclear factor kappa-B (NF-κB) and interleukin-1 beta (IL-1β). These discoveries reveal fresh details regarding a potential treatment option for kidney injury caused by rhabdomyolysis.

Keywords: Rhabdomyolysis, NF-κB, AKI, IL-1β.

التأثيرات الوقائية للسيترونيلول ضد إصابة الكلى الحادة الناجمة عن انحلال الربيدات في الفئران عن طريق تثبيط مسار اشارات العامل النووي كابا ب ومستويات التعبير الجيني بيتا إنترلوكين واحد[#]

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#المؤتمر العلمي الثاني لطلبة الدراسات العليا

١ وزارة الصحة والبيئة ، مديرية صحة كربلاء ، كربلاء ، العراق.

٢فرع الادوية والسموم ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق.

الخلاصة

إصابة الكلى الحادة هي حدث فيزيولوجي مرضي خطير ناتج عن انحلال الربيدات وتلعب الآليات الالتهابية دورا في تطور إصابة الكلى الحادة الناجمة عن انحلال الربيدات. سيترونيلول هو مونوتربين طبيعي في الزيوت الأساسية لأنواع النباتات العطرية. يوجد السترونيلول في شكلين: (+) - سيترونيلول ، والذي يوجد بشكل أساسي في زيوت السترونيلا وأميريس والأوكالبتوس سيتريودورا ، و (-) -سيترونيلول ، الموجود في الغالب في زيوت البلارجونيوم والورد (كلاهما سوائل عديمة اللون مع رائحة الورد). في هذه الدراسة ، استكشفنا الآثار الوقائية للسيترونيلول على إصابة الكلى الحادة الناتجة عن انحلال الربيدات الناجم عن الجلسرين. تم تحفيز انحلال الربيدات بحقن عضلي واحد من الجلسرين ٥٠٪ (١٠ مجم / كجم) في العضلة الذيلية للفخذ. تم تخصيص أربع مجموعات من الفئران ، السيطرة ، الفئران التي تدار الجلسرين كنموذج لإصابة الكلى الحادة الناجمة عن انحلال الربيدات ، والجلسرين بالإضافة إلى سيترونيلول (٥٠ مجم / كجم) ، والجلسرين بالإضافة إلى سيترونيلول (١٠٠ مجم / كجم) الفئران. تم تقييم الوظيفة الكلوية للفئران من جميع المجموعات عن طريق قياس اليوريا والكرياتينين. تم قياس مستوى الكرياتين كيناز للكشف عن انحلال الربيدات. تم تقييم الالتهاب بواسطة العامل النووي كابا ب ومستويات التعبير الجيني بيتا إنترلوكين واحد. سيترونيلول في كلتا الجرعتين ، ٥٠ و ١٠٠ مجم / كجم ، انخفض بشكل ملحوظ في اليوريا في الدم والكرياتينين كيناز مقارنة بمجموعة الجلسرين. بالإضافة إلى ذلك ، أدى السترونيلول إلى انخفاض كبير في التعبير عن كل من العامل النووي كابا ب وإنترلوكين واحد بيتا في الأنسجة الكلوية ، مما يشير إلى أن السترونيلول يمارستأثيرا مضادا للالتهابات في إصابة الكلى الحادة. أظهر سيترونيلول تأثيرا وقائيا رينو ضد إصابة الكلى الحادة الناجمة عن انحلال الربيدات ، والتي يمكن أن تعزى إلى آثاره المضادة للالتهابات. تشير النتائج إلى أن سيترونيلول قد يكون عاملا علاجيا واعدا لإصابة الكلى الحادة. توفر نتائج هذه الدراسة رؤى قيمة للبحث والتطوير المستقبلي لاستراتيجيات العلاج الفعالة لإصابات الكلى الحادة.

الكلمات المفتاحية: انحلال الربيدات، العامل النووي كابا ب، إصابة الكلى الحادة، بيتا إنترلوكين واحد

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Introduction

Rhabdomyolysis is a serious medical condition that occurs when muscle tissue is injured and releases its contents into the bloodstream [1]. This can happen due to various causes، including trauma، infections، drug use، and extreme exercise [2]. Acute kidney injury (AKI) is a major health problem resulting in end-stage renal disease (ESRD) and even death if not promptly-diagnosed and -treated [3]. Myoglobin is a protein that is freely filtered by the glomerulus of the kidneys and then reabsorbed by the proximal tubules [4]. When there is an excessive release of myoglobin into the bloodstream، such as in cases of rhabdomyolysis، it can lead to the accumulation of myoglobin in the tubular cells of the kidneys [5]. This can cause oxidative stress (OS)، inflammation، and cell death، ultimately resulting in AKI [6]. One of the ways myoglobin induces AKI is by generating free radicals، which are highly reactive molecules that can damage cells and tissues [7]. These free radicals can activate NF-κB، which is an important transcription factor that regulates the expression of genes involved in immune and inflammatory responses [8]. Activation of the NF-κB signaling pathway can lead to the production of proinflammatory cytokines، such as interleukin-1 beta (IL-1β)، which contribute to the development of AKI [9]. Glycerol injection is a commonly used method to induce rhabdomyolysis in animal models [10].

Citronellol (CT) is a naturally-occurring monoterpene alcohol (3،7-Dimethyl-6-often-1-ol) found in some species such as Cymbopogon citrates، Cymbopogon winteriness، and *Lippia alba*. commonly used as a fragrance and flavoring agent; and it is also used in various industries، including the food، cosmetic، and pharmaceutical industries [11]. Moreover، citronellol exists in two forms: (+)-CT، which is found primarily in citronella، Amyris and eucalyptus citriodora oils، and (-)-CT، which is mostly present in pelargonium and rose oils (both are colorless liquids with a rose fragrance) [12].

Additionally، citronellol has been shown to have antibacterial، antifungal and repellent properties in vitro، as well as cardiovascular، antidiabetic، and antinociceptive properties *in vivo* [11]. There is no current medication that may be used as treatment or protection for AKI or rhabdomyolysis.

Aim

The present study aimed to evaluate whether citronellol may have a protective effect on kidney function and pathology in a mice model of glycerol-induced AKI by uncovering some unique processes underlie glycerol-induced AKI، as well as how they affect prognostic indicators of AKI، Rhabdomyolysis، and inflammation.

Materials and Methods

Animals and Experimental Protocol

The College of Pharmacy at the University of Baghdad provided the mice used in this study; where، 32 BALB/c Albino mice weighing 25-32 g; and had free access to water and a standard diet. All procedures performed on the animals are strictly adhered to both institutional and international regulations governing the ethical treatment and use of laboratory animals. Citronellol was purchased from Sigma-Aldrich، Germany.

To induce rhabdomyolysis in mice by depriving them of water for 24 hours and then injecting them with glycerol 50% 10 mg/kg [13].

Four groups of mice were used (n=8، 4male and 4 female).; as follows:

Group I/Control: Mice orally given 0.1ml normal saline (N/S) for 4 days.

Group II/The model group: Mice received a single IM injection of glycerol 50% (10mg/kg) [14].

Group III/Citronellol (50mg/kg). Mice were orally administered 50mg/kg citronellol [14] for 4 days and single glycerol 50% IM injection (10mg/kg) at day 4.

Group IV/Citronellol (100mg/kg). Mice were orally-administered 100mg/kg orally citronellol [14] for 4 days and single glycerol 50% IM injection (10mg/kg) at day 4.

All Mice were euthanized 24hrs after glycerol injection by diethyl ether followed by cervical dislocation [15]. Then right kidneys were extracted and homogenized [16]; and blood was collected and serum separated [17] to be used for the colorimetric measurement of urea and creatinine (Linear chemicals، Spain)، and creatinine kinase (MY BioSource، USA) in addition to the analysis of NF-kB mRNA and IL-1β mRNA levels.

Biochemical measurements

Serum urea and Cr were assessed as crucial indicators of the severity of the renal injury following the manufacturer's instructions (Linear Chemicals/ Spain)، a semi-automated biochemical analyzer. Moreover، CK from My BioSource/USA was measured [18].

Gene Expression analysis

The gene expression analysis of NF-κB and IL-1β was performed by the measurement of mRNA levels in kidney tissue using standard qRT-PCR protocol [19]. In summary، the kidney homogenate with TRIzol was sed for the isolation of total RNA using TransZol Up Plus RNA Kit (TransGen، biotech); subsequently، a complementary DNA (cDNA) synthesis was performed using the EasyScript® one-step gDNA removal and cDNA synthesis (TransGen، biotech). The mRNA expression levels were performed by SYBR Green Supermix (TransGen، biotech) with GAPDH as housekeeping gene. The sequences of primers were as follows: forward GAPDH

CGGGTTCCTATAAATACGGACTG and reverse CCAATACGGCCAAATCCGTTC; NF-κB forward AAGACAAGGAGCAGGACATG and reverse AGCAACATCTTCACATCCC; IL-1β forward TGCCACCTTTTGACAGTGATG and reverse TGATGTGCTGCTGCGAGATT.

Statistical analysis

The outcome of a statistical study carried out with SPSS software version 25 was displayed using the mean and SEM. One-way ANOVA was performed to compare data from various groups، and Tukey's multiple comparison tests was employed to identify significant differences between all groups. $P<0.05$ was used as the threshold for statistical significance، if the calculated $P<0.05$، that means it was statistically significant.

Results

Effect of Citronellol on Kidney Function and Injury

Glycerol injection in mice/**Group II** has been shown to cause deterioration in renal function which is reflected by the significant elevation of serum urea and creatinine (43.1 ± 0.34 vs 20.35 ± 0.662 mg/dL and 0.93 ± 0.02 vs 0.34±0.03 mg/dL) respectively، compared to such levels in the control/**Group I** mice (figures 1A، B).

Furthermore، pre-treatment of mice with CT 50gm/kg/**Group III**، ameliorated the renal function deterioration as measured by significant decrease in serum-urea and -creatinine (34.75 ± 0.53 vs 43.1 ± 0.34 and 0.65 ± 0.02 vs 0.93 ± 0.02) levels، respectively compared to such serum levels in model/**Group II**. Additionally، in group of mice orally-administered CT at a dose of 100 mg/kg/**Group IV**، there were better results; where، further enhancement in renal function was resulted as measured by the significant decrease in urea (22.75 ± 0.84 vs 43.1 ± 0.34) and creatinine (0.48 ± 0.01 vs 0.93 ± 0.02) compared to model/**Group II**، in a dose-dependent manner.

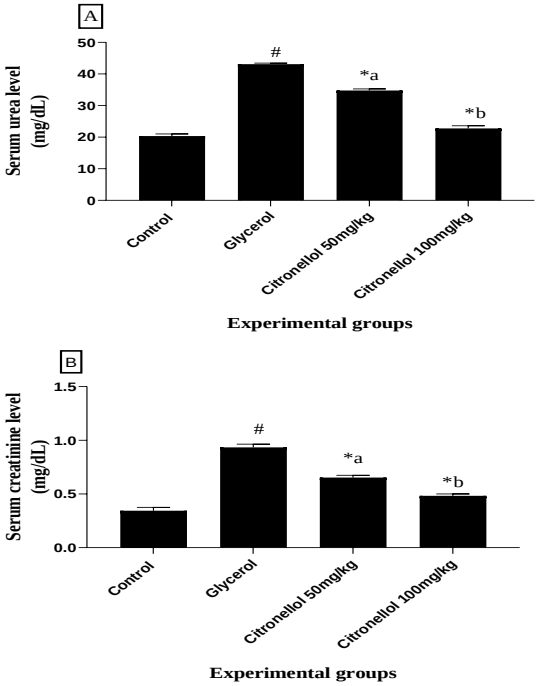

Figure 1. The effect of citronellol on functional renal damage associated with rhabdomyolysis. A) Serum urea B) Serum creatinine. The results are shown as means ± SEM، and statistical significance was determined by comparing the glycerol-injected mice (#) with the control group and the citronellol-treated mice (*) with the glycerol-injected mice. #$P<0.05$ or *$P<0.05$) refers to statistical significance. A and b referred to treatment groups.

Effects of Citronellol on Serum Creatine Kinase (CK) Enzyme Level

Measurement of serum CK was done to assess rhabdomyolysis. Injection of glycerol/**Group II** resulted in spike elevation of CK (68.33 ± 1.43 vs 32.73 ± 1.17) levels compared to the control /**Group I** as shown in Figure (2). Interestingly، mice that received CT 50&100mg/kg for 4 days/**Group III & Group IV**، respectively، revealed a significant dose-dependent reduction in serum CK (55.13 ± 0.71 & 33.11 ± 1.23 vs 68.33 ± 1.43) as compared to the model group/**Group II**، implying an improving effect on muscle rhabdomyolysis.

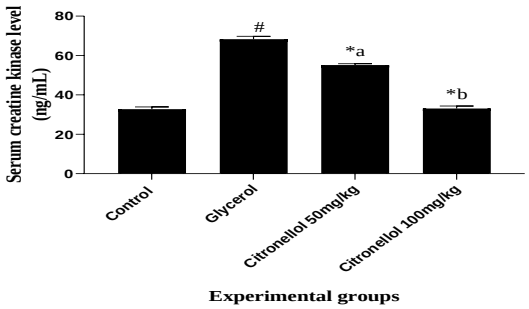

Figure 2. The effect of citronellol on serum CK: The results are expressed as means ± SEM، and statistical significance was determined by comparing the glycerol-injected mice (#) with the control group and the citronellol-treated mice (*) with the glycerol-injected mice. (#$P<0.05$ or *$P<0.05$) indicates statistical significance. A and b referred to treatment groups.

Effects of Citronellol on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and interleukin-1 beta (iL-1β) mRNA levels

Injection of glycerol/in **Group II** mice resulted in a significant spike of both NF-kB and IL-1β mRNA levels compared to corresponding levels in the control/**Group I** mice (10.50 ± 3.60 vs 1.07 ± 0.13 and 21.35± 3.40 vs 1.09 ± 0.16)، respectively; Figure (3A، B). Moreover، pre-treatment of mice with CT (both 50mg/kg/**Group III** and 100 mg/kg/**Group IV**) resulted in a significant decline in NF-kB gene expression (2.82 ± 0.38 & 3.10 ± 0.36 vs 10.50 ± 3.60) each compared to the model/**Group II** mice.

Consistently، the IL-1β also showed significant downregulation (4.01± 1.23 &5.46 ± 0.95 vs 21.35± 3.40) after CT treatment with either 50mg/kg/**Group III** or 100 mg/kg/**Group IV** each compared to such level in the model mice/**Group II**.

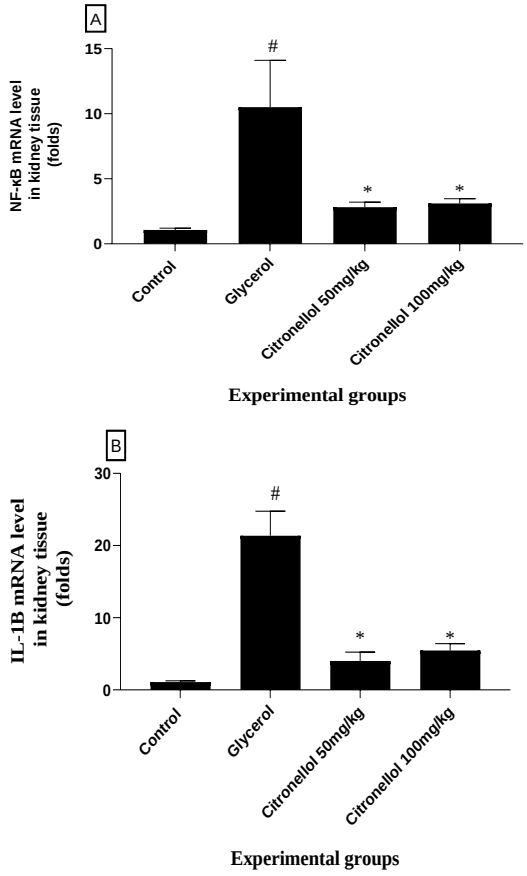

Figure 3. Effect of Citronellol on inflammation
A: Effect of Citronellol on NF-kB mRNA in glycerol-induced AKI model. B: Effect of Citronellol on iL-1B mRNA in glycerol-induced AKI model. The results are expressed as means ± SEM، and statistical significance was determined by comparing the glycerol-injected mice (#) with the control group and the citronellol-treated mice (*) with the glycerol-injected mice. (#P<0.05 or *P<0.05) indicates statistical significance.

Discussion

Acute kidney injury (AKI) is a serious complication of rhabdomyolysis، which is a feature of the breakdown of skeletal muscle fibers and the release of myoglobin، electrolytes، and other cellular contents into the bloodstream [20]. Glycerol-induced renal damage is a widely used experimental model for studying the mechanisms underlying AKI and developing new approaches for its treatment [21][22]. In this study، glycerol is injected into the muscle، which causes the destruction of muscle cells and the release of myoglobin، creatine kinase and other toxic substances into the bloodstream [23]. These substances can overwhelm the kidney's filtering capacity، leading to delete the damage of the renal tubules and impaired kidney function. Depending on the outcomes of this study، it appears that glycerol injection induced rhabdomyolysis in the tested groups، as evidenced by the significant increase in serum CK concentration (as observed in previous studies [24]) compared to the control group. Additionally، in the Glycerol/**Group II** mice there was significant kidney damage، as indicated by increased serum -urea and -creatinine levels as observed in other studies [25،26]. However، the administration of citronellol at both 50 and 100 mg/kg doses each appeared to have a protective role on the kidneys of the tested animals; since، the treatment significantly-decreases serum -urea and -creatinine levels in addition to serum-CK; and the observed improvement in kidney function suggests that citronellol may have an effect in preventing rhabdomyolysis-induced kidney injury.

Furthermore، myoglobin and other chemicals generated by injured cells can cause OS، and can lead to the activation of the NF-kB signaling pathway، and this in turn can induce cytokines mediators such as IL-1β which can cause inflammation and renal tissue damage in rhabdomyolysis-induced AKI [27،28].

Additionally، in the present study، in **Group II mice**/Glycerol-induced AKI model، there was increased expression of the transcription factor NF-κB and the pro-inflammatory cytokine IL-1β in the kidney compared to such factor in **Group I mice** (Figure 3A and B، respectively); and such results are consistent with those of others [29][30] concerning this respect. Moreover، evidence suggested that IL-1β is important in the pathogenesis of the renal disease [31،32]. Furthermore، treatment with citronellol resulted in a significantly lower expression of both NF-κB and IL-1β in the renal tissue، indicating that citronellol may have an anti-inflammatory effect on AKI (Figure 3A and B، respectively).

Additionally، by inhibiting the expression of NF-κB and IL-1β، citronellol may have attenuated the inflammation-induced damage in AKI، which is agreeable with the earlier findings reported by Redha SM. et at. 2022 that citronellol exerted anti-inflammatory effects in mice. The effects resulted

from the inhibition of the NF-κB signaling pathway، particularly the TLR4/MyD88-dependent and MyD88-independent pathways [14]. Also، several other Studies suggest that citronellol has anti-inflammatory activities that could be helpful for the treatment of various inflammatory diseases [33-34].

Conclusion

In conclusion، the study showed that citronellol has a reno-protective effect against rhabdomyolysis-induced acute kidney injury in mice، which may be attributed to its anti-inflammatory effect; since the results suggest that citronellol may be a promising therapeutic agent for AKI; and also، the results of this study provide valuable insights for future research and development of effective treatment strategies for AKI. However، more studies are required to validate the efficacy and safety of citronellol in human subjects.

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Ethics Statements

It was approved by the Ethical committee of the College of Pharmacy/University of Baghdad before the start of the study.

Conflict of Interest

The authors have no conflict of interests.

Author contributions

The first author did the practical work and result analysis. The second author supervised the whole work.

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