

## Original Article

## Antihyperglycaemic and tissue-repair effects of *Myrmeleon formicarius* extract in streptozotocin-induced diabetic mice



Jekti Prihatin, Dr.<sup>a</sup>, Erlia Narulita, Ph.D.<sup>a,\*</sup>, Lailatul Mufidah, M.S.<sup>a</sup>,  
Alief Kurniawan, S.Pd.<sup>a</sup>, Dwi Wulandari, S.Pd.<sup>a</sup> and Slamet Hariyadi, Dr.<sup>a</sup>

<sup>a</sup> Department of Biology Education, University of Jember, Jember, Indonesia

Received 25 September 2018; revised 12 January 2019; accepted 20 January 2019; Available online 14 February 2019

### المخلص

**أهداف البحث:** تهدف هذه الدراسة إلى دراسة تأثير أخذ المستخلص مايرمليون فورميكاروس (ليث عفرين) عن طريق الفم على أنسجة الكبد والكلية في الفئران المصابة بالسكري الناتج عن الستربتوزوتوسين.

**طرق البحث:** تم تحضير ٢٤ فأراً عن طريق حقنهم بجرعة واحدة من الستربتوزوتوسين داخل الصفاق وتم تقسيمهم إلى ست مجموعات. مجموعة المراقبة السلبية، ومجموعة المراقبة الإيجابية التي عولجت بغليبينكلاميد. تلقت أربع مجموعات علاجية مستخلص مايرمليون فورميكاروس (ليث عفرين) بجرعة ٢.٥، ٥، ٧.٥، و ١٠ مجم/كجم من وزن الجسم، على التوالي. ثم استخدمت مقاطع رقيقة دائمة لدراسة أنسجة الكبد والكلية للفئران.

**النتائج:** أظهرت النتائج أن الجرعة الأنسب لخفض مستويات الجلوكوز في الدم بعد يومين من العلاج كانت ١٠ مجم/كجم من وزن الجسم لمستخلص مايرمليون فورميكاروس (ليث عفرين). أظهر الفحص النسيجي للكبد والكلية أن مستخلص ليث عفرين ١٠ مجم/كجم من وزن الجسم و ٥ مجم/كجم من وزن الجسم ينتج تأثيرات إصلاحية أكثر على الأنسجة التالفة.

**الاستنتاجات:** مستخلص مايرمليون فورميكاروس (ليث عفرين) كانت له القدرة على خفض مستوى السكر في الدم كما كانت له أيضاً القدرة على إصلاح تلف الأعضاء الناتج عن ارتفاع السكر في الدم.

**الكلمات المفتاحية:** ليث عفرين؛ علم الأنسجة؛ ارتفاع السكر في الدم؛ الكلية؛ الكبد

### Abstract

**Objectives:** In this study, we aimed to investigate the effects of oral administration of *Myrmeleon formicarius* (antlion) extract on liver and kidney histology in streptozotocin-induced diabetic mice.

**Methods:** Twenty-four mice received a single intraperitoneal injection of streptozotocin and were then divided into six groups. Untreated diabetic mice served as the negative control group, and glibenclamide-treated mice served as the positive control group. Mice in the other four groups, namely T1, T2, T3, and T4 groups, received *M. formicarius* (antlion) extract at 2.5, 5, 7.5, and 10 mg/kg, respectively. Permanent thin sections were used to examine liver and kidney histology.

**Results:** The most appropriate antihyperglycaemic dosage of the *M. formicarius* extract was 10 mg/kg for 2 days. Histological examination of the liver and kidneys showed that the antlion extract at 10 and 5 mg/kg exhibited significant tissue-repair effects.

**Conclusion:** *M. formicarius* (antlion) extract can not only reduce blood glucose levels but also repair hyperglycaemia-induced tissue damage.

**Keywords:** Antlion; Histology; Hyperglycaemia; Kidney; Liver

© 2019 The Authors.

Production and hosting by Elsevier Ltd on behalf of Taibah University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding address: Centre for Development of Advance Science and Technology, University of Jember, JL. Kalimantan 37 Kampus Tegalboto, Jember 68121, Indonesia.

E-mail: [erlia.fkip@unej.ac.id](mailto:erlia.fkip@unej.ac.id) (E. Narulita)

Peer review under responsibility of Taibah University.



## Introduction

Diabetes mellitus (DM), a degenerative disease characterised by high blood glucose levels (hyperglycaemia) owing to metabolic disruption in the body,<sup>1,2</sup> is associated with long-term complications in various organs, particularly the eyes, kidneys, heart, nerves, and blood vessels.<sup>3</sup> In 2015, the International Diabetes Federation (IDF) reported that 415 million people are affected by DM worldwide, and it is expected to increase to 642 million patients in 2040. In addition, the prevalence of DM among people aged 20–79 years in Indonesia reached 6.2%.<sup>4</sup> Furthermore, the World Health Organisation (WHO) showed that DM was the 6th leading cause of mortality in Indonesia in 2016.<sup>5</sup> The lifestyle and eating behaviours of Indonesian people contribute to the rapidly increasing prevalence of DM in Indonesia.<sup>6</sup> DM result from either improper response to insulin or insufficient insulin production.<sup>7</sup>

Sulphonylureas have been widely used for DM management to stimulate insulin production and reduce insulin resistance for approximately 50 years.<sup>8–10</sup> They are derivatives of sulphonamides; however, they do not exhibit antibacterial activity.<sup>11</sup> Sulphonylureas stimulate pancreatic  $\beta$  cells to produce more insulin and restore glucose homeostasis<sup>12</sup>; thus, they are most effective in the management of type 2 DM,<sup>13</sup> when the pancreatic  $\beta$  cell function is still somewhat preserved.<sup>10,14</sup> Therefore, certain extent of  $\beta$  cell viability is required for their effectiveness.<sup>15,16</sup>

Since “back to nature” has become a trend, natural medicines have gained much interest as generally safe and effective therapeutic agents.<sup>17,18</sup> Many medicinal plants, such as *Allium cepa* L. (onion), *Allium sativum* L. (garlic), and *Annona squamosa* L. (sugar-apple), are used to lower blood glucose levels.<sup>19</sup> However, the mechanisms underlying the antihyperglycaemic actions of these medicinal plants are different. For example, *Ocimum sanctum* inhibits  $\alpha$ -glucosidase activity and reduces inflammation and oxidative stress.<sup>20</sup> Besides plants, animals present a wide source of useful natural products. In Muncar (Banyuwangi, Indonesia) and Jember Lor (Jember, Indonesia) districts, people consume *Myrmeleon formicarius* (antlion) larvae as a natural medicine for DM.<sup>21</sup> The antihyperglycaemic effects of *M. formicarius* (antlion) have been verified in various studies. Compounds isolated from *M. formicarius* (antlion) have been shown to decrease blood glucose levels via a sulphonylurea-like mode of action<sup>21,22</sup>; however, further studies are required to confirm these findings. A previous study showed that *M. formicarius* (antlion) extract at 7.5 mg/kg was effective in lowering blood glucose levels in streptozotocin-treated mice. Another study showed that antlion larvae contained a compound with  $\alpha$ -glucosidase inhibitory activity.<sup>23</sup> DM could result in cardiovascular complications.<sup>24</sup>

In this study, we aimed to investigate the effects of the oral administration of *M. formicarius* (antlion) extract on liver and kidney histology in streptozotocin-treated mice.

## Materials and Methods

### *Drugs and M. formicarius (antlion) extract*

Glibenclamide was obtained from Jember pharmacy. Antlion extract was prepared as previously described by Rahma et al.<sup>25</sup> Antlions were collected from Mayang village, Jember, Indonesia and identified at the Laboratory of Zoology, Department of Biology Education, University of Jember. They were freshly dried at  $-80^{\circ}\text{C}$ . The antlion extract was prepared by cold maceration. Antlions were soaked in 70% (v/v) ethanol for 72 h at room temperature, followed by filtration. The filtrate was evaporated in a rotary evaporator at  $40\text{--}50^{\circ}\text{C}$  under reduced pressure to remove the solvent. Then, the extract was kept in a refrigerator at  $4^{\circ}\text{C}$  for future use. Sulphonylureas present in the antlion extract were detected by thin layer chromatography (TLC).<sup>26</sup>

### *Animals and experimental design*

Male Balb/C mice weighing 20–30 g were selected for the current study. The animal experiments were carried out at the Biomedical Laboratory of Faculty of Dentistry, University of Jember. All animals were kept under standard laboratory conditions of temperature ( $25 \pm 2^{\circ}\text{C}$ ) and humidity with 12 h:12 h light/dark cycle. Twenty-four mice were randomly divided into six experimental groups ( $n = 4/\text{group}$ ). Mice were acclimatised for 7 days prior to the experiment. Mice were given standard pellet diet and water *ad libitum* during the whole experiment.

All mice were rendered diabetic by a single intraperitoneal injection of streptozotocin (65 mg/kg, dissolved in 0.1 M citrate buffer, pH 4.5). Diabetes was allowed to develop and stabilise in streptozotocin-injected mice over 1 week. On day 7 post-streptozotocin injection, initial blood glucose levels were measured after 3–4 h fasting using a blood glucose meter. Mice were divided into six groups, as follows:

- Negative control (NC) group: Mice received normal water.
- Positive control (PC) group: Mice received glibenclamide.
- Group T1: Mice received *M. formicarius* (antlion) extract at 2.5 mg/kg.
- Group T2: Mice received *M. formicarius* (antlion) extract at 5 mg/kg.
- Group T3: Mice received *M. formicarius* (antlion) extract at 7.5 mg/kg.
- Group T4: Mice received *M. formicarius* (antlion) extract at 10 mg/kg.

*M. formicarius* (antlion) extract was orally administered once daily (volume, 0.5 mL/day) for 5 days. Fasting blood samples were collected at 7, 14, 16, and 20 days post-treatment (dpt) for blood glucose measurement.

### *Histological examination*

Histology specimens were prepared as previously described by Carleton and Drurry.<sup>27</sup> After 20 days, mice

were sacrificed, and kidneys ( $\pm 4$  gr) and liver ( $\pm 1.3$  gr) were removed, fixed in Bouin's solution for at least 24 h, then and dehydrated in an alcohol series (70, 80, 90, 95, and 100%) for 30 min. They were cleared with xylene for 1.5 h until the colour of xylene turned pale, and then cleared with xylene/paraffin substitute (3:1, 1:1, and 1:3, v/v, respectively) each for 30 min in an oven at 45–50 °C. Then, they were infiltrated with hard paraffin twice daily and embedded in paraffin. Sections were cut and stained with eosin.

#### Data analysis

All data are presented as the means  $\pm$  standard deviation (SD). Data were analysed using SPSS software version 20. The effects of treatments on blood glucose levels were analysed using one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) test. A  $P$ -value  $< 0.05$  indicated statistical significance. Data regarding tissue-repair effects are presented as percentages.

### Results

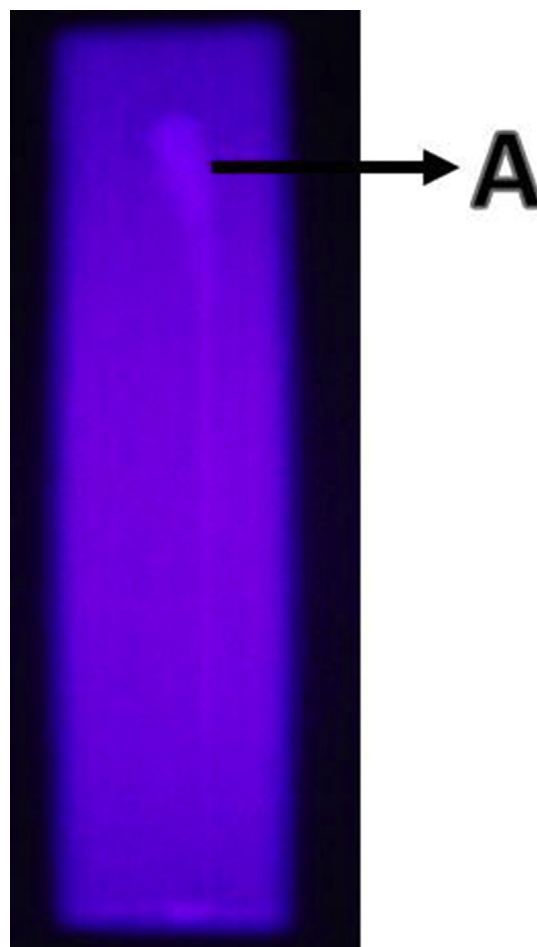
#### *Antlion extract contained sulphonylureas and decreased blood glucose levels*

In this study, TLC was used for determination of sulphonylurea content in *M. formicarius* (antlion) extract. TLC plates were developed in a twin trough glass chamber containing a mixture of EtOAc + EtOH + H<sub>2</sub>O (10:2:1, v/v) as a mobile phase. The plates were removed from the chamber when the solvent moved to the top of the plates and were subsequently allowed to evaporate. Then, spots on the plates were visualised under visible light, or fluorescent bands were visualised under ultraviolet (UV) light at 366 nm. Result showed that *M. formicarius* (antlion) extract contained sulphonylureas, indicated by yellow stain (Figure 1).

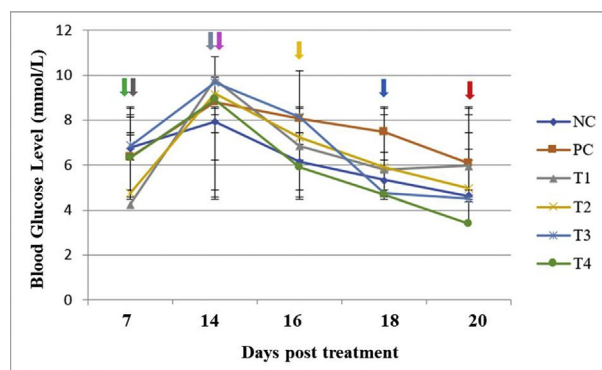
As shown in Figure 2 and Table 1, oral administration of the antlion extract at 2.5, 7.5, and 10 mg/kg for 2 days significantly decreased blood glucose levels, without significant differences among different doses. The effects of antlion extract at these doses were comparable to those of glibenclamide. On the last day (day 6 after antlion extract treatment), blood glucose levels in mice treated with antlion extract at 7.5 and 10 mg/kg were not significantly different from those in mice treated with glibenclamide. Additionally, the results showed that the most appropriate antihyperglycaemic dose of antlion extract was 10 mg/kg.

#### *Antlion extract affected liver and kidney histological architecture in streptozotocin-induced diabetic mice*

Streptozotocin-induced diabetic mice showed hepatocellular injury, as manifested by presence of inflammatory cells (IC), congestion (C), pyknosis (P), vacuole degeneration (VD), and necrosis (N) (Table 1). Representative images of liver histological examination are shown in Figure 3A–G. Liver sections from untreated streptozotocin-induced diabetic mice showed the most severe histological damages (Figure 3A). Oral administration of antlion extract at 10 mg/kg resulted in minimal liver histological deficits in streptozotocin-induced diabetic mice (Figure 3F).



**Figure 1:** Results of TLC of antlion extract. (a) Sulphonylureas TLC stain.

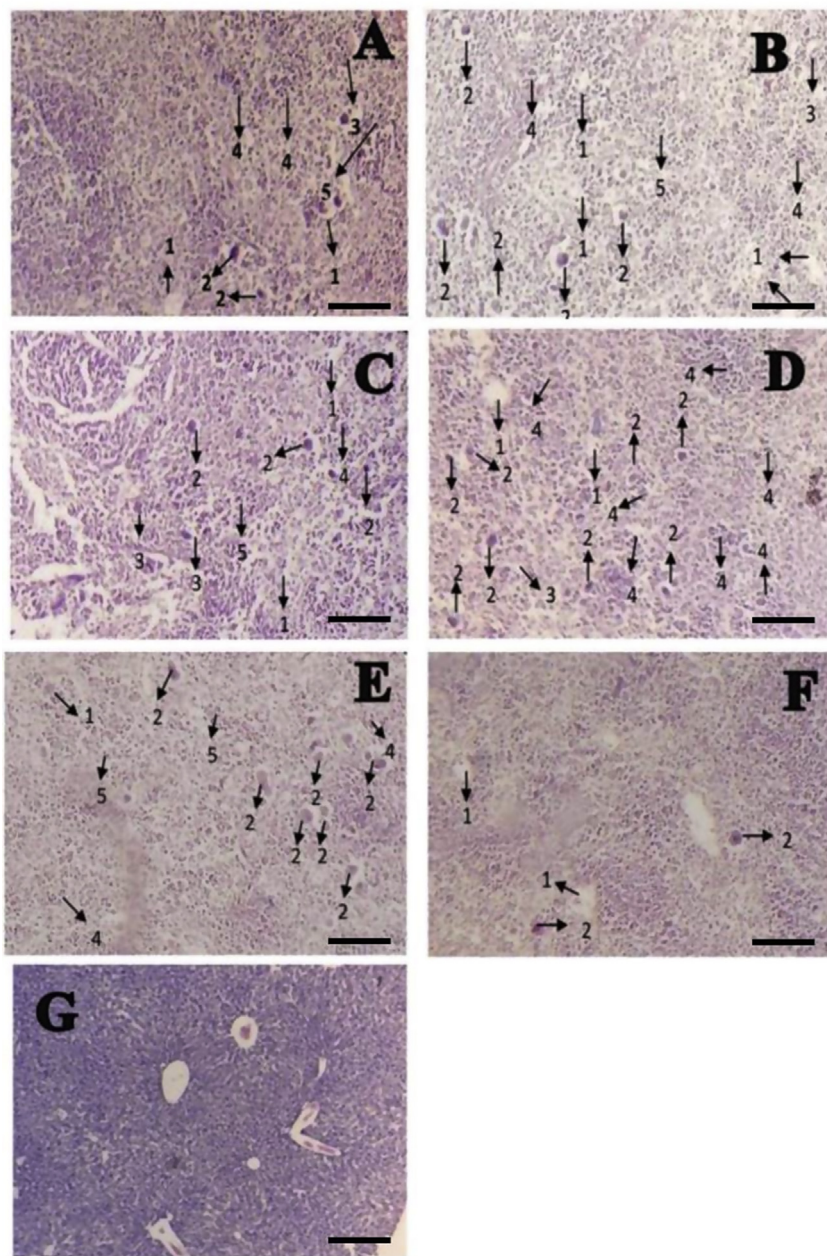


**Figure 2:** Effects of antlion extract on blood glucose levels. ■, end of acclimatisation stage; ■, induction by streptozotocin; ■, end of diabetic stage; ■, recovery stage; ■, collection of blood at 16 days post treatment (dpt); ■, collection of blood at 18 dpt; ■, collection of blood at 20 dpt; NC, negative control (normal water); PC, positive control (glibenclamide, 0.45 mg/kg); T1, antlion extract at 2.5 mg/kg; T2, antlion extract at 5 mg/kg; T3, antlion extract at 7.5 mg/kg; and T4, antlion extract at 10 mg/kg.

**Table 1: Average blood glucose levels.**

Treatment	Average blood glucose level (mg/dL)				
	7 dpt	14 dpt	16 dpt	18 dpt	20 dpt
NC	114.75 ± 15.94	158.25 ± 11.95	145.5 ± 8.1 <sup>b</sup>	134.75 ± 8.53 <sup>b</sup>	109.25 ± 7.27 <sup>c</sup>
PC	121.75 ± 15.39	142.75 ± 8.42	110.75 ± 23.5 <sup>a</sup>	96 ± 22.16 <sup>a</sup>	83.25 ± 11.35 <sup>a</sup>
T1	76.5 ± 11	176.5 ± 15.5	123.25 ± 8.99 <sup>a</sup>	104.25 ± 20.1 <sup>a</sup>	107.25 ± 25.55 <sup>b</sup>
T2	85.5 ± 15.24	165.25 ± 20.61	130.25 ± 16.56 <sup>a</sup>	106.5 ± 18.57 <sup>a</sup>	89.25 ± 24.14 <sup>b</sup>
T3	123.5 ± 14.88	174.25 ± 19.43	146.5 ± 13.22 <sup>b</sup>	85.5 ± 13.82 <sup>a</sup>	81 ± 17.53 <sup>a</sup>
T4	113.75 ± 11.32	160.5 ± 15.24	106.25 ± 21.06 <sup>a</sup>	84.25 ± 8.46 <sup>a</sup>	61 ± 14.02 <sup>a</sup>

NC, negative control; PC, positive control; T1, dosage of 2.5 mg/kg; T2, dosage of 5 mg/kg; T3, dosage of 7.5 mg/kg; T4, dosage of 10 mg/kg; dpt, days post treatment. Values with similar superscripts within a column are not significantly different at 0.05 probably level.

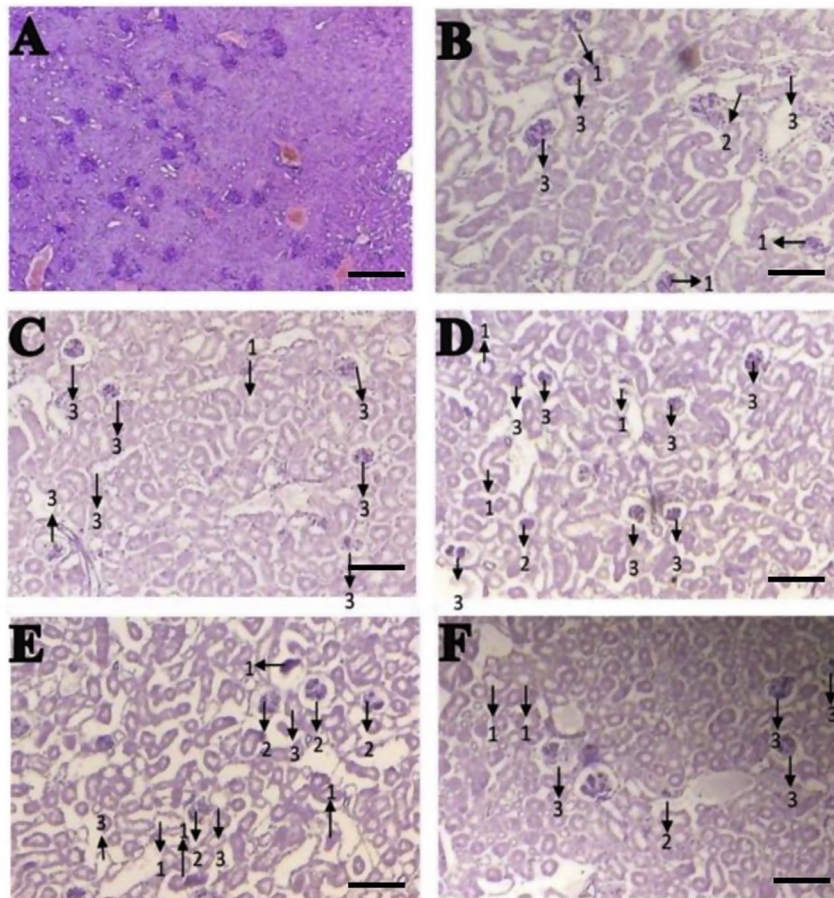


**Figure 3:** Histological structure of the liver in male mice (*Mus musculus*). (A) Negative control group (normal water), (B) positive control group, (C) T1 group, (D) T2 group, (E) T3 group, (F) T4 group, and (G) normal liver. 1, vacuole degeneration; 2, necrosis; 3, congestion; 4, inflammatory cells; and 5, pyknosis. Bar = 1  $\mu$ m.

**Table 2: Average liver damage.**

Treatment	The average liver damage (%)				
	IC	C	P	VD	N
Normal	18.03 ± 0.32 <sup>a</sup>	26 ± 0.2 <sup>a</sup>	0 ± 0 <sup>a</sup>	50.03 ± 0.06 <sup>a</sup>	0 ± 0 <sup>a</sup>
NC	50.1 ± 0.25 <sup>b</sup>	50.13 ± 0.06 <sup>b</sup>	83.17 ± 0.49 <sup>f</sup>	85.47 ± 0.25 <sup>d</sup>	78.27 ± 0.12 <sup>d</sup>
PC	50.03 ± 0.16 <sup>b</sup>	50.1 ± 0.36 <sup>b</sup>	50.17 ± 0.35 <sup>c</sup>	50.13 ± 0.12 <sup>ab</sup>	50.43 ± 0.31 <sup>b</sup>
T1	50.23 ± 0.25 <sup>b</sup>	50.23 ± 0.25 <sup>b</sup>	50.37 ± 0.06 <sup>c</sup>	50.37 ± 0.15 <sup>b</sup>	50.47 ± 0.31 <sup>b</sup>
T2	50.1 ± 0.17 <sup>b</sup>	50.07 ± 0.16 <sup>b</sup>	62.13 ± 0.15 <sup>d</sup>	50.4 ± 0.1 <sup>b</sup>	66.5 ± 0.3 <sup>c</sup>
T3	50 ± 0.25 <sup>b</sup>	50.07 ± 0.42 <sup>b</sup>	71.1 ± 0.17 <sup>e</sup>	69.13 ± 0.15 <sup>c</sup>	66.4 ± 0.3 <sup>c</sup>
T4	50.03 ± 0.06 <sup>b</sup>	50.03 ± 0.21 <sup>b</sup>	45.17 ± 0.29 <sup>b</sup>	50.2 ± 0.23 <sup>ab</sup>	50.4 ± 0.2 <sup>b</sup>

NC, negative control; PC, positive control; T1, dosage of 2.5 mg/kg; T2, dosage of 5 mg/kg; T3, dosage of 7.5 mg/kg; T4, dosage of 10 mg/kg; IC, inflammatory cells; C, congestion; P, pyknosis; VD, vacuole degeneration; N, necrosis. Values with similar superscripts within a column are not significantly different at 0.05 probably level.



**Figure 4:** Histological structure of the kidneys in male mice (*Mus musculus*). (A) Normal kidney, (B) negative control group, (C) positive control group, (D) T1 group, (E) T2 group, and (F) T4 group. 1, proximal convoluted tubule degeneration; 2, proximal convoluted tubule necrosis; and 3, glomerular damage. Bar = 1  $\mu$ m.

Additionally, streptozotocin-induced diabetic mice exhibited altered renal histological structure, including proximal convoluted tubule degeneration (PD), proximal convoluted tubule necrosis (NP), and glomerular damage (GD) (Table 2). Representative images of the histological examination of the kidneys are shown in Figure 4A–F. Figure 4B represents kidney sections isolated from

untreated streptozotocin-induced diabetic mice showing severe damage, whereas Figure 4C represents kidney sections from glibenclamide-treated diabetic mice, showing moderate damage in necrotic tubular cells. The results indicate that oral administration of *M. formicarius* (antlion) extract at 5 mg/kg resulted in minimal kidney histological deficits in streptozotocin-induced diabetic mice (see Table 3).

**Table 3: Average kidney damage.**

Treatment	The average kidney damage (%)		
	Proximal convoluted tubules degeneration	Proximal convoluted tubule necrosis	Glomerular damage
Normal	0 ± 0 <sup>a</sup>	0 ± 0 <sup>a</sup>	14.27 ± 0.23 <sup>a</sup>
NC	50.4 ± 0.26 <sup>c</sup>	50.33 ± 0.25 <sup>c</sup>	76.47 ± 0.31 <sup>d</sup>
PC	50.27 ± 0.31 <sup>c</sup>	48.2 ± 0.2 <sup>c</sup>	50.43 ± 0.31 <sup>b</sup>
T1	50.4 ± 0.3 <sup>c</sup>	50.33 ± 0.35 <sup>c</sup>	76.3 ± 0.3 <sup>d</sup>
T2	40.37 ± 0.38 <sup>b</sup>	45.37 ± 0.21 <sup>b</sup>	50.23 ± 0.38 <sup>b</sup>
T3	50.13 ± 0.06 <sup>c</sup>	50.37 ± 0.26 <sup>d</sup>	50.27 ± 0.57 <sup>b</sup>
T4	50.12 ± 0.31 <sup>c</sup>	50.27 ± 0.21 <sup>c</sup>	55.43 ± 0.3 <sup>c</sup>

NC, negative control; PC, positive control; T1, dosage of 2.5 mg/kg; T2, dosage of 5 mg/kg; T3, dosage of 7.5 mg/kg; T4, dosage of 10 mg/kg. Values with similar superscripts within a column are not significantly different at 0.05 probably level.

## Discussion

Results of this study showed that *M. formicarius* (antlion) extract exhibited glucose-lowering effects in streptozotocin-induced diabetic mice. This effect could be attributed to the presence of sulphonylurea- and metformin-like compounds in *M. formicarius* (antlion) larvae.<sup>21,22,28,29</sup> The presence of sulphonylurea compound was verified by the observation of a yellow band on the TLC plate, which is in line with the findings of a previous study.<sup>26</sup> Sulphonylureas are insulin secretagogues that stimulate endogenous insulin secretion by binding to sulphonylurea receptor protein on  $\beta$  cells, resulting in inhibition of ATP-dependent potassium channels and  $K^+$  efflux from  $\beta$  cells, which depolarises the cell membrane and allows  $Ca^{2+}$  influx. Increased intracellular calcium concentration stimulates the exocytosis of insulin secretory granules.<sup>10,33</sup> Metformin reduces blood glucose levels by various mechanisms,<sup>30</sup> mainly *via* reduction of hepatic glucose production (gluconeogenesis) and improvement of insulin sensitivity in muscle and liver cells.<sup>31,32</sup>

Another compound present in antlion larvae extract is a chaperone protein, which was shown to stimulate cell regeneration. A study reported that the saliva of antlion larvae contained a chaperone protein that could induce the secretion of proinflammatory cytokines, where it was shown to play a role in the adaptation of inflammatory cells to stress-induced damage.<sup>34</sup> Heat shock proteins (HSPs) constitute a group of chaperone proteins implicated in insulin resistance.<sup>35</sup> HSP70 is the most common HSP in humans. It confers resistance against cell death induced by tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), where it could inhibit TNF- $\alpha$ -induced free radical formation, lipid peroxidation, and apoptosis.<sup>36</sup> Thus, the chaperone protein present in antlion extract might be responsible for its tissue-repair effects, whereas the anti-hyperglycaemic effects might be attributed to the presence of sulphonylureas in antlion larvae extract.

The most severe liver damage was observed in untreated streptozotocin-induced diabetic mice (receiving normal water). However, glibenclamide-treated streptozotocin-induced diabetic mice showed repair of cell damage. Glibenclamide belongs to sulphonylureas,<sup>37</sup> increasing endogenous insulin secretion. Therefore, it could normalise blood glucose levels and prevent further cell damage.<sup>21,22</sup>

Similarly, the most severe kidney damage was also observed in untreated streptozotocin-induced diabetic mice (receiving normal water). Mice treated with glibenclamide showed moderate damage with tubular cell necrosis. Blood reaching the kidneys firstly passes through the glomeruli then the tubules. Thus, hyperglycaemia-induced damage mainly affects the glomeruli. The insulin secretagogue activity of glibenclamide could prevent kidney damage until the tubules.

Results of this study showed that the doses of antlion extract required for repairing hyperglycaemia-induced liver and kidney damage were different. Histological examination of liver and kidney sections showed that antlion extract treatment at 5 and 10 mg/kg resulted in minimal damage in the kidneys and liver, respectively. This difference in the dose required for repairing tissue damage in the liver and kidneys could be explained that the liver is responsible for detoxification of toxic substances reaching it *via* blood vessels from all organs. Thus, the liver required a higher concentration of antlion extract for repairing hyperglycaemia-induced cell damage than that required for the kidneys. Since the kidney is the second highly vascularised organ after the liver; therefore, it needed a low dose of antlion extract for repairing cell damage.

## Conclusions

Mice treated with *M. formicarius* (antlion) extract at 10 mg/kg showed a significant decrease in blood glucose levels. The doses of *M. formicarius* (antlion) extract required for repairing liver and kidney damage were different, where a dose of 10 mg/kg was required for repairing liver damage, whereas only 5 mg/kg was sufficient for repairing kidney damage. Further studies are needed to confirm the compounds responsible for these favourable effects and the molecular mechanisms of sulphonylurea and chaperone protein present in antlion larvae.

## Source of funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The author(s) have no conflict of interest to declare.

## Ethical approval

The experimental protocol was approved by the Animal Ethics Committee of the Medical Faculty University of Jember, Indonesia. Animal experiments were carried out in accordance with the ethical norms of the National Ethics Committee for Research in Health (NECRH), Government of Indonesia.

## Authors' contributions

JP, EN, LM, AK, DW, and SH conceived and designed the study, conducted the experiments, provided research materials, and collected and organised the data. EN and JP analysed and interpreted the data. EN and SH wrote the initial and final drafts of the manuscript. All authors have critically reviewed

and approved the final draft and are responsible for the content and similarity index of the manuscript.

### Acknowledgments

The authors would like to thank Tamyis and Ratna Sari Dewi for assisting with the oral administration of antlion extract and permanent thin section processing, respectively.

### References

- Riaz S. Study of protein biomarkers of diabetes mellitus type 2 and therapy with vitamin B1. *J Diabetes Res* 2015; 1–10.
- Mamun A, Islam S, Alam AK, Rahman MA, Rashid M. Effects of ethanolic extract of *Hibiscus rosa-sinensis* leaves on alloxan-induced diabetes with dyslipidemia in rats. *Bangl Pharm J* 2013; 16: 27–31.
- Soumya D, Srilatha. Late stage complications of diabetes and insulin resistance. *J Diabetes Metab* 2011; 2: 167.
- International Diabetes Federation. *Diabetes in Indonesia*; 2015 <http://www.idf.org/membership/wp/indonesia/>; 2015 [cited 2017 Sep 5].
- World Health Organization. *Diabetes country profiles in Indonesia*; 2016 [http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf); 2016 [cited 2017 Sep 5].
- Sami W, Ansari T, Butt NS, Hamid MRA. Effect of diet on type 2 diabetes mellitus. *Int J Health Sci* 2017; 11(2): 65–71.
- Haghvirizadeh P, Haghvirdizadeh P, Mohamed Z, Haerian MS, Abdullah NA, Haerian BS. KCNJ11: genetic polymorphisms and risk of diabetes mellitus. *J Diabetes Res* 2015; 1–9.
- De Fronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The multicenter metformin study group. *N Engl J Med* 1995; 333: 541–549.
- Nathan DM, Buse JB, Davidson MB, Ferrannini E. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 2009; 31(1): 193–203.
- Sola D, Rossi L, Schianca GPC, Maffioli P, Bigliocca M, Mella R, Corliano F, Fra GP, Bartoli E, Derosa G. Sulfonylureas and their use in clinical practice. *Arch Med Sci* 2015; 11(4): 840–848.
- Zessel K, Mohring S, Hamscher G, Kietzmann M, Stahl J. Biocompatibility and antibacterial activity of photolytic products of sulphonamides. *Chemosphere* 2014; 100: 167–174.
- Broichhagen J, Schönberger M, Cork SC, Frank JA, Marchetti P, Bugliani M, Shapiro AMJ, Trapp S, Rutter GA, Hodson DJ, Trauner D. Optical control of insulin release using a photoswitchable sulfonylurea. *J Nat Commun* 2014; 1–11.
- Ibrahim R. Diabetes mellitus type II: review of oral treatment options. *Int J Pharm Pharmaceut Sci* 2010; 2(1): 21–30.
- Mkele G. What's the latest on sulfonylureas in the management of type 2 diabetes? *S Afr Pharm J* 2013; 80(5): 12–16.
- Fowler MJ. Diabetes treatment: oral agents. *Clin Diabetes* 2010; 28(3): 132–136.
- Hanefeld M. Pioglitazone and sulfonylureas: effectively treating type 2 diabetes. *Int J Clin Pract* 2007; 61(153): 20–27.
- Kunle, Folashade O, Egharevba, Omoregie H, Ahmadu, Ochogu P. Standardization of herbal medicines. *Int J Biodivers Conserv* 2012; 4(3): 101–112.
- Nasry H, Shirzad H. Toxicity and safety of medicinal plants. *J Herb Med Pharmacol* 2013; 2(2): 21–22.
- Osadebe PO, Odoh EU, Uzor PF. Natural products as potential sources of antidiabetic drugs. *Br J Pharm Res* 2014; 4(17): 2075–2095.
- Mandare PA, Neelam D, Smita VP, Gaikwad PB. Study of total cholesterol, triacylglycerols, high-density lipoprotein cholesterol in type 2 diabetes mellitus. *Asian J Pharmaceut Clin Res* 2017; 10(2): 116–118.
- Narulita E. Uji Efektifitas Undur-undur Darat terhadap Penurunan Gula Darah Mencit (*Mus musculus*) [Affectivity of antlion in decreasing blood glucose level of mice]. *J Sains Teknol* 2008; 7(1): 6–11.
- Kurniasih T, Isma'il M, Susilowati F, Lestari SP. *Kajian potensi undur-undur darat (Myrmeleon sp.) sebagai antidiabetes [Study of antlion as antidiabetic agent]*. Yogyakarta: Faculty of Biology, Universitas Gadjah Mada; 2006.
- Tjay TH, Rahardja K. *Obat-Obat Penting: Khasiat, Penggunaan, dan Efek-Efek Sampingnya [Important medicine: benefit, dosage and side effect]*. 7th ed. Jakarta: PT Elex Media Komputindo; 2007.
- Mehta V, Arum S, Pallavi K, Udayabanu, Malairaman. Anti-oxidant, anti-inflammatory, and antidiabetic activity of hydro-alcoholic extract of *Ocimum sanctum* : an in-vitro and in-silico study. *Asian J Pharmaceut Clin Res* 2016; 9(5): 44–49.
- Rahma HH, Sundhani E, Nurulita NA. Antidiabetic activity of powder and ethanolic extract of antlion (*Myrmeleon sp.*) on Wistar strain white male rats with glucose preload. In: *Proceeding of the ICMHS*; 2016. Jan 7–8; Singapore.
- Lestari I. *Identifikasi Komponen Kimia Undur-undur Darat (Myrmeleon sp.) secara Kromatografi Lapis Tipis [Identification of chemical compound of Myrmeleon sp using thin layer chromatography]*; 2011 <http://2009/03/kencing-manis-diabetes-mellitus.html>; 2011 [cited 2017 Sep 5].
- Carleton HM, Drurry RAB. *Histological technique for normal and pathological tissue and the identification of parasites*. 3rd ed. London: Oxford University Press; 1957.
- Mujahid MZ, Agistia DD, Sa'adah M, Nugroho AE. A combination of bitter gourd ethanolic extract with ant lion larvae aqueous extract for a blood glucose-lowering agent. *Int Food Res J* 2013; 20(2): 851–855.
- Muadifah A, Sulistyarti H, Prasetyawan S. Liquid chromatography for analysis of metformin in *Myrmeleon sp.* *J Pur App Chem Res* 2017; 6(3): 196–206.
- Tandiawan F. Pengaruh varian organik cation transporter 1 (OCT-1) terhadap bioavailabilitas dan intoleransi metformin [Effect of organic cation transporter 1 (OCT-1) variant on bioavailability and metformin intolerance]. *CDK-254* 2017; 44(7): 512–515.
- Giannarelli R, Aragona Coppelli, Prato Del. Reducing insulin resistance with metformin: the evidence today. *Diabetes Metab* 2003; 29(4): 6S28–6S35.
- Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanism of metformin: an overview. *Clin Sci* 2012; 122(6): 253–270.
- Kramer W, Muller G, Geisen K. Characterization of the molecular mode of action of the sulfonylurea, glimepiride, at beta-cells. *Horm Metab Res* 1996; 28(9): 464–468.
- Kumar V, Cotran RS, Robbins SL. *Robbins & cotran pathologic basis of disease*. 7th ed. Philadelphia: PA Saunders Elsevier Publisher; 2005.
- Widjaja FF, Santoso LA, Waspadji S. Peran heat shock protein terhadap resistensi insulin [Role of heat shock protein to insulin resistance]. *Majalah Kedokteran Indonesia* 2009; 58(3): 121–128.
- Burkart V, Liu H, Bellmann K, Wissing D, Jaattela M, Cavallo MG, Pozzilli P, Briviba K, Kolb H. Natural resistance of human beta cells toward nitric oxide is mediated by heat shock protein 70. *J Biol Chem* 2000; 276(26): 19521–19528.
- Snyder KC, Keegan C. *Pharmacology for surgical technologist*. 4th ed. Missouri: Elsevier, Inc.; 2017.

**How to cite this article:** Prihatin J, Narulita E, Mufidah L, Kurniawan A, Wulandari D, Hariyadi S. Anti-hyperglycaemic and tissue-repair effects of *Myrmeleon formicarius* extract in streptozotocin-induced diabetic mice. *J Taibah Univ Med Sc* 2019;14(2):149–155.