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ORIGINAL ARTICLE

Tualang Honey Exerts Antioxidant and Antidepressant-like Effects in Stress-exposed Rats

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Abstract

Recent evidence has exhibited dietary influence on the manifestation of depressive-like behaviour induced by stressor tasks. The present study examined the effects of Tualang honey supplement administered with the goal of preventing or attenuating the occurrence of depressive-like behaviour in male rats subjected to noise stress. Forty-eight adult male rats were randomly divided into the following groups: i) nonstressed with placebo, ii) nonstressed with honey, iii) stressed with placebo, and iv) stressed with honey. Tualang honey (200 mg/kg body weight) was administered for 28 days. Stressed rats were subjected to loud noise 100 dB(A) 4 hours daily for 14 days. Forced swimming test was performed to evaluate depressive-like behaviour. Stressed control rats displayed significant increase in depressive-like behaviour, serum adrenocorticotropic hormone (ACTH), corticosterone, and brain oxidative stress markers levels, with significant decrease in antioxidant enzymes activities and total antioxidant status. Honey supplementation successfully counteracted the stress effects whereby the honey treated rats exhibited significant decrease in depressive-like behaviour and levels of ACTH, corticosterone, and oxidative stress markers, with significant increase in antioxidant enzymes activities and total antioxidant status. In conclusion, Tualang honey mediated antidepressant-like effects in stressed rats, possibly acting via restoration of hypothalamic-pituitary-adrenal axis through its antioxidant properties.

Keywords: depression; stress; oxidative stress; honey; antioxidant

Introduction

Stress exposure may induce deleterious effects on brain structure and increase the risks of developing neurodegenerative and psychiatric disorders (O'Farrell and Harkin, 2017). Noise is a non-specific stressor that arouses the autonomic nervous system and endocrine system. Previous studies demonstrated that noise plays a role for the development of cardiovascular as well as metabolic disease (Munzel et al., 2018) which is associated with oxidative stress (Demirel et al., 2009, Yildirim et al., 2007) via generation of free radicals and depletion of

antioxidant enzymes activities in plasma and tissues (Ilhan et al., 2004, Srikumar et al., 2006). In addition, noise exposure may cause disturbances to the hypothalamo-pituitary-adrenocortical (HPA) axis such as adrenal cortex (Oliveira et al., 2009) and increase in glucocorticoids (Anderson et al., 2011). Persistent increase in glucocorticoids after prolonged exposure to stress may cause extensive damage to the central nervous system, triggering the onset of depression (Rocha et al., 2005).

Depression is one of the most prevalent psychiatric disorders that can affect a person's thoughts, behaviour, feelings, and sense of well-being (Krishnan and Nestler, 2008, Lang and Borgwardt, 2013). Patients with depression and experimental animal models of depression display structural alterations in some brain areas including the prefrontal cortex, hippocampus, and amygdala (Krishnan and Nestler, 2008, Lang and Borgwardt, 2013), which may be related to aberrations in neurotrophic factors, disturbances in the HPA axis, and oxidative stress (Bakunina et al., 2015). Currently, patients with depression are normally treated with antidepressants (neurotransmitter-related medicines), such as serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors (SSRIs) (Holtzheimer and Nemeroff, 2006). However, the classical antidepressants are only beneficial in about 60% of patients (Souery et al., 2006) and often produce significant adverse effects, such as agitation, headache, dizziness, anxiety, constipation, nausea, and lethargy (Lang and Borgwardt, 2013). Therefore, a more efficient and safer treatment for depression are required.

Honey is a natural product produced by honeybees. Tualang honey, a type of honey, is a wild pure multi-floral honey produced by Asian rock bee species (*Apis dorsata*), which builds hives on the branches of Tualang tree (*Kompassia excelsa*) located mainly in the rainforest of northern Peninsular Malaysia. Tualang honey exhibits significant antioxidant activities attributed to its phenolic contents (Ahmad et al., 2017, Sairazi et al., 2017, Ranneh et al., 2018). Honey also contains choline and acetylcholine which are essential for brain function and as neurotransmitters (Aljadi and Kamaruddin, 2004, Beretta et al., 2007, Kishore et al., 2011). Recently, our research reported that Tualang honey decreased depressive-like behaviour in stress-exposed rats (Azman et al., 2015), however, the mechanisms involved remains unreported. Therefore, this study aims to evaluate the possible mechanism of action of the antidepressant-like effect of Tualang honey in stressed rat model.

Materials and Methods

Experimental Animals

Male Sprague-Dawley rats (2 months old; *n* =48) weighing 325-375 g) were obtained from Animal Research and Service Centre, Universiti Sains Malaysia. The rats were maintained in standard polypropylene cages (40 × 25 × 16 cm) under a reversed 12-h light/dark cycle (lights off at 08:00 h) at a consistent room temperature of 27 ± 1°C. The rats received commercial rat chow food pellets (Gold Coin Ltd., Malaysia) and water *ad libitum*. Rats were allowed to acclimatize to the holding room for 24 h before the behavioural procedures. The procedures in this study were approved by Animal Ethics Committee of Universiti Sains Malaysia (Ref. No. USM/Animal Ethics Approval/2013(85)(444), conformed to the guidelines of the Principles of Laboratory Animal Care (NIH Publication No. 80-23, revised 1996) to ensure that number of rats and their suffering were kept to a minimum.

Honey Supplementation

The Tualang honey used was from a single batch honey supplied by Federal Agricultural Marketing Authorities (FAMA), Malaysia. The honey was filtered by FAMA to remove solid particles, concentrated in an oven at 40°C and evaporated to achieve a water content of about 20%. It was then subjected to γ irradiation at 25 kGy at Steril Gamma (M) Sdn. Bhd. (Selangor, Malaysia) for sterilization and bottled 230 g per jar. The final concentration of the bottled Tualang honey was 1.3 g/mL. Tualang honey at 200 mg/kg body weight/day (Al-Rahbi et al.,

2014, Othman et al., 2011) was administered via oral gavage 14 days prior to stress procedure and the treatments were continued throughout the 14 days of stress procedure. The Tualang honey was freshly dissolved in 1 mL of distilled water prior administration. Control groups received an identical volume of distilled water as placebo for the same period.

Experimental Design

The animals were randomly assigned to the following groups (n = 12): i) nonstressed with placebo, ii) nonstressed with Tualang honey, iii) stressed with placebo, and iv) stressed with Tualang honey. As illustrated in Figure 1, honey supplementation was started on day 1 and continued for a period of 28 days. On day 15 until 28, noise stress procedure was implemented. All rats were subjected to forced swimming test following the final day of stress procedure and killed by decapitation upon completion of the test. Individual bodyweight was recorded weekly using electrical balance. Blood samples (5 ml) were collected immediately. All blood samples were left to clot for 2 h prior to centrifugation for 15 min at 4000 rpm. Approximately 2 ml of serum was collected and stored at −20°C until assay. The brain of each animal was quickly harvested and homogenated (10% w/v) in ice-cold 0.1 M phosphate-buffered saline at pH 7.4. The homogenate was then centrifuged at 10000 x g for 10 minutes and kept at -80°C until analysed.

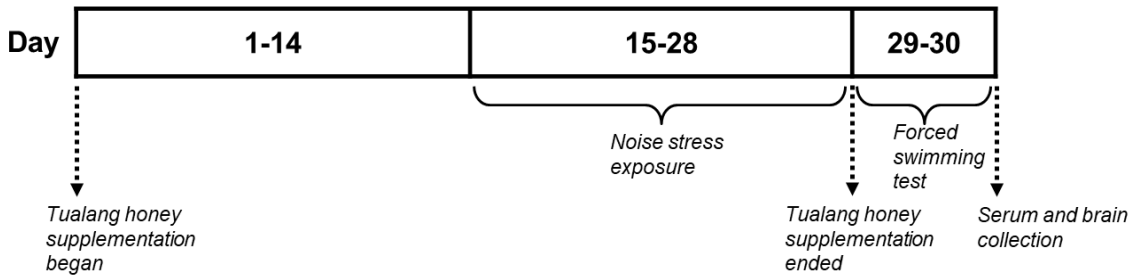


Figure 1. Methodology timeline.

Forced Swimming Test

The test employed was similar to that described elsewhere (Porsolt et al., 1977a, Porsolt et al., 1977b), with slight modification. The alterations consisted of increasing the water depth from 15-18 cm in the original to a depth of 30 cm and moving from a cumulative timing measure to a time-sampling technique wherein the predominant behaviour over each 5-s period of the 300-s test was rated (Slattery et al., 2005). All the animals were individually placed in a transparent plastic cylinder (40 cm in height × 18 cm in diameter) filled with water (25-27°C) to a level of 30 cm. The experimental session consisted of two trials: conditioning trial and test trial. During the conditioning trial, the rats were placed in the water-filled cylinder for 15 min. After the trial, the rats were dried and placed in a warm cage with paper towels for 10-15 min before being returned to their home cages. Twenty-four hours later, the animals were placed again in the cylinder for a 5 min test session, that is, the test trial.

The test sessions were videotaped for subsequent quantitative behavioural analysis. The total duration was calculated for each of the predominant behaviours; climbing (intense movements with all four limbs, with the two forepaws breaking the surface of the water and being directed against the walls of the cylinder), swimming (rigorous horizontal movements throughout all radiuses of the cylinder), and immobile (the animal remaining in water with all four limbs motionless except for the occasional alternate movement of paws and tail necessary to prevent sinking and to keep the head/nose above water). The water was changed before the next animal was placed in the water tank.

Noise Stress Exposure

The animals of the test groups (iii and iv) were exposed to white noise for 4 hours (09:00 – 13:00 h) daily for 14 days. Noise was recorded from the generator and amplified by speakers in a separate room. Speakers were located 30 cm above the cages. The noise level was set at 100 dB(A) and intensity was measured by a sound level meter CENTER 325 (Range: 80–130 dB(A), Accuracy: +1.5 dB(A), made in Taiwan). Sound levels were verified in the centre of the cage before each exposure and varied by less than 1 dB(A) in the space the cage occupied. The control groups were kept in the same room for the same period without switching on the noise.

Serum Corticosterone and Adrenocorticotropic Hormone (ACTH) Levels

Serum levels of corticosterone and ACTH were measured by enzyme-linked immunosorbent assay (ELISA) kits using polyclonal antibody specific for corticosterone (LDN Labor Diagnostika Nord GmbH & Co. KG, Nordhorn, Germany) and monoclonal antibody specific for ACTH (Cloud-Clone Corp., Houston, USA).

Brain Oxidative Stress Markers

The evaluation of oxidative stress in the brain homogenates was performed by measuring the levels of plasma malondialdehyde (MDA) and protein carbonyl (PCO). The concentration of MDA was analysed using commercially available kits from Northwest Life Sciences Specialties, Washington, USA, whereas the level of PCO was determined by commercially available kits from Cayman Chemical, Michigan, USA.

Brain Antioxidant Enzymes Activities

The activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR) in the brain homogenates were measured using commercially available kits from Northwest Life Sciences Specialties, Washington, USA. Commercially available kits from Oxford Biomedical Research, Michigan, USA was used to determine the total antioxidant status.

Protein Concentration

Following homogenization, an aliquot was removed from each brain sample to determine its protein concentration using commercially available kits from Bioassay Systems, California, USA. Briefly, protein concentration was quantified by comparing the colorimetric intensity of the reaction product from each sample with a series of protein standards. The levels of oxidative stress markers, antioxidant enzymes activities, and total antioxidant status were normalized to their total protein concentration in the sample in order to account for possible differences in protein concentrations between samples.

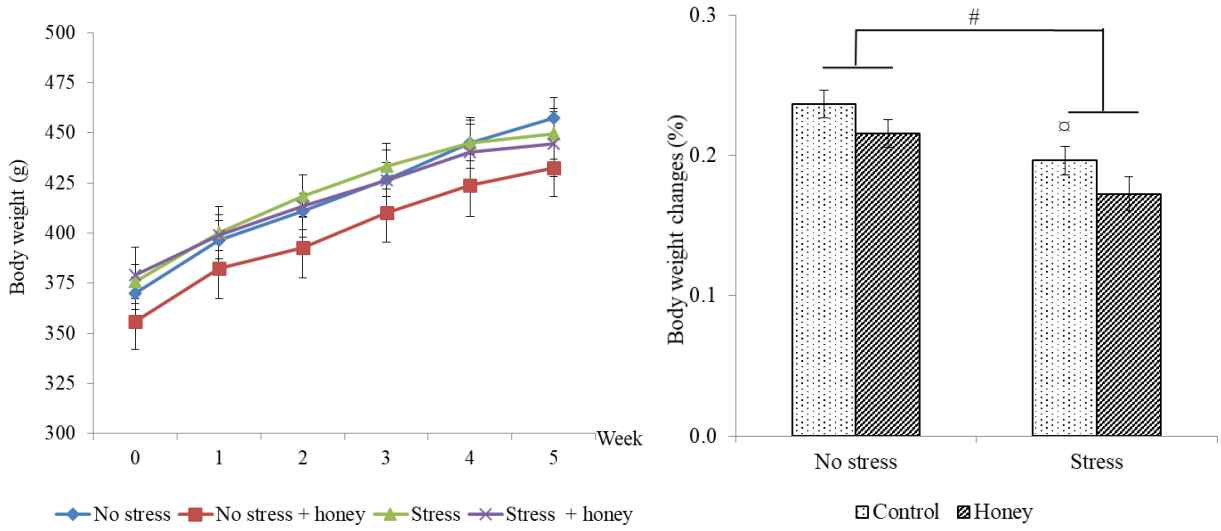
Statistical Analysis

All analyses were performed using IBM SPSS Statistics Campus Edition V24.0 for Win/Mac. Statistical data are expressed as mean ± S.E.M, and a result was deemed to be statistically significant if $P < 0.05$. Factorial analyses of variance (ANOVA) was utilized to examine the main effects of stress (nonstressed vs. stressed) and honey treatment (placebo vs. honey). After confirming the normality and the homogeneity of variance of data, the significance of the differences between the means of the test and control studies was established by one-way ANOVA coupled with *post hoc* Tukey HSD test.

Results

Effects of Tualang Honey on Body Weights

Mean body weights of all groups over five weeks experimental period was illustrated in Figure. 2 (a). Figure 2(b) illustrates the percentage of body weight changes calculated as [(Final body weight-Initial body weight)/Initial body weight] x 100%. There was significant effect of stress ($P < 0.05$) on percentage of body weight changes. Stress exposure significantly ($P < 0.05$) decreases body weight gain.



(a) (b)

Figure 2. Effects of stress and honey treatment on (a) body weight and (b) percentage of body weight changes. The values are expressed as mean ± SEM. Significant main effect of stress ($^{\#}P < 0.05$). Significant difference between no stress and stress control ($^{¤}P < 0.05$).

Effects of Tualang honey on depressive-like behaviour

There were significant effects of stress on durations of climbing ($P < 0.05$), swimming ($P < 0.01$), and immobility ($P < 0.01$) (Table 1). The stressed rats exhibited significantly lower climbing ($P < 0.05$) and swimming ($P < 0.01$) durations, and significantly higher immobility durations compared to nonstressed rats ($P < 0.01$), indicating depressive-like symptoms in the stressed rats. There were significant effects of honey treatment on durations of climbing ($P < 0.05$), swimming ($P < 0.01$), and immobility ($P < 0.01$). Stressed rats treated with honey exhibited significantly higher climbing ($P < 0.05$) and swimming ($P < 0.01$) durations, and significantly lower immobility duration ($P < 0.01$), which reflected antidepressant-like effects of honey.

Table 1. Effects of Tualang honey on duration of climbing, swimming, and immobility behaviour in forced swimming test

Groups	Climbing	Swimming	Immobility
No stress + control	109.58 ± 19.17	85.00 ± 18.52	105.42 ± 21.50
No stress + honey	170.42 ± 18.88	148.18 ± 17.46	26.79 ± 21.22
Stress + control	76.36 ± 9.13$^{\#¤}$	48.75 ± 13.87$^{\#\#¤¤}$	161.67 ± 11.01$^{\#\#¤¤}$
Stress + honey	112.08 ± 23.68$^{*♣}$	93.33 ± 11.05$^{**♣♣}$	94.58 ± 17.95$^{**♣♣}$

Data are displayed as mean ± S.E.M. Significant main effects of stress ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$) and honey treatment ($^{*}P < 0.05$, $^{**}P < 0.01$). Significant difference between no stress and stress control ($^{¤}P < 0.05$, $^{¤¤}P < 0.01$). Significant difference between stress control and stress treated with honey ($^{♣}P < 0.05$, $^{♣♣}P < 0.01$).

Effects of Tualang honey on serum corticosterone and adrenocorticotropic hormone levels

There were significant effects of stress on corticosterone ($P < 0.05$) and ACTH levels ($P < 0.01$), and significant effects of honey treatment on corticosterone and ACTH levels ($P < 0.01$) (Table 2). Stress exposure significantly increases both corticosterone and ACTH levels ($P < 0.05$), whereas honey treatment significantly decreases corticosterone and ACTH levels in the stressed rats ($P < 0.05$).

Table 2. Effects of Tualang honey on serum corticosterone and adrenocorticotropic hormone levels

Groups	Corticosterone	Adrenocorticotropic hormone
No stress + control	54.39 ± 3.06	72.98 ± 3.73
No stress + honey	31.02 ± 3.29	47.27 ± 3.85
Stress + control	68.48 ± 3.11$^{\#¤}$	88.00 ± 5.18$^{\#\#¤}$
Stress + honey	34.70 ± 3.72$^{**♣}$	65.27 ± 6.11$^{**♣}$

Data are displayed as mean ± S.E.M. Significant main effects of stress ($^{\#}P < 0.05$, $^{\#\#}P < 0.01$) and honey treatment ($^{**}P < 0.01$). Significant difference between no stress and stress control ($^{¤}P < 0.05$). Significant difference between stress control and stress treated with honey ($^{♣}P < 0.05$).

Effects of Tualang honey on brain oxidative stress markers

Factorial ANOVA revealed significant effects of stress on the levels of MDA and PCO ($P < 0.05$) (Table 3). Stress exposure caused oxidative stress as evident by significant higher MDA and PCO levels in the stressed control rats compared to nonstressed rats. There were significant honey treatment effects on the levels of MDA and PCO ($P < 0.05$). Tualang honey seemed to offer protection against the stress-induced oxidative stress as shown by the suppression of MDA and PCO levels.

Table 3. Effects of Tualang honey on brain malondialdehyde and protein carbonyl levels

Groups	Malondialdehyde	Protein carbonyl
No stress + control	4.05 ± 0.26	9.30 ± 0.75
No stress + honey	3.33 ± 0.18	8.96 ± 0.58
Stress + control	5.05 ± 0.20$^{\#¤}$	13.16 ± 0.41$^{\#¤}$
Stress + honey	3.61 ± 0.11$^{*♣♣}$	9.28 ± 0.78$^{*♣}$

Data are displayed as mean ± S.E.M. Significant main effects of stress ($^{\#}P < 0.05$) and honey treatment ($^{*}P < 0.05$). Significant difference between no stress and stress control ($^{¤}P < 0.05$). Significant difference between stress control and stress treated with honey ($^{♣}P < 0.05$, $^{♣♣}P < 0.01$).

Effects of Tualang honey on brain antioxidant enzymes activities

There were significant effects of stress on the levels of SOD, GPx, GR, and total antioxidant status ($P < 0.01$) (Figure 6). Stressed rats exhibited significantly lower levels of SOD ($P < 0.01$), GPx, GR, and total antioxidant status ($P < 0.05$) compared to nonstressed rats. There were significant honey treatment effects on the levels of SOD and total antioxidant status ($P < 0.01$). Stressed rats treated with honey exhibited significantly higher levels of SOD ($P < 0.01$), GPx, GR, and total antioxidant status ($P < 0.05$) compared to stressed control rats.

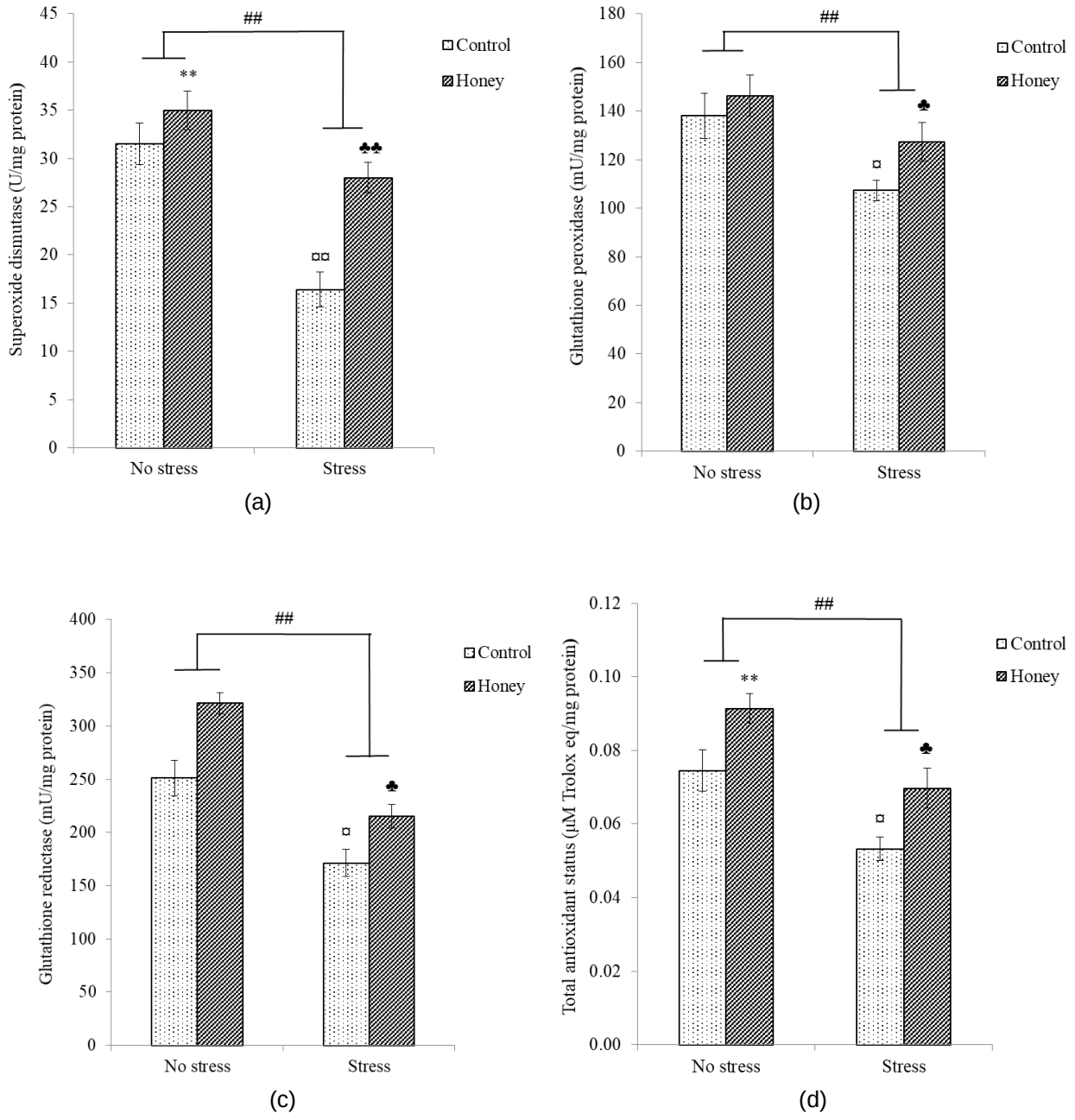


Figure 6. Effects of Tualang honey on brain antioxidant enzymes activities (a) superoxide dismutase, (b) glutathione peroxidase, (c) glutathione reductase, and (d) total antioxidant status. Data are displayed as mean ± S.E.M. Significant main effects of stress ($^{\#\#}P < 0.01$) and honey treatment ($^{**}P < 0.01$). Significant difference between no stress and stress control ($^{¤}P < 0.05$). Significant difference between stress control and stress treated with honey ($^{♣}P < 0.05$).

Discussion

Stress responses are considered to play an important role in mental disorders (Jaco, 2017), whereby chronic noise exposure is associated with cognitive as well as affective disorders of psychological stress (Jafari et al., 2018). In the present study, a noise intensity of 100 dB(A) was used for four hours daily per day for 14 days. The noise stress procedure used in this study was according to previous studies where the method used was shown to alter brain biogenic amines (Ravindran et al., 2005) and induce depressive-like behaviour (Naqvi et al., 2012) in adult male rats. The level of 100 dB(A) was chosen as it was comparable with the noise level detected in discos and some industrial workplaces. In the present study, the rats exposed to noise stress exhibited significant decreases in climbing and swimming duration as well as increase in immobility duration, indicating depressive-like behaviour. These findings are consistent with previous studies (Bulduk and Canbeyli, 2004, Naqvi et al., 2012). Other types of stress have also been shown to increased depressive-like behaviour such as social instability stress and chronic unpredictable stress (Al-Rahbi et al., 2013, Lagunas et al., 2010).

While the precise mechanism by which loud noise can modulate behavioural despair is not known, the HPA axis is implicated since it constitutes the major neuroendocrine response to stress (Jafari et al., 2017). Sufficient exposure to noise can cause physical damage to structures within the HPA axis, which may have both short- and long-term effects on maintenance of homeostasis. There are evidences that the hormones involved in the HPA axis in response to stress, such as altered levels of corticosterone and vasopressin can modulate forced swimming and behavioural despair (Engelmann et al., 2006). The biochemical results obtained in the current study confirmed those facts where the stressed rats exhibited significant higher serum corticosterone and ACTH levels compared to the unstressed rats. Relationship between stress exposure, HPA responses and body weight gain have also been discussed, whereby stressed rats increased HPA responses along with reduced body weight gain (Bhatnagar et al., 2006). Similarly, our results demonstrated that stressed rats possessed lower weight gain compared to unstressed rats. However, it was unknown whether this reduction in weight gain was due to decreased food intake as food intake was not measured in this study. Therefore, future studies should investigate the relationship between noise stress exposure, body weight gain and food intake to elucidate the effects of stress.

The negative effects of noise on cell structure and function could be, at least in part, mediated by the increase in reactive oxygen species (ROS) (Lenzi et al., 2003). In the present study, noise stress exposure was shown to induce oxidative stress as evidenced by elevated levels of MDA and PCO in the brain of the stressed rats. These findings are in agreement with previous studies (Cheng et al., 2011, Demirel et al., 2009, Samson et al., 2007). It was also observed that stressed rats showed reduced antioxidant enzymes activities and total antioxidant status. The decrease in antioxidant enzymes activities accompanied by increased oxidative indices, suggest that brain oxidative stress might be the underlying cause related to the pathophysiology of depression.

The current study revealed the ability of Tualang honey in reducing depressive symptoms in rats exposed to loud noise; a result paralleled with our previous work (Azman et al., 2015). In a closely related study, Tualang honey has been shown to ameliorate depressive-like behaviour and reduce ACTH and corticosterone levels in ovariectomized rats exposed to social instability stress (Al-Rahbi et al., 2013). Similarly, our current work demonstrated that Tualang honey was able to reverse the increase of corticosterone and ACTH levels in the stressed rats. These findings suggest that Tualang honey reduced the adverse effects of stress and may be beneficial for the nervous system and vasculature, and protect the brain and body from stress-induced damage. Tualang honey may have modulated corticosterone and ACTH levels either by suppressing HPA mobilization in response to stress or by facilitating elevated plasma corticosterone and ACTH levels back to baseline following the termination of stress.

It is also suggested that the anti-depressant like effects of Tualang honey is due to its antioxidant property. Tualang honey has been reported to possess antioxidants contents in the form of flavonoids, enzymatic (e.g. catalase, glucose oxidase, peroxidase) and non-enzymatic

substances (e.g. ascorbic acid, α-tocopherol, carotenoids) (Khalil et al., 2011a, Kishore et al., 2011, Moniruzzaman et al., 2013). It has also been reported to have a higher level of antioxidant activity compared to other local Malaysian honeys, such as Gelam, Acacia, Indian forest, and Pineapple honeys (Kishore et al., 2011, Moniruzzaman et al., 2013, Khalil et al., 2011b). Accordingly, the present study demonstrated that Tualang honey significantly improved brain oxidative status in the stressed rats as shown by elevated antioxidant enzymes activities and total antioxidant status, and reduced oxidative stress markers. Other studies have also demonstrated that Tualang honey is able to increase antioxidant enzymes activities and ameliorate oxidative stress in plasma and other tissues such as renal and pancreas (Erejuwa et al., 2010, Erejuwa et al., 2011, Shafin et al., 2014). It is suggested that the flavonoids contents and enzymatic and non-enzymatic substances in honey are responsible for its antioxidative effects. In relation to these, it is suggested that Tualang honey reduces depressive-like behaviour in the stressed rats via preventing hypersecretion of glucocorticoids and improving brain oxidative status.

Limitations and Future Research

This study utilises whole honey compounds, hence it is not known which specific compounds exert the beneficial effects. Therefore, future study should focus on isolating the active compounds in the Tualang honey and to determine their effects. Aside from restoring the HPA axis, there may be other possible mechanism of action of honey in reducing depressive-like behaviour such as inhibiting monoamine oxidase (MAO), hence further study is required.

Conclusion

It can be concluded that administration of Tualang honey reduces depressive-like behaviour and oxidative stress induced by stress exposure. These effects might be mediated by its antioxidant property and restoration of HPA axis.

Acknowledgments

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