

# Acacia tortilis leaf extract alters brain serotonin turnover and stress-induced heart rate variability in laboratory mice

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## ABSTRACT

This study aimed to evaluate brain serotonin turnover and its impact on heart rate variability during stress. Six groups of Sprague-Dawley mice received oral treatment for fifteen days. On the 7<sup>th</sup> day, after the respective treatments, mice were first subjected to restraint stress for 30 min in Decapicone to induce acute stress, and then antidepressant action was assessed by the forced swim test (FST). On the 14<sup>th</sup> day, ECG was also recorded in anesthetized mice using micro-hook electrodes (AD instrument, PowerLab), and heart rate (HR: beats per minute) and heart rate variability (HRV) were calculated. At the end of the study, brain serotonin (5HT), 5-hydroxyindole acetic acid (5HIAA), and serotonin turnover rate were measured by using a high-performance liquid chromatographic (HPLC) method. Stress Control (SC) mice showed an increased serotonin (5HT;  $P < 0.05$ ) turnover rate and thus displayed significant anxiogenic behavior after experiencing acute restraint stress for 30 mins. Meanwhile, a significant dose-dependent reduction in 5HT ( $P < 0.05$ ) turnover rate, along with anxiolytic activity, was observed in mice (G3-6) pretreated with imipramine and different doses of ATEL ( $p < 0.05$ ), respectively. Additionally, heart rate (HR) and HRV revealed an improvement in imipramine- and ATEL-treated stressed mice. Pre-treatment with ATEL enhances neurochemical (5-HT) availability and decreases its turnover rate, resulting in antidepressant effects and a reduction in stress-induced tachycardia, along with improved HRV. Therefore, ATEL appears to be a beneficial plant extract that could be useful for patients experiencing acute stress-induced tachycardia and depression.

**Keywords:** *Acacia tortilis* leaves ethanolic extract (ATEL), Heart rate variability (HRV), Anxiolytic activity, DMT, Serotonin (5HT)

## Introduction

### Background

*Acacia tortilis* is one of the frequently used Medicinal plants for Traditional Unani medicine (TUM) due to its antioxidant and

anti-inflammatory properties [1-5]. However, to date, the potential of *Acacia tortilis* in treating depression- and stress-induced tachycardia has not been explored [6, 7].

Cardiovascular disorders and mood disorders like depression are interlinked [8, 9] with profound impact on vital organs like the heart [9]. Literature has evidence that supports the effect of *Acacia tortilis* on neurobiological mediators and its positive impact on cardiovascular outcomes and stress [10, 11]. The primary effect of *Acacia tortilis* mainly involves stress-induced imbalance of the autonomic nervous system (ANS), which reduces parasympathetic tone and increases sympathetic drive, resulting in reduced heart rate variability (HRV) [12]. In addition, a positive correlation between the HRV index and depression severity is also reported in literature [13].

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Conversely, serotonin or 5-hydroxytryptophan (5-HT), a biogenic amine, plays a part in the pathophysiology of depression and heart disease. It has been suggested that stress disrupts the 5-HT system, increasing an individual's vulnerability to depression [14]. Currently used medications appear to be safe when treating depression and cardiovascular disease (CVD) simultaneously [15, 16], although some cardiovascular drugs can worsen depression by interfering with biogenic amines [17, 18]. Some traditional Chinese medicines [19-21] and plant extracts [22, 23] have been said to treat both depression and heart disease with few side effects. Native medicinal plants and their remedies are easily accessible and deeply rooted in culture, used to treat ailments with few adverse effects. *Acacia*, a native, drought-resistant plant of Saudi Arabia, possesses various medicinal properties [2-4]. Therefore, it is important to investigate how the ethanolic extract of *Acacia tortilis* leaves (ATEL) influences depression, HRV, and serotonin turnover in stressed mice.

## Materials and Methods

An experimental study was conducted using albino mice. All experiments were successfully carried out in accordance with regulations compliant with the Declaration of Helsinki (2000) regarding the use of animals in research [24], also approved by the Umm Al Qura University Ethics Board of the College of Medicine (ethical approval number HAPO-02-K-012-2015-11-125).

### *Plant material*

In the spring of 2021, *Acacia tortilis* leaves were collected from Makkah, Saudi Arabia (specifically, the area around Umm Al-Qura University). The plant was verified and documented by a taxonomist under the reference of No. PHG128 at the Department of Pharmacognosy, College of Pharmacy, Umm Al-Qura University.

### *Extraction of the plant*

After collecting the leaves, they were washed and cleaned before being extracted using the method described by Serafi *et al.* (2018) [2]. Leaves (500 g) were steeped in 1000 mL of 95% ethanol for two days (48 hours) at  $25 \pm 3^\circ\text{C}$ . After 48 hours, the filtrate was transferred and concentrated with a rotary evaporator (R-300). This method produced 19% (98 g) extract. This extract (ATEL) was then refrigerated, and several doses were utilized throughout the trial (50, 100, and 150 mg/kg) [4, 25]. The same thin-layer chromatography (TLC) method was used to confirm dimethyltryptamine (DMT) in ATEL, with a methanol:ammonia (100:2.5) solvent system [4], as previously described. ATEL was also screened using established procedures [26] to detect flavonoids, glycosides, phenols, saponins, alkaloids, and tannins.

### *Experimental animals*

In the animal facility, healthy albino mice (20–30 g) were kept in cages (6 mice per cage) with free access to water and a standard

diet, maintained at  $25 \pm 3^\circ\text{C}$  under a 12-hour light/dark cycle for 7 days before the experiment.

The sample size for the current study was calculated using G\*Power [27]. For each activity, 36 mice (6 mice per group) were subdivided as described below. All treatments were orally administered for 15 days in respective groups of mice, and on the day of the experiment (7<sup>th</sup> and 15<sup>th</sup> days), 120 minutes prior to the experiments. All experiments were conducted between 9 a.m. and 3 p.m.

G1	Control (C; 10 ml/kg distilled water: no stress)
G2	Stressed control (SC; 10 ml/kg distilled water)
G3	Imipramine (15 mg/kg)
G4	ATEL (50 mg/kg)
G5	ATEL (100 mg/kg)
G6	ATEL (150 mg/kg)

The mice (G2-G6) were initially kept in 50 mL plastic conical tubes (Decapicone) with holes for breathing. Mice were restrained in Decapicone for thirty minutes. Each mouse experienced restraint stress only twice: on the 7<sup>th</sup> day before FST and on the 15<sup>th</sup> day before measurement of ECG [28-34].

### *Antidepressant activity by FST*

Thirty-six mice (6 groups) received the treatments orally (via feeding needle) for 7 consecutive days, 120 minutes prior to the experimental day. The antidepressant activity in control (G1) and stressed mice (G2-G6) was investigated using the FST by following the same procedure as described earlier [4]. The periods of mobility and immobility were recorded using a stopwatch for over 6 minutes [35-43].

### *ECG acquisition for HR and HRV analysis*

For ECG recording, control mice (G1) and acutely stressed mice (G2-G6) on the 15<sup>th</sup> day were anesthetized with ketamine (i.p., 100 mg/kg), which did not significantly affect the heart rate of mice [44]. Anesthetized mice (unresponsive to toe pinch) were positioned dorsally on an ECG station equipped with a lamp to maintain normal body temperature. After fixing, the mouse limbs were cleaned, then three non-sterile micro-hook electrodes (1.5 mm), designed for use with the FE231 Bio Amp to record biopotentials, were inserted subcutaneously in the standard lead II position [45].

- Left forelimb                      Positive (red) electrode
- Right forelimb                    Negative (black) electrode
- Left hindlimb                     Reference (green) electrode

After placing the electrodes, start LabChart 8 to continuously record the ECG for 5 minutes. This recorded ECG was used to calculate HR and HRV (time- and frequency-domain) using LabChart 8 software [45].

### *Neurochemical analysis*

At the end of experiments (14<sup>th</sup> day: after ECG recording), mice were immediately beheaded. The brains were frozen at  $-70^\circ\text{C}$ .

Using HPLC-EC [46], the concentrations of brain serotonin 5-Hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid (5-HIAA: metabolite) were determined. The 5-HT turnover rate was calculated using the following formula.

$$5-HT \text{ turnover} = \frac{5 - HIAA}{5 - HT} \tag{1}$$

### Statistical analysis

The sample size N = 36 (6 mice per group) was determined to detect the effect size of Cohen’s d = 0.7, power = 0.8, and α = 0.05, based on the G\*Power [25] analysis. This analysis showed that 6 mice per group would provide a statistical power of 0.8 if the parameters were as follows: groups = 6, α = 0.05, total sample size = 36, critical F = 2.533 (d.f. = 5, 30). For statistical analysis, analysis of variance (ANOVA) in Minitab 17 software, along with Tukey’s multiple-range test, was used to compare the treatment and control groups [35-42].

## Results and Discussion

According to the statistics, mobility ( $F_{(5,30)} = 18.25, p < 0.0001$ ) and immobility time ( $F_{(5,30)} = 18.31, p < 0.0001$ ) are considerably impacted by different treatments (IMP and ATEL) during a period of seven consecutive days. In comparison to the control group (G1; **Table 1**: 223.637±15.38), acute stress (G2; restricted in Decapicone for 30 minutes) significantly ( $p < 0.05$ ) increased the immobility time in mice (SC group: 269.17±20.93 s) during the FST. Compared to the control (G1) and SC groups (G2), mice pre-treated with positive control (G3; Imp) and

various doses of ATEL (G4-6) showed a substantial ( $p < 0.01$ ) dose-specific decrease in immobility and improved mobility time.

To examine the consequences of acute stress (G-2) in ATEL- and imipramine-treated groups (G 3-6) on HR and HRV, ECGs were recorded on the 15<sup>th</sup> day in Decapicone-restrained mice. Data revealed significant effects on HR ( $F_{(5,30)} = 52.37, p < 0.05$ ). A significantly increased heart rate (tachycardia) was observed in SC mice ( $p > 0.05$ ). Pretreated mice (G3 – G6) showed a statistically significant reduction in heart rate (**Table 2**).

HRV (time and frequency domain parameters), SDNN ( $F_{5,30} = 13.58, p < 0.001$ ), rMSSD ( $F_{5,30} = 9.02, p < 0.0001$ ), and HF power ( $F_{5,30} = 7.83, p < 0.001$ ) all showed statistically significant decreases in the acute stress (G2) mice. In contrast, acutely stressed mice had dose-dependent increases in SDNN, rMSSD, and HF power % values. **Table 2** illustrates that this rise was statistically significant ( $p < 0.05$ ) in mice treated with Imp and ATEL at dosages of 100 and 150 mg/kg. LF power ( $F_{5,30} = 5.87, p < 0.001\%$ ) and the ratio of LF/HF ( $F_{5,30} = 4.27, p < 0.005$ ) both rose in severely stressed mice, whereas mice pretreated with Imp and various doses of ATEL (G3-6) showed a substantial decrease in these values.

Turnover rate ( $F_{5,30} = 15.19, p < 0.0001$ ) and 5-HT ( $F_{5,30} = 11.41, p < 0.0001$ ) were shown to be significantly impacted. In comparison to the control and mice pre-treated with the positive control (G3; Imp) and various doses of ATEL (G4-6), acute stress (G2; restrained in Decapicone, 30 min) resulted in a statistically significant ( $p < 0.05$ ) decrease in brain 5HT level, while an increase in brain 5HIAA and turnover rate was noted.

**Table 1. Antidepressant effect (FST) of different doses of ethanolic extract of *Acacia tortilis* leaves (ATEL) on stress induced mice**

Category	FST Immobility time	FST Mobility time	Brain 5HT	Brain 5HIAA	Turnover rate
G1 (C)	223.637±15.38	136.33±15.37	122.13±13.43	12.36±1.53	0.101±0.005
G2 (SC)	269.17±20.93*	91.00±21*	78.46±19.71*	19.55±2.73*	0.267±0.091*
G3 (Imp; 15 mg/kg)	176.83±23.63* <sup>#</sup>	183.17±23.63* <sup>#</sup>	126.92±2.09 <sup>#</sup>	13.25±2.39 <sup>#</sup>	0.104±0.018 <sup>#</sup>
G4 (S+ATEL; 50mg/kg)	214.17±21.24 <sup>#</sup>	145.83±21.24 <sup>#</sup>	109.26±6.72 <sup>#</sup>	17.68±1.35	0.162±0.012 <sup>#</sup>
G5 (S+ATEL; 100mg/kg)	195.50±27.3 <sup>#</sup>	164.50±27.3 <sup>#</sup>	116.10±11.70 <sup>#</sup>	15.75±1.49	0.135±0.008 <sup>#</sup>
G6 (S+ATEL; 150mg/kg)	157.50±24.35* <sup>#</sup>	202.50±24.35* <sup>#</sup>	119.65±14.56 <sup>#</sup>	13.08±3.32 <sup>#</sup>	0.109±0.026 <sup>#</sup>
	$F_{(5,30)}=18.31$ *P= 0.0001 Effect Size = 0.83 Critical F= 2.53 Power = 0.99	$F_{(5,30)}=18.25$ *P= 0.0001 Effect Size = 1.43 Critical F= 3.10 Power = 0.99	$F_{(5,30)}=11.41$ *P= 0.0001 Effect Size = 0.79 Critical F= 2.47 Power = 0.99	$F_{(5,30)}=9.81$ *P= 0.0001 Effect Size = 0.71 Critical F= 2.43 Power = 0.99	$F_{(5,30)}=15.19$ *P= 0.0001 Effect Size = 1.9 Critical F= 8.6 Power = 0.99

The values are presented as mean ± SD

n = 6. "Time was in indicates second"

\* Indicates the significant difference when compared with control (P<0.05)

<sup>#</sup> Indicates the significant difference when compared with SC (P < 0.05)

**Table 2. Effect of ethanolic extract of *Acacia tortilis* leaves (ATEL) on different hemodynamic parameters**

Parameters	Control (G1)	SC (G2)	SC+ Imp	HC+ATEL (G3)	HC+ATEL (G4)	HC+ATEL (G5)
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<b>Heart Rate (beat/min)</b>	365.10±25.4	526.3±58.2*	192.3±48.9*#	447.4±27.0#	376.9±29.3#	283.8±38.9#	F <sub>(5,30)</sub> =52.37 *P= 0.0001 Effect Size=1.79 Power=0.99
<b>SDNN</b>	82.47±19.9	11.12±6.4*	89.51±20.6#	41.2±29.9	71.4±28.8#	142.4±52.2#	F <sub>(5,30)</sub> =13.58 *P= 0.0001 Effect Size=0.68 Power=0.99
<b>rMSSD</b>	61.6±17.7	13.32±9.36*	83.1±25#	53.0±24.6	69.6±26.8#	139.9±64.9#	F <sub>(5,30)</sub> =9.02 *P= 0.0001 Effect Size=0.5820 Power=0.99
<b>LF</b>	20.69±3.7	24.09±2.6	19.32±4.9	23.06±11.0	19.87±3.9	8.27±4.1#	F <sub>(5,30)</sub> =5.87 *P= 0.001 Effect Size=0.5 Power=0.99
<b>HF</b>	64.38±12.9	37.84±13.1*	64.24±8.9#	48.23±15.3	66.20±5.4#	68.56±4.4#	F <sub>(5,30)</sub> =7.83 *P= 0.0001 Effect Size=0.75 Power=0.99
<b>LF/HF ratio</b>	0.33±0.08	0.73±0.3	0.31±0.08	0.57±0.52	0.30±0.05	0.12±0.06#	F <sub>(5,30)</sub> =4.27 *P= 0.005 Effect Size=1.01 Power=0.99

The values are presented as mean ± SD, n=6

\*Indicates the significant difference when compared with control (G1; P<0.05)

#Indicates the significant difference when compared with HC (G2; P < 0.05)

This study demonstrated the beneficial effects of ATEL in stressed mice. Oral treatment with ATEL shows promising antidepressant effects and significant improvements in HRV and serotonin turnover rate in stressed mice. The FST results revealed that, in SC mice, depressive activity was evident, as mobility time was significantly reduced (91.00±2: P<0.0001) compared to control mice (136.33±15.37: P<0.0001). Literature reveals that stress and depression are strongly associated [47]; stress affects the central nervous system, leading to depression [48], and our findings agree with this. Both ATEL- and Imp-pre-treated mice showed dose-dependent changes in swimming dynamics (increased mobility time) in the FST (**Table 1**). It was previously published that the serotonergic system plays an important role in depression [49]. In the present result, SC mice showed significantly low levels of 5HT, suggesting that 5HT deficiency may lead to decreased motility and increased depression [50].

However, antidepressant medication (a centrally acting serotonergic agonist) alleviates depression by increasing brain 5-HT levels and reducing 5HIAA and 5-HT turnover [51]. The neurochemical serotonin profile confirmed in the present study that ATEL pretreatment increased 5-HT and significantly reduced 5HIAA (**Table 1**), resulting in antidepressant activity [28-32, 43]. High brain serotonin turnover is also considered a primary cause of depression [52]. The significant reduction in serotonin turnover (**Table 1**) following ATEL and Imp treatment in the present study improved depressive symptoms, resulting in increased mobility in mice. Another breakthrough is the presence of N,N-dimethyltryptamine (analogous to

serotonin, DMT) [4] in acacia leaves. DMT is said to be far more effective than currently available antidepressants [53].

Further, an established connection between depression, stress, tachycardia, and HRV [54] has already been cited in the literature. Acute stress in the present study affects HR and HRV (**Table 2**). In our present results, it's evident that stress caused a considerable reduction in HRV in SC (Group 2). **Table 2** showed that rMSSD and SDNN (HRV, time domain parameters) and HF% (frequency domain parameters) declined significantly, while the LF% and LF/HF ratio increased significantly [55]. It is suggested that lower HRV may be a phenotypic marker for depression. Pretreated mice with ATEL and Imp both showed significant antidepressant activity in stressed mice; thus depressed symptoms were resolved, resulting in improved HRV. **Table 2** indicates that pretreatment with Imp and ATEL results in increased HRV (an increase in cardiac parasympathetic flow) due to the presence of DMT and 5HT. Depression and stress have been linked to disturbances in 5-HT transmission and have resulted in decreased HRV [56]. During stress-induced sympathetic activity, 5-HT or DMT activates the 5-HT1A receptor, which enhances parasympathetic activity and exerts beneficial effects on the ANS and heart [57, 58] and improves HRV.

It is necessary to highlight some limitations. In the present research, only mice were used. To further explore the neuropharmacological and cardiovascular potential of *Acacia tortilis* found in the Kingdom of Saudi Arabia, more research needs to be conducted.

## Conclusion

The current findings conclude that acute stress results in anxiogenic behaviors and tachycardia (increased heart rate). The availability of neurochemicals (5HT) might be due to the presence of DMT in ATEL and a decrease in the 5HT turnover rate in pre-treated mice, leading to antidepressant effects, which in turn reduced stress-induced tachycardia and showed an improved HRV. Hence, it is concluded that ATEL appears to be a beneficial plant extract that can be useful for adjunct therapy in patients who suffer from acute stress-induced tachycardia and depression. However, further extensive studies are required for elucidating the exact mechanism of action of ATEL.

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**Conflict of interest:** None

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**Ethics statement:** During experimental work, appropriate animal handling guidelines were followed (Code of Practice for the Housing and Care of Animals Used in Scientific Procedures: Scientific Procedures Act 1986; [26]). The research project was approved by the Animal Ethics Board of the College of Medicine (ethical approval number HAPO-02-K-012-2015-11-125).

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