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Research article

Cipadesin A, a bioactive ingredient of Xylocarpus granatum, produces antidepressant-like effects in adult mice

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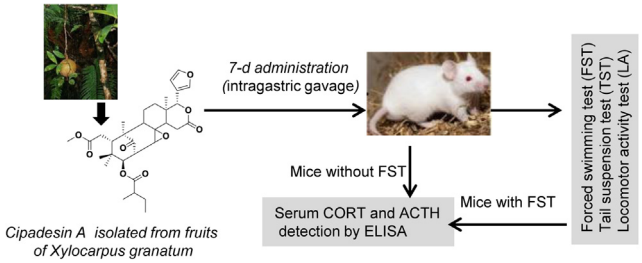
HIGHLIGHTS

- Cipadesin A produces antidepressant-like effects in mice.
- Cipadesin A decreases immobility time in forced swimming test.
- Cipadesin A decreases immobility time in tail suspension test.
- Antidepressant-like activities of cipadesin A are associated with inhibition of HPA axis activity.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Xylocarpus granatum Koenig, widely used in folk medicine in southeast countries, has been reported to exert neuropharmacological activities as well as mood regulation. The neuroprotective activities of limonoids, riches in *X. granatum*, are poorly understood.
Hypothesis/Purpose: To investigate the potential antidepressant-like effects and the underlying mechanisms of cipadesin A, one limonoid component, extracted from *X. granatum*, in acute stress-induced depression mouse models.
Study design: Antidepressant-like effects of cipadesin A were investigated through behavioral tests, and potential mechanism was assessed by neuroendocrine system.
Methods: Antidepressant-like effects of cipadesin A (5, 15, 50 mg/kg/day for 7days, intragastrically) were estimated through forced-swimming test (FST), tail suspension test (TST) and open field test (OFT). Effects of cipadesin A on hypothalamus-pituitary- adrenal (HPA) axis were evaluated by analysis of serum corticosterone (CORT) and adrenocorticotropic hormone (ACTH) using enzyme-linked immunosorbent assay (ELISA).
Results: Cipadesin A administration significantly reduced the floating time in the FST and immobility time in the TST (15–50 mg/kg). Cipadesin A dose-dependently increased the time in the central zone in the OFT (5–50 mg/kg), without altering the locomotor activity. Moreover, repeated cipadesin A treatment significantly inhibited the increase levels of serum CORT (5–50 mg/kg), ACTH (15–50 mg/kg) following the forced swimming, but not in the absence of stress.

Abbreviations: ATCH, adrenocorticotropic hormone; CORT, corticosterone; ELISA, enzyme-linked immunosorbent assay; FST, forced swimming test; HPA, axishypothalamic-pituitary-adrenal axis; LAT, locomotor activity test; LPS, lipopolysaccharide; OFT, open field test; SPT, sucrose preference test; TST, tail suspension test.

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Conclusions: Cipadesin A has antidepressant-like activities in acute stressed mice model of depression, which likely occurs by inhibiting the HPA axis activity response to stress. These data support further exploration for developing cipadesin A as a potential agent to treat depression and anxiety disorders.

1. Introduction

Depression is a common psychiatric disorder that affects about 21% of individuals worldwide, imposing a major burden on our society [21]. Stress, especially chronic stress, is well known to be one of the most important factors responsible for depressive disorders [5]. Maladaptive response to stress causes hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis by stimulating adrenocorticotropic hormone (ACTH) release and subsequent peripheral release of steroids/cortisol from the adrenal grand [10,12,25]. Despite the clinical availability of antidepressants for several decades, most of them are not totally effective. Only 33% depressed patients are sensitive to the first antidepressant medication, and are associated with serious adverse-effects [8,15].

Recent research interest has turned progressively to traditional herbal medicines in a quest for new antidepressant drugs [6,34]. Herbal therapies are being provided as desirable alternative treatment for depression [40,42,44]. Increasing evidence showed that many natural compounds have antidepressant-like activities and are being introduced into the clinical practice, most of which have comparable efficiency to prescription medications with no or reduced side effects [3,28]. Usage of natural compounds in the treatment of patient with depression is preliminary supported by the evidence that their activities were demonstrated in experimental models of depression [1,42].The antidepressant-like effects of those plant-derived compounds are associated with inhibition of hypothalamus-pituitary-adrenal (HPA) axis, inflammation, as well as the regulation of genes expression, which plays critical roles in depression [19,36,37,43].

The genus *Xylocarpus* (Meliaceae) has proved to be a major source of diverse limonoids with analogous structures [26,31]. The mangrove plant *Xylocarpus granatum* Koenig, mainly distributed along the seashore of the Indian Ocean and in Southeast Asia, is used as a folk medicine for treating cholera, diarrhea, and fever diseases in Southeast Asia. Sarker and colleagues firstly reported that the methanol extracts from stem and roots of *Xylocarpus moluccensis,* another plant of genus *Xylocarpus,* have inhibitory effects on the central nervous systems, including sleep time prolongation and anxiolytic activity [29]. More than 50 limonoid derivatives have been isolated from *X. granatum* with comprehensively biological effects, including neuroprotective activities [27]. Most recently, we reported that xylocarpin H, a limonoid isolated from the seeds of *X. granatum*, produces antidepressant-like activities in mouse behavioral model of depression, highlighting the potential neuroprotective effects of limonoids on depression [41]. Cipadesin A ($C_{32}H_{42}O_9$), one limonoid isolated from *Cipadessa fruticose* [18] and *Cipadessa cinerascens* [7] as well as from *X. granatum* is reported for the first time here. Cipadesin A represents a mexicanolide-type limonoid with ring oxidation and unusual 9,10-bond cleavage [7,18]. Unfortunately, the role of cipadesin A in central nervous system, especially in regulating psychiatric disorders, is still poorly investigated.

Based on the previous findings, the present study aimed to examine the potential antidepressant-like effects of cipadesin A in two validated mouse models of depression, forced-swimming test (FST) and tail suspension test (TST). In addition, we assessed the HPA activity by measuring serum corticosterone and ACTH levels to clarify the potential mechanisms underlying the action of cipadesin A.

2. Materials and methods

2.1. Animals

Male ICR mice (weighing 18–22 g upon arrival) were housed at a constant temperature (23 ± 2 °C) with 12 h/12 h light/dark cycles (lights on at 20:00 pm and off at 08:00 am) and free access to food and water. All animal procedures were approved by the Local Animal Use Committee of Hebei Medical University under license number USIP201443A and performed in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals of China*. All behavioral tests and drug administration were performed in the dark phase.

2.2. Drugs

Cipadesin A ($C_{32}H_{42}O_9$, purity >95%, chemical structure shown in Fig. 1A) was obtained from Prof. Qinwen Shi (Hebei Medical University, China). Sodium Carboxy Methyl Cellulose (CMC-Na) was bought from Sinopharm Chemical Reagent Co., Ltd. Cipadesin A was freshly suspended in a solution of 0.5% CMC-Na. Venlafaxine (Chengdu Daxi'nan Pharmaceutical Co., Ltd Chengdu, China) was dissolved in saline before the experiment. Cipadesin A, venlafaxine and saline were given by intragastric gavage once daily for 7 days in all experiments.

2.3. Extraction and isolation of Cipadesin A

Dried seeds (5 kg) of *X. granatum* were extracted with 95% ethanol at room temperature. After evaporation of the solvent under reduced pressure, the residue was suspended in water and extracted with petroleum ether and dichloromethane, successively. The dichloromethane extract (120 g) was chromatographed on silica gel and eluted using a petroleum ether/ethyl acetate system (30:1 to 1:10) to yield 9 fractions. Fraction (9 g) was subjected to **Silica gel column chromatography** by using petroleum ether/acetone (3:1) to yield cipadesin A (2 g).The Purity of cipadesin A (95%, tR = 20.3 min) is detected by HPLC with methanol/water (from 70% to 100% in 30 min) as a mobile phase with ELSD detector (75 °C, 2.1 L/min) (Fig. 1B). The structure of cipadesin A was postulated on the basis of ^{1}H NMR and ^{13}C NMR was also determined as described in the literature [18]. Cipadesin A from this genus is reported for the first time here.

2.4. Forced-swimming test

The forced-swimming test (FST) was conducted based on previous studies [9,32]. Mice were placed into a 20 cm diameter × 35 cm height plastic cylinder filled to 20 cm with 23–25 °C water. This test was videotaped and the immobility time was measured. **Floating** was defined as the absence of movement except motions required to maintaining the animal's head above the water. Results were expressed as floating time of mice in the last 4 min during the 6 min session.

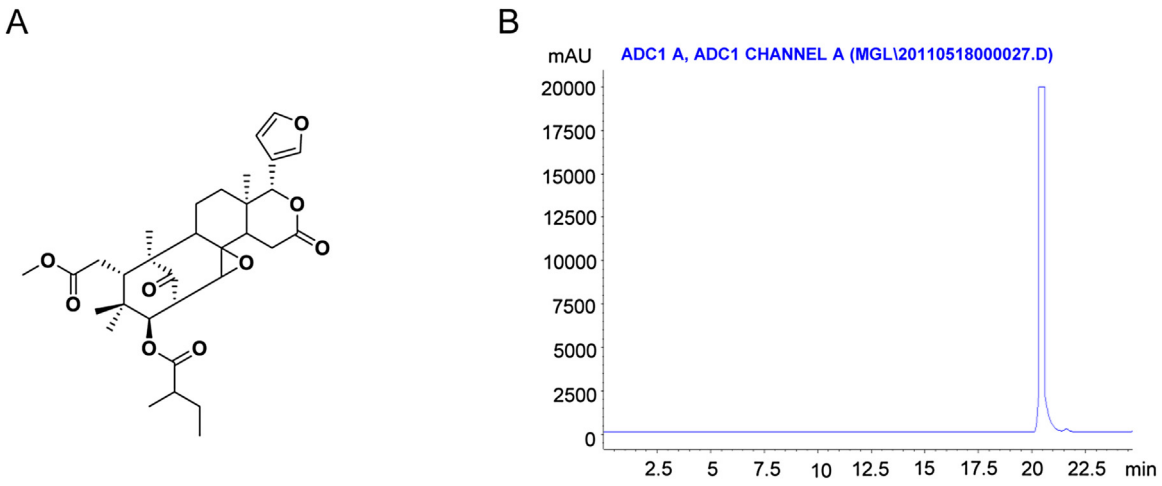

Fig. 1. Chemical structure of cipadesin A and purity analysis by HPLC.
(A) Chemical structure of cipadesin A from *X. granatum*. (B) The purity of cipadesin A (95%, tR = 20.3 min) is detected by HPLC with methanol/water (from 75% to 100% in 25 min) as a mobile phase with ELSD detector (75 °C, 2.1L/min).

2.5. Tail suspension test

The tail suspension test was performed according to previous reports [9,44]. In brief, mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. The session was videotaped and immobility time during 6 min was measured. Immobility was defined as the absence of limb or body movements, except for those caused by respiration when they hung passively and completely motionless. During the test, mice were separated from each other to prevent possible visual and acoustical associations. The number of seconds spent in immobility was scored as measurement parameter. Observers were blind to treatment groups.

2.6. Locomotor activity test

The locomotor activity was tested in an open field by an activity-monitoring system developed by Ji-Liang Co., Ltd. (Shanghai, China) [32,44]. Each mouse was placed in the center of the apparatus and monitored for 10 min. The parameters were recorded by video camera and registered in a computer. The total distance traveled during the last 6 min was recorded to evaluate the locomotor activity. The time spent in the central zone of the apparatus during the last 6 min was also recorded. Upon experiment completion, animals were returned to their homecages.

2.7. Serum corticosterone and ACTH measurement

Detection of serum corticosterone and ACTH levels was performed according to our previous study [44]. Briefly, 1 ml of blood was collected from decapitation bleeding immediately after FST. Blood samples were kept at room temperature for 1 h, and then centrifuged at 3000 rpm for 10 min. The serum (supernatant fraction) was transferred into a new tube for subsequent assays. Serum corticosterone and ACTH levels were measured with commercially available enzyme immunoassay kits (corticosterone ELISA, ml001959, mlbio, China; ACTH ELISA, ml001895, mlbio, China) according to the manufacturer's instructions. To exclude the potential impact of diurnal rhythm on mouse hormone levels, blood samples were collected in the same time window of 4:00 to 6:00 pm from each mouse immediately after 6 min of FST. Data were expressed as ng/l for corticosterone and ACTH levels.

2.8. Experimental design

2.8.1. Experiment 1: effects of cipadesin A on floating time in the forced-swimming test

Mice **(55–57 days old)** were divided into six groups: saline, cipadesin A (0, 5, 15, and 50 mg/kg) or venlafaxine (10 mg/kg) as a positive control. The mice received the drugs orally once daily for 7 consecutive days. On day 7, 30 min after the last treatment, mice were subjected to FST for 6 min (n = 9–11 per group).

2.8.2. Experiment 2: effects of cipadesin A on immobility time in the tail suspension test

A separate group of mice **(55–57 days old)** was divided into six groups: saline, cipadesin A (0, 5, 15, and 50 mg/kg) and venlafaxine (10 mg/kg). The mice received the drugs orally once daily for 7 consecutive days. On day 7, 30 min after the last treatment, mice were subjected to TST for 6 min (n = 9–11 per group).

2.8.3. Experiment 3: effects of cipadesin A on locomotion in the locomotor activity test

In this experiment, independent mice **(55–57 days old)** were orally received saline, cipadesin A (0, 5, 15, and 50 mg/kg) or venlafaxine (10 mg/kg). All mice received the drugs once daily for 7 consecutive days. On day 7, 30 min after the last treatment, total distance traveled was measured to assess the locomotor activity. Time spent in the central zone were also measured during the last 6 min to reflect the anxiety-like behavior (n = 9–12 per group).

2.8.4. Experiment 4: effects of cipadesin A on serum corticosterone and ACTH levels in mice exposed to FST

Immediately after the FST, mice were sacrificed by decapitation and the blood was collected for measurement of corticosterone and ACTH concentrations (n = 4-7 per group). To determine whether cipadesin A can affect the HPA axis activities in normal physiological state, another group of mice were divided into six subgroups and were orally received saline, cipadesin A (0, 5, 15, and 50 mg/kg) or venlafaxine (10 mg/kg) for 7 consecutive days and sacrificed without the forced swimming test. Serum corticosterone and ACTH levels were assessed by ELISA.

2.9. Data analysis

Data are expressed as mean ± SEM. the statistical analysis of behavioral and biochemical data in control and drug-treated mice

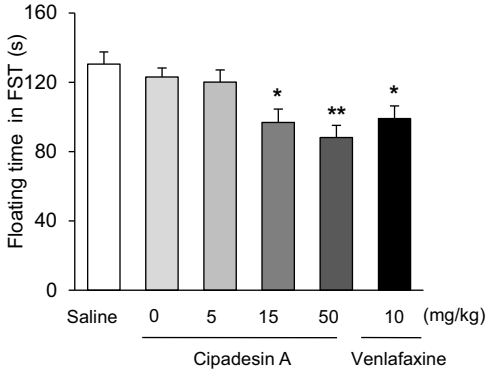

Fig. 2. Effect of cipadesin A on the floating time in the forced-swimming test.
Mice were administrated with saline, 0.5% CMC-Na, Cipadesin A (5, 15, 50 mg/kg) or venlafaxine (10 mg/kg). Data are expressed as mean ± SEM. with 9–11 mice in each group. * p < 0.05, ** p < 0.01 vs. saline group.

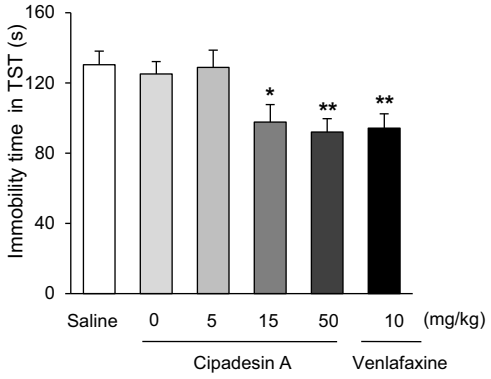

Fig. 3. Effect of cipadesin A on the immobility time in the tail suspension test.
Mice were administrated with saline, 0.5% CMC-Na, cipadesin A (5, 15, 50 mg/kg) or venlafaxine (10 mg/kg). Data are expressed as mean ± SEM. with 9–11 mice in each group. *p < 0.05, **p < 0.01 vs. saline group.

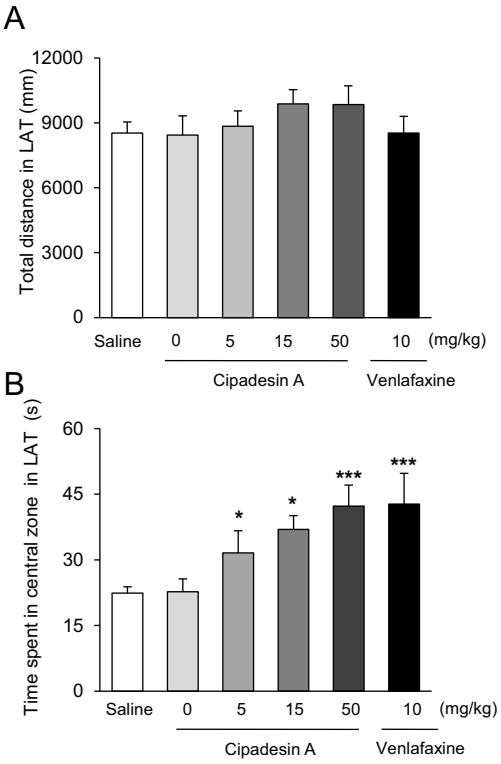

Fig. 4. The effect of cipadesin A on the locomotion activity in locomotor activity test.
Mice were administrated with saline, 0.5% CMC-Na, cipadesin A (5, 15, 50 mg/kg) or venlafaxine (10 mg/kg). 7 days of cipadesin A treatment resulted in no effects on total distance traveled during the last 6 min of a 10 min-test session (A), while cipadesin A administration at 5, 15 and 50 mg/kg doses and venlafaxine (10 mg/kg) administration for 7 days increased the time spent in the central zone (B). Data are expressed as mean ± SEM with 9–12 mice in each group. *p < 0.05, **p < 0.01 and ***p < 0.005 vs. saline group.

was performed by One-way analysis of variance (ANOVA), followed by a Tukey's *post-hoc* test. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of cipadesin A on the floating time in the forced-swimming test

The potential antidepressant-like effects of cipadesin A were firstly evaluated by FST as shown in Fig. 2. One way ANOVA revealed that cipadesin A treatment significantly decreased the floating time [$F_{(5,56)} = 5.980$, $p < 0.01$] in the FST. Post-hoc analyses indicated that 0.5% CMC-Na treatment had no significant effects ($p > 0.05$), while the classic antidepressant agent venlafaxine (10 mg/kg) significantly reduced the floating time in FST compared with saline group ($p < 0.05$); Cipadesin A treatment at 15 and 50 mg/kg doses significantly decreased the floating time compared with saline group ($p < 0.05$, $p < 0.01$ respectively), but had no significant difference compared to venlafaxine group ($p > 0.05$).

3.2. Effect of cipadesin A on the immobility time in the tail suspension test

The potential antidepressant-like effects of cipadesin A were further evaluated by TST in mouse model as shown in Fig. 3. One way ANOVA indicated that cipadesin A treatment significantly decreased the immobility time [$F_{(5,60)} = 3.979$, $p < 0.01$] in the TST. Post hoc analyses indicated that 0.5% CMC-Na treatment had no significant effects on immobility time compared with saline group ($p > 0.05$); Venlafaxine (10 mg/kg) significantly reduced the immobility time in TST ($p < 0.01$). Cipadesin A treatment at 15 and 50 mg/kg doses significantly decreased the immobility time compared with saline group ($p < 0.05$, $p < 0.01$ respectively), but had no significant difference compared to venlafaxine group ($p > 0.05$) (Fig. 3).

3.3. Effect of cipadesin A on the time spent in central zone in the locomotion test

We measured the effects of cipadesin A on locomotor activity. One-way ANOVA showed that cipadesin A treatment had no effects on total distance [$F_{(5,58)} = 0.839$, $p > 0.05$]. Post-hoc analysis revealed that venlafaxine and cipadesin A at any doses did not significantly alter the total distance during LA test ($p > 0.05$, Fig. 4A). To determine the potent anxiolytic effects of cipadesin A, time spent in the central zone during LA test was also evaluated. One-way ANOVA revealed that cipadesin A treatment significantly increased the time spent in central zone [$F_{(5,58)} = 4.187$, $p < 0.01$]. Post-hoc analysis indicated that venlafaxine significantly increased the time spent in the central zone, compared with saline group ($p < 0.005$), and although the cipadesin A administration at 5, 15 and 50 mg/kg doses significantly increased the time spent in central zone of mice ($p < 0.05$, $p < 0.05$, $p < 0.005$ respectively), no difference occurred among venlafaxine and cipadesin A groups ($p > 0.05$ Fig. 4B).

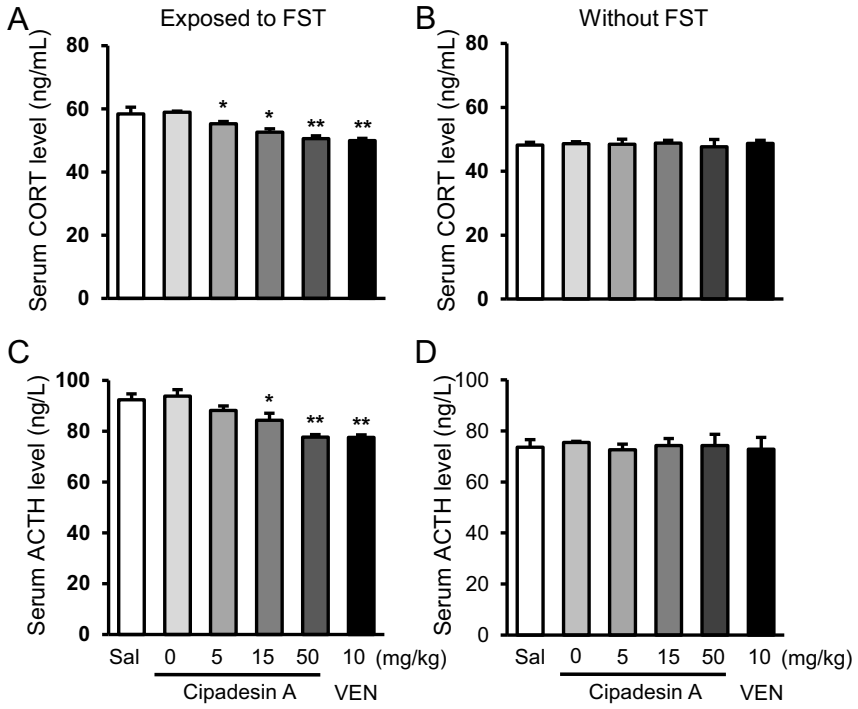

Fig. 5. The effect of cipadesin A on serum corticosterone (CORT) and adrenocorticotropic hormone (ACTH) levels in mice.
Cipadesin A (5–50 mg/kg) and venlafaxine (10 mg/kg) administered orally for 7 days decreased serum levels of CORT (A) and ACTH (C)in mice exposed to FST, while had no effects on serum levels of CORT (B) and ACTH (D) in mice without exposure to FST. Data are expressed as mean ± SEM with 4–7 mice in each group. * $p < 0.05$, ** $p < 0.01$ vs. saline group. Sal: saline, VEN, Venlafaxine; CORT, corticosterone; ACTH, adrenocorticotropic hormone.

3.4. Effects of cipadesin A on serum CORT and ACTH in mice exposed to forced swimming test

To explore the mechanisms underlying the **antidepressant-like effects** of cipadesin A, we tested the serum corticosterone levels in mice exposed to FST as shown in Fig. 5.One-way ANOVA indicated that cipadesin A treatment significantly decreased the serum level of CORT [$F_{(5,28)} = 11.584$, $p < 0.01$]. Post-hoc analyses indicated that cipadesin A at 15 and 50 mg/kg doses significantly reduced serum CORT ($p < 0.05$, $p < 0.01$ respectively; Fig. 5A). For serum corticosterone level measurement of mice in the absence of acute stress, One-way ANOVA showed no significant effects of cipadesin A doses [$F_{(5,29)} = 0.099$, $p > 0.05$]. Post hoc analysis confirmed that none of cipadesin A doses significantly altered the serum corticosterone level in mice without FST ($p > 0.05$, Fig. 5B).

Besides to serum level of corticosterone measurement, we also measured the ACTH serum level of mice after the FST. One-way ANOVA indicated that cipadesin A also inhibited the serum ACTH levels in mice exposed to FST [$F_{(5,28)} = 10.523$, $p < 0.01$]. Post-hoc analyses indicated that cipadesin A at 15 and 50 mg/kg doses significantly reduced serum ATCH levels ($p < 0.05$, $p < 0.01$ respectively; Fig. 5C). Treatment with cipadesin A at all doses studied had no effects on the baseline ACTH level in mice with no FST [$F_{(5,29)} = 0.107$, $p > 0.05$; Fig. 5D]. The ELISA data showed that 7-day cipadesin A administration significantly inhibited CORT and ACTH secretion in mice exposed to FST compared with saline-treated controls, but had no effects in mice in normal physiological state, indicating that cipadesin A specially regulated the activated HPA axis but not normal physiological state of HPA system.

4. Discussion

In the present study, we found that a 7-day oral administration of cipadesin A significantly decreased depressive-like behaviors in two validated models of depression, the forced-swimming test (FST) and the tail suspension test (TST). In addition, cipadesin A significantly increased the time spent in the central zone in the open field test (OPT), without any effects on the total distance during the test. The results indicated that cipadesin A has potential antidepressant- and anxiolytic-like effects. Finally, we found that cipadesin A suppressed HPA axis hyperactivity by reducing serum CORT and ACTH levels in mice exposed to acute stress with no effects on that in mice in normal physiological state, suggesting that the antidepressant- and anxiolytic-like effects of cipadesin A could be associated with the regulation of the activated HPA axis activity.

Both the water extract and ethanol extract from the fruit, **bark** of *X. granatum* have been used to treat various diseases, but recently pharmacological studies only begin to discern the active components of this plant that are responsible for its multiple therapeutic actions [17,26,38,39]. The unique structural patterns and biological activities of limonoids from *X. granatum* have attracted considerable attention from medicinal chemists and chemical biologists [27]. Since limonoid gedunin was isolated from *X. granatum* in 1989 [13], more than 50 limonoid derivatives have been isolated from *X. granatum*, which have diverse biological effects [31,35]. The methanolic extracts of the barks and pneumatophores of *Xylocarpus moluccensis* produce regulatory effects on sleep [29]. Cipadesin A was isolated from the fruits of *X. granatum* for the first time, and represented a mexicanolide-type limonoid with ring oxidation and unusual 9,10-bond cleavage. Unfortunately, the potential biological activity of cipadesin A is not clearly demonstrated.

Animal models are widely used to **assess putative antidepressant compounds** and to provide insights into the neuropathology of depression [9,15,36]. FST and TST are two standard models used for assessment of putative antidepressant-like activity of compounds. The immobility time in these assays reflect the antidepressant-like activity [22,32]. We found that 7-day oral administration of cipadesin A resulted in significant antidepressant-like effect both in the tail suspension and forced

swimming tests in mice in the present study. The antidepressant-like activity of cipadesin A was comparable to venlafaxine, a classical antidepressant. A potential anxiolytic activity of cipadesin A at 5 mg/kg or higher doses was also observed. Furthermore, 7-day cipadesin A administration had no significant effect on locomotor activity in mice, which excludes the possibility that action of cipadesin A are attributable to stimulatory effects on locomotion activity. Meanwhile, repeated cipadesin A administration significantly increased the time spent in central zone in the LA test. Although the potential effects of higher doses of cipadesin A are still not conclusive, our present data highlight the potential antidepressant- and anxiolytic-like activities of cipadesin A in mouse models.

HPA axis dysfunction, exhibited by elevation in circulating glucocorticoids (corticosterone in rodents; cortisol in humans), contributes to the development of depression in humans [2,30]. It is known that most depressive patients produce higher plasma cortisol levels compared with healthy subjects [4]. Moreover, acute restraint stress increased serum corticosterone levels in mice, which is attributed to increased immobility in FST and TST, and associated with depressive-like behaviors [23]. To determine whether HPA axis activity induced by forced swimming test is affected by cipadesin A, we measured the serum corticosterone and ACTH levels in mice in response to FST. We found that oral cipadesin A administration (15–50 mg/kg) reduced serum corticosterone and ACTH levels in mice exposed to FST in the current study, which indicates that the antidepressant action of cipadesin A might be associated with regulation of HPA homeostasis to increase the ability of mice to cope with stressful conditions. The effects of cipadesin A and venlafaxine in the present study are consistent with previous findings that agents with antidepressant-like efficacy decrease the levels of glucocorticoids like corticosterone [20,24]. The present study raised the possibility that cipadesin A can reduce the HPA axis activity in response to stress. Hyperactivity of the HPA axis decreases the function of the glucocorticoid receptor (GR), particularly in the hippocampus, consequently leading to the impairment of glucocorticoid feedback inhibition. Dysfunction of GR causes reduction of neurogenesis leading to the development of depressive performance [16]. Considering that GR plays a key role in the development and treatment of depression, the regulatory effect of cipadesin A on GR expression and the target genes involved in its antidepressant-like activity needs to be addressed in the future. The neuroprotective effects and the underlying molecular mechanism of cipadesin A are still elusive. Increasing evidence indicated that several signaling pathways, including phosphatidyl Inositol-3 Kinase pathway, nitric oxide synthase pathway, and nuclear factor-kappa B pathway are involved in the effects of other limonoid molecules and are associated with depressive-like behaviors[11,14,32,33]. The potential role of the related signaling pathways in the antidepressant-like effects of cipadesin A should be carried out in the future.

5. Conclusion

In summary, the present study demonstrated that oral cipadesin A administration

(15–50 mg/kg) has antidepressant-like activity in two mouse models of depression, and displays potential anxiolytic activity without apparent adverse effects (locomotor activity alteration). The antidepressant-like effects of cipadesin A was associated with a normalization of HPA axis dysfunction induced by stress. These findings indicate that cipadesin A will be a promising candidate for treatment of mood disorders.

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