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ORIGINAL ARTICLE

Pineapple (*Ananas comosus*) Ameliorates Depressant-like Behaviors in Rats Induced by Lipopolysaccharide

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Background: Lipopolysaccharide (LPS) injection can lead to depression and mood disorders by reducing tryptophan availability through increased activity of the enzyme indoleamine 2,3-dioxygenase. Tryptophan, sourced from fruits such as pineapple (*Ananas cosmosus*), is vital for the body, especially the serotonergic system. **Aim:** This study aims to assess how pineapple pulp (PP) counters LPS-induced depressive behaviors in male Wistar rats. **Methods:** The experiment involved force-feeding PP for 28 days before LPS injection (0.5 mg/kg intraperitoneal [i.p.]) in 30 male Wistar rats, divided into five groups. Groups I (normal) and II (LPS control) received 15 ml aquadest/kg/day. Test Groups III, IV, and V were given varied doses of PP; low dose (3.75 ml/kg/day), medium dose (7.5 ml/kg/day), and high dose (15 ml/kg/day). At the study's end, rats underwent the open field test (OFT) and the tail suspension test (TST). In addition, blood and brain samples were analyzed for neuroendocrine markers related to depression. **Results:** LPS triggers depressive symptoms, as evidenced by increased immobility time in the TST and altered behaviors indicative of anxiety in the OFT, especially in groups not receiving PP. This is followed by decreased serotonin levels in both plasma and brain when compared to groups given PP. In addition, higher corticosterone levels were observed in the LPS group than in the PP-treated group. Administering PP at 7.5 ml/kg/day for 28 days can alleviate the depressive effects induced by LPS injection. **Conclusion:** PP may have antidepressant properties, potentially by mitigating behaviors leading to depressive symptoms.

Key words: *Ananas cosmosus*, lipopolysaccharide, immobility time, serotonin, corticosterone

INTRODUCTION

Comorbid major depressive disorder is more common with a variety of illnesses, including premature aging, obesity, atherosclerosis, and heart failure, all of which produce chronic inflammation.[1] This pathogenesis increases the activity of the tryptophan catabolism enzyme, indoleamine 2,3-dioxygenase (IDO),[2] which is an extrahepatic enzyme that degrades tryptophan through the kynurenine pathway present in macrophages and other cells. Pro-inflammatory cytokines such as interferon-gamma and tumor necrosis factor-alpha (TNF-α) activate this enzyme.[3] Activation of IDO through chronic inflammatory conditions significantly correlates with the intensity of depressive symptoms.[4]

Acute activation of the peripheral innate immune system in rats by cytokine-inducing lipopolysaccharide (LPS) injection might impact the onset of symptoms leading to depression, indicated by an increase in the kynurenine/tryptophan ratio.[5] The changes in tryptophan metabolism produced by pro-inflammatory cytokines as a result of LPS injection will cause tryptophan to share pathways with serotonin (encouraging the kynurenine pathway and preventing the serotonin pathway from utilizing tryptophan), thereby reducing serotonin production. Scientific speculation concerning this process is connected to the major depression monoamine hypothesis.[6]

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The endogenous tryptophan metabolite pathway produces serotonin, kynurenine, and other downstream metabolites that are involved in a variety of immunological processes in both health and sickness. The synthesis of serotonin from tryptophan occurs in two stages, with the rate of synthesis determined by the quantity of tryptophan in the brain.[7] Because serotonin is important in mood and anxiety regulation, decreased brain serotonin levels contribute to an increased prevalence of anxiety and depression.[7,8]

The availability of serotonin is determined by the amount of tryptophan consumed.[9] However, research on the influence of tryptophan levels in the blood on mood and anxiety in people has yielded conflicting results. If low tryptophan levels occur in rats, it will trigger them to exhibit depressive symptoms. Because it is difficult to alter plasma tryptophan levels only through food, most research has focused on tryptophan supplementation and depletion.[10] Food not only serves as fuel in the body's metabolic processes but it also has an effect on brain function, mood, and cognition. A diet high in both tryptophan and antioxidants can improve mood and cognition, which are especially important for people suffering from low-grade inflammatory disorders.[11] Because tryptophan cannot be manufactured by the body, it must be supplied from outside the body. Pineapple (*Ananas cosmosus*) is a good source of tryptophan and is a popular tropical fruit in Indonesia. In this case, determining the level of tryptophan in pineapple fruit will open up new exploration opportunities because it is a low-cost source of bioactive phytochemicals, adding nutritional value and increasing the sustainability of the pineapple sector, which provides economic, social, and environmental benefits. The presence of tryptophan in pineapple has previously been investigated with levels of 19.83 mg/kg.[12]

Based on prior research, this study aimed to explain the advantages of pineapple pulp (PP) as a dietary source containing the serotonin precursor chemical, tryptophan, in reducing the emergence of depression symptoms caused by LPS induction. This study examined the characteristics of serotonin levels, and corticosterone levels in plasma samples and rat brains to clarify the involvement of these substances.

MATERIALS AND METHODS

The animal study protocol was approved by The Medical and Health Research Ethics Committee (MHREC) with approval number: KE/FK/0313/EC/2020 and date of approval: 13, March 2020.

Preparation of pineapple pulp

The pineapple fruit used in this research is produced by PT Great Giant Pineapple, Lampung, Indonesia. The fresh pineapple was weighed, sliced, crushed, blended, and homogenized with a homogenizer (Armfield L4R, 8033 rpm, for 20 min) into a pulp, with a soluble solid content of 12.15 ± 0.07° Brix.

The tryptophan and proximate analysis

Determination of tryptophan

To prepare a standard solution for tryptophan, 25 mg standard L-tryptophan was dissolved in 10 ml aqua bidest. As much as 0.3 mL HCl was added and sonicated for 15 min before diluting to 25 mL with aqua bidest. 1 mL stock solution was diluted to 10 mL with aqua bidest and properly mixed. From the stock solution, individual working standard solutions of eight concentrations were made.[13] Although free amino acids are often examined without hydrolyzing the material, acid hydrolysis (typically 100-120°C, 6N HCl, and 22-24 h) is required to estimate total amino acids in a protein, since tryptophan is unstable under these circumstances.[14]

Proximate composition analysis

The proximate components of the PP, which comprised ash, carbohydrates, fat, moisture, protein, and dietary fiber, were analyzed using standard protocols at the Chemistry and Biochemistry Laboratory, Faculty of Agricultural Technology, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Animals

Wistar rats (201.48 ± 14.95 g) were provided by an animal testing farm, Sleman, Yogyakarta, Indonesia, and maintained in propylene cages (40 cm × 30 cm × 20 cm) acclimatized to laboratory conditions. Male Wistar rats were used for the present study to prevent bias in the outcomes of evaluating depression in rats, as depression has been observed to have a stronger impact on female rats compared to male rats.[15] Rats were housed at a controlled temperature with lighting regulated by light-dark duration (12 h). The study produced neuroinflammation in Wistar rats by injecting LPS to investigate the potential of tryptophan in PP in reducing anxiety-related behavior. 0.5 mg/kg/day of LPS from *Escherichia coli*, diluted in 0.9% NaCl, was administered by intraperitoneal injection.[16] The rats in this study had free access to food and drink. After 1 week of acclimatization period, the rats were grouped into five groups, including Groups I-normal and II-LPS control groups were treated with 15 ml aquadest/kg/day. The test Groups III-low dose, IV-medium dose, and V-high dose received 3.75; 7.5; and 15 ml/kg/day of PP by oral gavage (force-feeding) for 28 days. All the above-mentioned treatments and Group II were given 0.3 mg/kg/day of LPS injected (i.p.) on days 26, 27, and 28. During the treatment schedule on day 28, animal behavioral tests were conducted for animals. Afterward, the rats were euthanized ketamine by decapitation. The blood samples were taken two times: pre (after 25 days of PP ingestion), and post (after 3 times

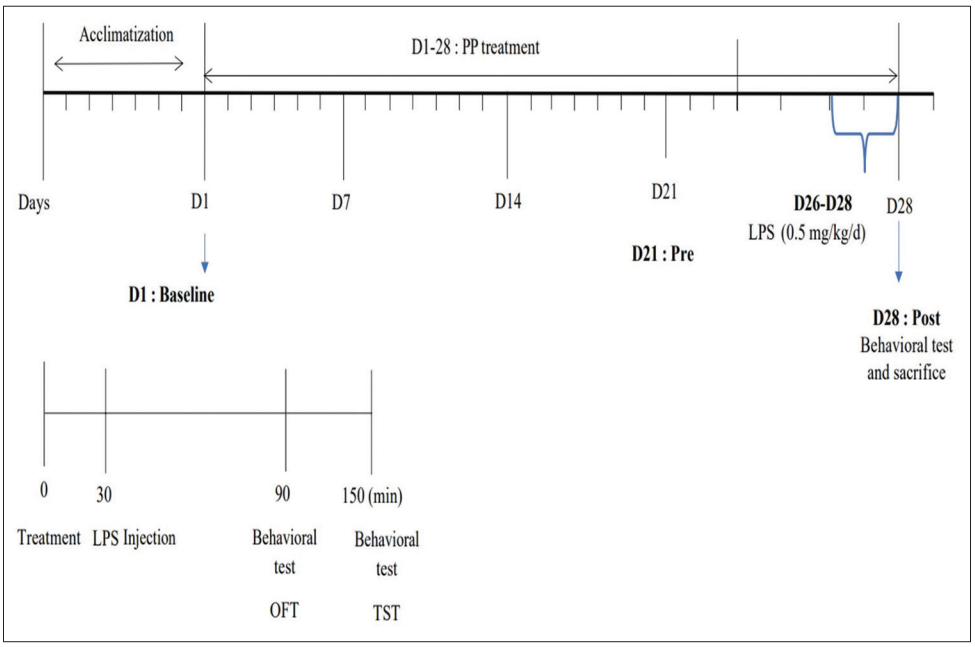

Figure 1: The timeline of the experimental design

of LPS injection on day 26, 27, and 28 and behavioral test on day 28). Figure 1 shows a schematic representation of the experimental technique.

Behavioral tests

Open field test

The open field tool was made out of a 100 cm × 100 cm arena enclosed by 50 cm high wood and glass barriers. The open field's floor was split into 16 equal-size squares (25 cm × 25 cm) by black lines. The experiment began by randomly placing a rat in the center of the arena. Behavioral evaluations were conducted throughout a 5-min trial session. The number of squares crossed with the four paws (crossing), time spent in the center area, time spent in the peripheral zone, and the grooming episodes (washing of the coat) were recorded in a 10-min session.

Tail suspension test

The effects of the PP on LPS-induced depressive-like behavior in rats after LPS injection were assessed using the tail suspension test (TST) as previously reported,[14] with minor modifications. The rats were hung by the tail 60 cm above the floor using cotton yarn immediately after the open field test (OFT). For the latter 4 min of a total 6-min session, the time each rat stayed motionless was recorded (in seconds).

Collection of plasma

Blood collection was done in two stages; Pre (after administration of PP) and post (after injection of LPS). Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged at 4°C for 5 min at 2300 ×*g* so that it separates. Next, the top part (plasma) was frozen at −20°C until analysis.

Collection of brain samples

After the mice were euthanized and decapitated, parts of the brain were immediately removed and dissected on the operating table, then stored at −80°C until further analysis. Brain areas were weighed, then each placed in a cold tube, containing 1 ml 25 mM Tris-HCl, pH 7.4, 1 mM EDTA, and 1 mM EGTA, then homogenized. The resulting homogenate was then centrifuged at 11,000 ×*g* for 30 min, 4°C, then filtered on the resulting supernatant using a 0.45 µm syringe filter (Spartan-3, Aldrich Chemical, Milwaukee, WI, USA).

The levels of serotonin and corticosterone in both the plasma and rats' brain were measured using ELISA kits according to the manufacturer's instruction. Product General 5-Hydroxytryptamine ELISA Kit (5-HT) for serotonin analysis (ABCLONAL, USA) and General Corticosterone ELISA Kit (RK00640, ABCLONAL, USA) for corticosterone analysis.

Statistical analysis

Fold changes in serotonin and corticosterone in plasma were determined as the average of the final/initial values and adjusted to percentage changes (i.e. 1.60-fold = 60% increase and 0.60-fold = 40% reduction). All of the data had a normal distribution and were reported as mean and standard deviation. To compare the initial and final values, a paired sample *t*-test was used. To compare the means of fold change in all groups, one-way analysis of variance and LSD *post hoc* test were

used. At $P < 0.05$, differences were considered significant. Pearson's correlation coefficient was used to analyze the correlation between oxidative stress parameters, with a level of significance of $P < 0.05$. SPSS version 23 for Windows (IBM Corp., Chicago, USA) was used for the statistical analysis.

RESULTS

Compositional analysis

The chemical composition of PP was analyzed. Moisture content represents the major constituent of PP. The results of this research indicating the content of tryptophan, dietary fiber, and proximate PP are shown in Table 1. Recent research has succeeded in identifying the role of tryptophan as an antioxidant so that it can contribute as an anti-inflammatory agent.[17] The PP used in this study had tryptophan levels of 113.73 mg/kg, higher than the results of other studies of 19.83 mg/kg and compared to other fruits such as kiwi (3.32 mg/kg), banana (26.15 mg/kg), and apples (2.44 mg/kg).[18]

Behavioral effects of the pretreatment of pineapple pulp before and lipopolysaccharide injection

In the OFT, PP-3.75 + LPS, PP-7.5 + LPS, and PP-15 + LPS groups exhibited lower locomotor activity compared to Group I (normal) ($P < 0.05$). However, Group III (PP-15 + LPS) showed the highest locomotor activity [46.25 ± 16.25, and significantly different compared to LPS, PP-7.5 + LPS groups, $P < 0.05$, Table 2]. One method that can show how much influence preventive efforts have on consuming PP in mice for 4 weeks before LPS injection is OFT. The results showed that rats that experience stress due to LPS injection (without administration of PP) spent less time in the central area than normal rats. This finding showed that stressed rats were more comfortable in the peripheral areas, not in the center, compared to normal rats. When compared to the control group, all LPS-injected groups spend more time in the peripheral zone. The time spent in the peripheral zone did not differ significantly from the LPS group in the group given PP at doses of 7.5 and ml/kg/day, compared to the PP-15 + LPS and LPS groups, the PP-3.75 + LPS groups showed significantly higher peripheral endurance. The grooming time parameter in the OFT revealed that all groups that received LPS injections had a higher grooming time duration than the normal control group, which was greater in those with LPS injections that did not get PP administration with the PP-7.5 + LPS group.

In the TST, most interestingly all three doses of PP produced immobility more prominent than positive control, the lower dose (3.75 ml/kg/day) of PP decreased the immobility time to a greater extent than the higher dose, thus showed better antidepressant-like activity [Table 3].

Table 1: The measured bioactive compounds of pineapple pulp

	Number of analytes (mean±SD)
Carbohydrate (%)	13.08±0.15
Fat (%)	0.39±0.04
Moisture (%)	85.57±0.11
Crude Protein (N×6.25)	0.67±0.004
Ash	0.30±0.001
Tryptophan (mg/kg)	113.73±0.42

SD=Standard deviation

Effect of pineapple pulp on neuroendocrine marker

The analyses of serotonin data, shown in Figure 2 revealed that serotonin levels were lower in all groups after 4 weeks of PP administration and after three successive LPS injections, while the LPS group had the only significant difference. The administration of PP at various dosages for 4 weeks before LPS injection ensures the availability of tryptophan for eventual usage as a precursor in serotonin synthesis. Corticosterone data analysis, shown in Figure 2 revealed that corticosterone levels were higher in all groups after 4 weeks of PP administration and after three successive LPS injections. Significant differences were seen in the LPS injection group and the low-dose PP (3.75 ml/kg/day) group.

Table 4 shows the levels of serotonin and corticosterone in the brain in each group. Regarding serotonin levels in the

Table 2: Effect of pineapple pulp in lipopolysaccharide-induced depression in the open field test in rats

Groups	Total number of squares crossed in 10 min	Time spent in the center area (s)	Time spent in peripheral zone (s)	Grooming time (s)
Normal control	28.50±6.74$^{\#}$	22.17±1.81$^{\#}$	241.00±4.00$^{\#,£}$	13.00±4.60$^{\#}$
LPS	6.00±0.79*$^{,\$,£}$	7±2.86*$^{,¥}$	584.00±13.21$^{\$}$	30.97±1.34*$^{,¥}$
PP - 3.75 + LPS	29.83±20.68$^{\#}$	17.25±8.91	387.67±335.74$^{\#,£}$	19.50±17.85
PP - 7.5 + LPS	20.67±7.35$^{£}$	26.17±13.87$^{\#}$	569.00±41.01*	16.58±11.00$^{\#}$
PP - 15 + LPS	46.25±16.25$^{\#,¥}$	28.75±15.72$^{\#}$	598.80±18.36*$^{,\$}$	19.67±4.25

*$P<0.05$ as compared to normal control group; $^{\#}P<0.05$ as compared to LPS group; $^{\$}P<0.05$ as compared to PP-3.75 + LPS; $^{¥}P<0.05$ as compared to PP-7.5 + LPS; $^{£}P<0.05$ as compared to PP-15 + LPS. Values are mean±SD. Significant differences by LSD *post hoc* test. LPS=Lipopolysaccharide; PP=Pineapple pulp; SD=Standard deviation

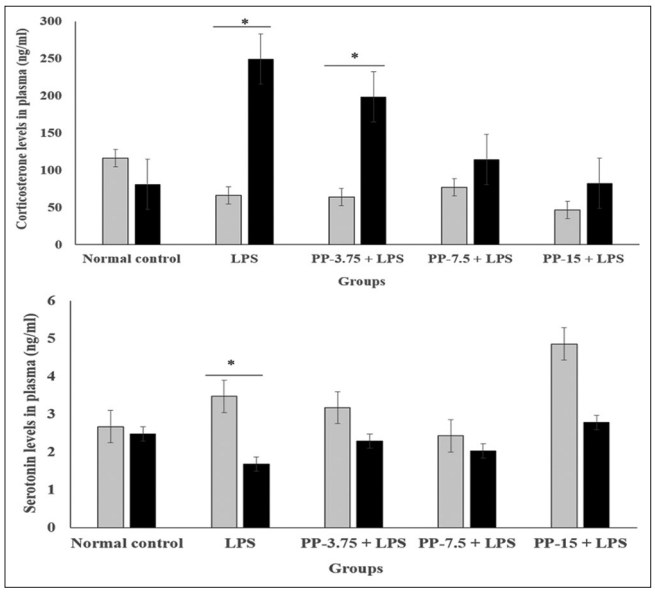

Figure 2: Effects of pineapple pulp on corticosterone and serotonin levels in plasma from rats. Comparison between pre- and postvalues of corticosterone and serotonin levels between before and after lipopolysaccharide injection. There is a significant difference ($P < 0.05$) between serotonin and corticosterone levels in plasma as indicated by the notation. Values are expressed as means ± standard deviation. One-way analysis of variance followed *t*-test. *$P < 0.05$. LPS = Lipopolysaccharide; PP = Pineapple pulp. ■ = Pre; ■ = Post

brain, administration of PP at a dose of 7.5 ml/kg/day showed a significantly higher value compared to the LPS group, but not significantly different compared to the normal group and PP at a dose of 3.75 ml/kg/day. The most significant finding was that high doses of PP do not instantly enhance brain serotonin levels and instead contribute to levels that are not significantly different from the LPS group. Regarding brain corticosterone levels, the group that received the LPS injection had higher corticosterone levels compared to the normal group, but only the LPS group had significantly higher corticosterone levels compared to the other groups.

DISCUSSION

Tryptophan is a neurotransmitter precursor involved in many functions in the brain, and one of its fundamental roles is serotonin synthesis. Several studies have revealed that administration of tryptophan or conditions of a high plasma ratio between tryptophan and large neutral amino acids (LNAA) can play a role in increasing tryptophan levels in the brain to near saturation of tryptophan hydroxylase substrates.[19] To be able to produce serotonin in the central nervous system (CNS), tryptophan must be able to cross the blood–brain barrier, which is delivered by a carrier protein that also transports isoleucine, leucine, phenylalanine, tyrosine,

Table 3: Effect of pineapple pulp in lipopolysaccharide-induced depression in the tail suspension test

Groups	Immobility time (s)
Normal control	83.42±18.27$^{\#}$
LPS	123.75±20.65*$^{,\$}$
PP-3.75+LPS	64.50±24.05$^{\#}$
PP-7.5+LPS	112.40±17.42$^{\$}$
PP-15+LPS	100.63±41.17

*P<0.05 as compared to normal control group; $^{\#}P$<0.05 as compared to LPS group; $^{\$}P$<0.05 as compared to PP-3.75 + LPS; $^{¥}P$<0.05 as compared to PP-7.5 + LPS; $^{£}P$<0.05 as compared to PP-15 + LPS. Values are mean±SD. Significant differences by LSD *post hoc* test; LPS=Lipopolysaccharide; PP=Pineapple pulp; SD=Standard deviation

Table 4: Levels of serotonin and corticosterone in the brain of the normal control and pineapple pulp-treated rats for 4 weeks before lipopolysaccharide injection (conducted following the termination stage)

Groups	Serotonin level (ng/mg)		Corticosterone level (ng/mg)	
	Mean±SD	Range	Mean±SD	Range
Normal control	19.47±4.28^{a,b}	14.67–22.88	154.13±72.66^{a}	102.75–205.50
LPS	13.33±5.76^{b}	7.45–18.97	314.83±11.03^{b}	302.10–321.20
PP-3.75 + LPS	16.07±5.16^{a,b}	11.87–22.46	163.80±63.80^{a}	100.00–237.70
PP-7.5 + LPS	24.39±9.14^{a}	15.57–36.59	192.17±11.58^{a}	184.60–205.50
PP-15 + LPS	10.82±2.35^{b}	8.63–13.95	192.73±15.50^{a}	174.90–202.90

Means with different superscripts in the same column significantly differ (P≤0.05) according to the Duncan multiple range test; LPS=Lipopolysaccharide; PP=Pineapple pulp; SD=Standard deviation

and valine.[20] This competition will reduce the quantity of tryptophan that enters the brain, limiting serotonin production. The majority of tryptophan is linked to plasma albumin, rendering it inaccessible for delivery to the brain.

Plasma tryptophan levels are determined by the balance between food intake and utilization as part of the important role of serotonin biosynthesis. Tryptophan, in addition to its involvement in serotonin production, serves as a precursor to a variety of metabolites, particularly kynurenine. Even though carbohydrate foods do not contain tryptophan, they can cause the release of insulin, which plays a role in reducing levels of LNAA in plasma, which usually competes with tryptophan for transport across the blood–brain barrier. Research on human subjects showed that consuming tryptophan and carbohydrate-rich foods can increase tryptophan and serotonin levels in the brain.[20] The carbohydrate content of the pineapple fruit utilized in this study was 13.08%. A study involving high carbohydrate consumers and low to noncarbohydrate consumers succeeded in determining a carbohydrate dose of 104 g that reduced levels of depression compared to the group that did not consume carbohydrates, who reported feeling less

alert, tired more quickly, and sleepy. Tryptophan will play a role in situations of inflammation such as those produced by LPS injection because, in addition to serotonin production, it is also needed for kynurenine synthesis, which accounts for about 90% of tryptophan metabolism.[21]

In this work, we established an inflammatory model of depression generated by LPS, a significant component of Gram-negative bacteria's outer membrane, which was facilitated by depression-like behavior and neuroendocrine biomarkers (serotonin and corticosterone). Furthermore, we found the antidepressant-like effects of pretreatment with PP, which could enhance our understanding of this natural compound's antidepressant potential. Low serotonin levels may be related to emotional stress and sadness. The most direct evidence for severely decreased central serotonergic system function comes from trials including tryptophan depletion, which decreases central serotonin production, and selective serotonin reuptake inhibitors, which are extensively, used antidepressants.[22] They increase the concentration of monoamines in the brain and as a result, aid in the management of well-being. Consuming PP can ensure the availability of tryptophan as a raw material for serotonin synthesis, lowering the risk of depression caused by LPS-induced neuroinflammation. Tryptophan metabolism in PP involves the conversion of tryptophan into serotonin catalyzed by the rate-limiting enzyme TRP hydroxylase (TPH). 5-hydroxy tryptophan is decarboxylated by aromatic amino acid enzymes. TPH is not fully saturated with tryptophan substrates under normal conditions. Increasing tryptophan levels in the brain can boost serotonin synthesis. However, this process is hindered during neuroinflammation or stress, as tryptophan availability is reduced due to kynurenine formation. Serotonin synthesis is limited by an enzyme, so there is an optimal dose of tryptophan that can be converted into serotonin. Beyond this dose, serotonin output cannot be increased.[23] This study determined that the optimum dosage of PP to facilitate serotonin synthesis in the brain is 7.5 ml/kg/day.

When compared to the vehicle group exposed to LPS, the rats pretreated with PP at a dosage of 7.5 mg/kg/day had greater locomotor activity measured in the OFT and lower corticosterone levels. Corticosterone deficiency has been associated with less depressive-like behavior,[24] and has been related to elevated serotonin levels in the blood. Low serotonin levels may be associated with emotional stress and depression; however, the most direct evidence for significantly reduced central serotonergic system function comes from research utilizing tryptophan depletion, which lowers central serotonin production. The best evidence that serotonin is involved in the pathophysiology of depression comes from studies of "tryptophan depletion," in which an acute dietary manipulation is used to produce a transient decrease in brain serotonin activity by decreasing the availability of tryptophan, its precursor amino acid. In healthy volunteers with no risk factors for depression, tryptophan restriction produces no clinically important alterations in mood; nonetheless, recovered depressed patients without therapy can demonstrate brief, clinically relevant depressive symptomatology.[25,26] High serotonin levels were detected in some pineapple at 60.092 ng/g and tryptophan at 24.929 ng/g,[27] while in our study, the tryptophan levels were higher than in previous studies at 113.730 ng/g.

A. cosmosus is reported to contain numerous brain monoamines namely serotonin, norepinephrine, and dopamine, thereby contributing positively to its antidepressant effect.[28] Most notably in the present study, all three doses of PP produced immobility lower than the group exposed to LPS without PP administration. Qualitative analysis of PP revealed that it contains carbohydrates, flavonoids, phenols, tannins, phenols, and tryptophan, which have already been reported to have remarkable effects on the CNS. Flavonoids, both aglycone and conjugated forms pass the blood–brain barrier. During the passage of the blood-brain barrier conjugates may be metabolized back to the parent aglycone, which then enters the CNS. The administration of antioxidants attenuated LPS-induced depression-like behaviors in rats by decreasing cerebral oxidative stress. In addition, this compound increased the activity of superoxide dismutase and glutathione peroxidase enzymes, as well as reduced MDA levels.[29]

As observed in the trials, LPS-treated rats remained considerably more immobile in comparison to normal controls. On the other hand, the PP at a dose of 3.75 ml/kg/d significantly showed a lowered immobility measure. The lower dose of PP (3.75 ml/kg/d) decreased the immobility time to a greater extent than the higher dose (7.5; and 15 ml/kg/d), thus showed better antidepressant-like activity. At higher dose of PP, there might be saturation of receptors, so the maximum effect was achieved at lower dose. There might also be a sedative effect a higher dose of PP, which might be responsible for less decrease in immobility time due to suppressing the CNS or awareness, leading to sleepiness

As a result, peripheral or central LPS injection can activate microglia and set off a cascade of inflammatory responses that lead to depression. Furthermore, the disruption of a subgroup of neurons that express parvalbumin interneuron promotes systemic inflammation-induced depression-like behavior and LPS-induced working memory impairment.[30] LPS injection is most widely used to create animal models of inflammation-related depression.

CONCLUSION

PP had antidepressant-like effects in rats with an inflammatory model of depression. This function is linked to the availability

of tryptophan for serotonin production. As a result, PP may be a viable functional meal for the treatment of depression. For future studies, it is advised to include IL-1b, IL-6, and TNF-α as measures affected by the neuroinflammatory state caused by LPS injection, which might induce stress and behavioral changes leading to depression in experimental rats.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, HAN, upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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