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# Effect of Jobelyn® on intruder- and isolation-induced aggressive behavior in mice

## Abstract

**Background:** Aggression is a violent behavior emitted against another organism that may lead to its harm or death and thus is of public health significance, which necessitates the search for agents with anti-aggressive property. This study investigated the effect of Jobelyn® (JB), a unique African polyherbal formulation, on intruder- and isolation-induced aggressive behaviors in mice.

**Methods:** Male mice that showed aggression after being housed individually with female counterparts for 3 weeks or kept in isolation for 4 weeks were treated orally (p.o.) with JB (5, 10 or 50 mg/kg), haloperidol (HP) (1 mg/kg), fluoxetine (FL) (10 mg/kg), *p*-chlorophenylalanine (PCPA) (20 mg/kg), mianserin (MS) (50 mg/kg) or distilled water (10 mL/kg) 60 min before being tested for aggression. Interaction studies involving oral administration of PCPA (20 mg/kg), FL (10 mg/kg) or MS (50 mg/kg) to aggressive mice that had received JB (5 or 10 mg/kg, p.o.) 30 min earlier were assessed. The effect of JB (5, 10 or 50 mg/kg, p.o.) on defensive behaviors was also evaluated.

**Results:** JB (5, 10 or 50 mg/kg) decreased aggressive behaviors without impairing the defensive mechanisms of mice. PCPA (20 mg/kg), an inhibitor of 5-hydroxytryptamine (5-HT) biosynthesis, increased aggressive responses and reduced the anti-aggressive effect of JB. FL (10 mg/kg), a 5-HT reuptake inhibitor, significantly suppressed aggression but did not alter the effect of JB on aggression. MS (50 mg/kg), a 5-HT receptor antagonist, reduced aggression and enhanced the effect of JB on aggression.

**Conclusions:** These findings suggest that JB has anti-aggressive activity, which may be related to the enhancement of serotonergic system.

**Keywords:** defensive mechanism; Jobelyn®; offensive aggression; serotonin.

## Introduction

Aggression is a violent behavior exhibited against another organism that may lead to its harm or death and currently becoming a major public health issue across the globe [1]. Apart from causing physical injury, aggression also inflicts long-term emotional damage to its victims [1]. Aggression is a common behavior seen in patients with mental illness, and stress has been implicated as a major factor that triggers violence in humans [1–3]. It is now known that aggression is a pathological disorder with defined neurochemical abnormalities and as such needs pharmacological interventions [4]. Most of the current drugs used for the treatment of aggression target various neural mechanisms such as dopaminergic, serotonergic, adrenergic and/or GABAergic systems [4]. Although these agents reduce aggressive acts, they also interfere with other behavioral functions, so the need for improved and more behaviorally selective therapies still persists [4]. As alternatives to these conventional drugs, a number of new medicines from plants that may be well tolerated are being sought as therapeutics for the treatment of aggression and violent behaviors [5].

Jobelyn® (JB) is a commercial dietary herbal supplement with active ingredients obtained majorly from the leaf of *Sorghum bicolor* [6, 7]. JB was further fortified with other phytochemicals obtained from *Harungana madagascariensis* and *Parquetina nigrescens* [6, 8]. JB was formulated principally for the treatment of moderate to severe anemia and arthritis [6, 7]. However, it has also gained international recognition as a remedy against stress and exhaustion and to restore the much needed energy during the period of recovery from debilitating diseases [6]. Thus, JB is widely used as a tonic in a vitamin-like fashion to ensure good health or general well being. In addition, JB also strengthened the immune system and enhanced the body's defensive mechanisms in response to stress or pathogenic invasions [6, 7].

The use of JB as a stress reliever and as an energizer during the period of exhaustion suggests that it might contain phytochemicals with central nervous system (CNS) activities. In fact, previous preclinical studies have confirmed that several lipophilic active constituents like

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apigeninidin, luteolinidin, apigenin, luteolin and naringenin, which are also found in JB, readily cross the blood brain barrier to exert CNS effects [6, 7, 9, 10]. Besides mental illness, stress is another major factor promoting aggression and violence in humans [2, 11]. In vulnerable individuals, stress in particular can lead to a subtype of depression characterized by anger, anxiety and display of aggression [2, 12, 13].

Stress is a critical factor that may precipitate aggression and predicts the severity of developing violence behaviors [2, 12]. Indeed, persistent stress has been shown to produce depletion of monoamines that play a crucial role in the regulation of emotion and behavior [12, 14]. In addition, aggressive individuals and those under intense traumatic stress are characterized by low tolerance to frustration and are more prone to exhibit an act of aggression [3, 15]. Thus, aggression is a prominent component of the stress responses and may serve as an outlet for dissipation of frustration on people [3, 15]. Because stress and aggression share similar behavioral and neurochemical components, it might be expected that JB, as an energizer, will likely exhibit anti-aggressive property. Thus, this present study was carried out to assess the effect of JB on intruder- and isolation-evoked aggression in mice.

## Materials and methods

### Experimental animals

Male albino Swiss mice of either sex (18–24 g) used in the study were obtained from the Central Animal House, College of Medicine, University of Ibadan and were housed in plastic cages (42 cm×30 cm×27 cm) at room temperature with 12:12-h light-dark cycle. They were fed with balanced rodent pellet diet and water ad libitum. The animals were acclimatized for 1 week prior to commencement of experiments. All experimental procedures were performed in compliance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving the Care and Use of Laboratory Animals [16].

### Drugs

JB (Health Forever Ltd, Lagos, Nigeria), haloperidol (HP) (Sigma-Aldrich, St. Louis, MO, USA), fluoxetine (FL) (Medibios Laboratories Pvt. Ltd, India), mianserin (MS) (Organon, OSS, Holland, Netherlands) and *p*-chlorophenylalanine (PCPA) (Sigma-Aldrich, St. Louis, MO, USA) were used in the study. Appropriate concentrations of JB and other drugs were prepared by dissolving them in distilled water before the start of the experiments. The doses of 5, 10 and 50 mg/kg of JB used in the study were selected on the basis of the results obtained from preliminary investigations. JB and other drugs were administered orally to the animals by gavage.

### Effect of JB on resident-intruder offensive aggression

The effect of JB on offensive aggression in mice was assessed using the resident-intruder paradigm as previously described [4, 17]. Adult albino Swiss mice of both sexes were used in this experiment. Prior to the start of experiments, each resident male mouse was paired with a female counterpart and housed in a plastic cage (20 cm×20 cm×23 cm) for 3 weeks. Thereafter, the baseline level of offensive behavior of the resident mouse was assessed for three consecutive days for a period of 5 min of confrontation with an unfamiliar male intruder of similar size. One hour before the start of the confrontation, the female partner of the resident mouse was removed from the cage. The naive intruder mice were socially housed in plastic cages (42cm×30cm×27cm) in groups of 15. Resident male mice that did not show marked offensive aggressive behaviors were excluded from the study. Resident male mice that showed marked offensive aggression were pretreated with JB (5, 10 or 50 mg/kg), HP (1 mg/kg), distilled water (10 mL/kg), PCPA (20 mg/kg) or FL (10 mg/kg), or MS (50 mg/kg). Sixty minutes later, a male intruder of similar size was introduced into the territorial cage of each resident male mouse and the confrontation between them was videotaped [4, 17].

In the interaction study, the effects of PCPA (20 mg/kg), FL (10 mg/kg) or MS (50 mg/kg) given in combination with JB (5 or 10 mg/kg) were also assessed. PCPA (20 mg/kg), FL (10 mg/kg), or MS (50 mg/kg) was administered to aggressive mice that had received JB (5 or 10 mg/kg) 30 min earlier. Thirty minutes later, the test for aggression was carried out as earlier described. The parameters assessed indicative of offensive aggression were latency to attack, frequency of attacks, aggressive postures, lateral threats, tail rattling, pursuit frequency and percentage of animals with injury [4, 17].

### Effect of JB on isolation-induced offensive aggression

The isolation-induced offensive behavior paradigm was further employed to evaluate the effect of JB on aggression [17]. Male albino mice (2 weeks old) were kept individually in transparent plastic cages for 4 weeks. Prior to drug treatment, baseline levels of offensive aggressive behaviors were assessed as earlier described. Isolated male mice that showed marked aggressiveness were given JB (5, 10 or 50 mg/kg), HP (1 mg/kg), FL (10 mg/kg), MS (50 mg/kg), PCPA (20 mg/kg) or distilled water (10 mL/kg) 60 min before testing for aggression [17].

### Effect of JB on defensive behaviors

The effect of JB on defensive behaviors was evaluated in mice using the resident-intruder paradigm as previously described [4]. The test involves a 10-min confrontation between aggressive resident male mice and intruder counterparts of similar size. However, only male intruders (and not the resident) mice were treated with JB (5, 10 or 50 mg/kg), HP (1 mg/kg), FL (10 mg/kg), MS (50 mg/kg) or distilled water (10 mL/kg). Sixty minutes after treatment, the ability of the intruder animal to defend itself against the offensive behaviors of the resident counterpart was videotaped during the 10-min confron-

**Table 1** Effect of Jobelyn on resident-intruder offensive behaviors in mice.

Treatment groups and dose	Frequency of attack	Tail rattling	Lateral threat	Pursuit frequency	Aggressive posture	Intruders with injury, %
Control	40.4±0.5	45.6±0.9	18.6±1.3	20.8±1.2	18.0±0.8	92.0
JB (5 mg/kg)	17.8±2.4 <sup>a</sup>	22.0±1.6 <sup>a</sup>	8.2±1.0 <sup>a</sup>	9.8±1.2 <sup>a</sup>	7.8±1.0 <sup>a</sup>	4.0
JB (10 mg/kg)	28.4±1.0 <sup>a</sup>	31.2±1.5 <sup>a</sup>	10.0±0.7 <sup>a</sup>	12.2±0.9 <sup>a</sup>	9.8±0.7 <sup>a</sup>	8.0
JB (50 mg/kg)	37.2±2.6	40.6±2.8	14.4±1.5	20.2±1.6	16.4±0.7	52.0
HP (1 mg/kg)	9.2±1.1 <sup>a</sup>	8.6±0.7 <sup>a</sup>	4.6±1.0 <sup>a</sup>	6.4±1.0	6.0±2.3 <sup>a</sup>	0.0
FL (10 mg/kg)	19.0±0.7 <sup>a</sup>	22.2±1.2 <sup>a</sup>	8.0±0.7 <sup>a</sup>	10.6±1.3 <sup>a</sup>	8.4±1.4 <sup>a</sup>	8.0
MS (50 mg/kg)	10.4±0.5 <sup>a</sup>	10.8±0.7 <sup>a</sup>	5.2±0.6 <sup>a</sup>	7.8±0.4 <sup>a</sup>	5.6±0.8 <sup>a</sup>	4.0
PCPA (20 mg/kg)	61.2±2.5 <sup>a</sup>	65.8±1.0 <sup>a</sup>	24.2±1.5 <sup>a</sup>	40.0±3.5 <sup>a</sup>	26.8±1.6 <sup>a</sup>	100.0

Values represent the mean±SEM for six animals per group. <sup>a</sup>p<0.05 compared to control group (ANOVA followed by Tukey's post hoc test).

tation. The parameters assessed were the number of flight, upright defensive postures and submissive postures [4].

## Statistical analysis

Data were expressed as mean±SEM and were analyzed with Graph-Pad Prism software (version 4.00). Statistical analysis of data was done by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A level of p<0.05 was considered as statistically significant.

## Results

### Anti-aggressive effects of JB

The effects of JB on intruder- or isolation-evoked offensive aggression, as measured by the total number of attacks, aggressive postures, aggressive pursuits and tail rattling in mice, are shown in Tables 1–3). JB (5–10 mg/kg, p.o.) significantly (p<0.05) decreased these offensive

aggressive behaviors in comparison with control, which suggest anti-aggressive activity. Similar effects were observed in animals pretreated with HP (1 mg/kg, p.o.), as it significantly (p<0.05) decreased offensive aggressive behaviors (Tables 1 and 2). FL (10 mg/kg, p.o.), a 5-hydroxytryptamine (5-HT) reuptake inhibitor, significantly (p<0.05) reduced aggression but did not significantly (p>0.05) change the effect of JB (5 or 10 mg/kg) on aggression (Tables 1 and 2). However, PCPA, an inhibitor of 5-HT biosynthesis, heightened aggression and also reduced the anti-aggressive activity of JB (Tables 1 and 2). On the other hand, MS (50 mg/kg, p.o.), a 5-HT receptor antagonist, significantly (p<0.05) reduced the aggressive responses and enhanced the effect of JB on aggressive performance (Tables 1–3). As shown in Figures 1 and 2, JB (10 or 50 mg/kg, p.o.) did not significantly (p>0.05) inhibit the initiation of aggression, as measured by the latency to first attack. In contrast, HP (1 mg/kg, p.o.), FL (10 mg/kg) or MS (50 mg/kg) significantly (p<0.05) prolonged the latency to first attack, which indicates an inhibitory effect against the initiation of aggression, or to engage in a fight (Figures 1 and 2). However, PCPA (20 mg/kg) did not significantly

**Table 2** Effects of serotonergic agents on Jobelyn in resident-intruder aggression paradigm.

Treatment groups and dose	Frequency of attack	Tail rattling	Lateral threat	Pursuit frequency	Aggressive posture	Intruders with injury, %
JB (5 mg/kg)	17.8±2.4	22.0±1.6	8.2±1.0	9.8±1.2	7.8±1.0	4.0
JB (10 mg/kg)	28.4±1.0	31.2±1.5	10.0±0.7	12.2±0.9	9.8±0.7	8.0
JB (5 mg/kg)+FL	15.6±0.5	18.0±0.3	5.6±0.2	9.8±0.7	6.4±0.8	4.0
JB (10 mg/kg)+FL	21.0±1.9	24.8±1.5	7.6±0.8	12.2±0.7	8.4±0.9	4.0
JB (5 mg/kg)+PCPA	37.4±2.6 <sup>a</sup>	39.8±2.8 <sup>a</sup>	14.0±1.1 <sup>a</sup>	21.2±1.2 <sup>a</sup>	16.6±0.8 <sup>a</sup>	48.0
JB (10 mg/kg)+PCPA	52.2±1.2 <sup>a</sup>	54.2±1.0 <sup>a</sup>	25.2±1.1 <sup>a</sup>	33.0±1.2 <sup>a</sup>	27.4±1.2 <sup>a</sup>	65.0
JB (5 mg/kg)+MS	6.6±0.6 <sup>a</sup>	10.0±1.2 <sup>a</sup>	2.8±0.4 <sup>a</sup>	2.4±0.2 <sup>a</sup>	1.8±0.4 <sup>a</sup>	0.0
JB (10 mg/kg)+MS	9.2±0.7 <sup>a</sup>	8.4±0.5 <sup>a</sup>	4.8±0.4 <sup>a</sup>	4.4±0.5 <sup>a</sup>	3.2±0.4 <sup>a</sup>	0.0

Values represent the mean±SEM for six animals per group. <sup>a</sup>p<0.05 compared with JB-treated groups (ANOVA followed by Tukey's post hoc test).

**Table 3** Effect of Jobelyn on isolation-induced offensive behaviors in mice.

Treatment groups and dose	Frequency of attack	Tail rattling	Lateral threat	Pursuit frequency	Aggressive posture	Intruders with injury, %
Control	43.6±1.6	47.6±1.5	16.8±1.1	24.2±1.6	21.0±1.1	96.0
JB (5 mg/kg)	21.2±1.0 <sup>a</sup>	24.2±1.3 <sup>a</sup>	7.2±0.7 <sup>a</sup>	10.8±1.0	8.4±0.8 <sup>a</sup>	8.0
JB (10 mg/kg)	29.6±1.1 <sup>a</sup>	35.8±2.0 <sup>a</sup>	11.8±1.2 <sup>a</sup>	18.8±1.3	10.8±2.0 <sup>a</sup>	16.0
JB (50 mg/kg)	38.6±0.8	41.4±0.8	14.2±0.7	23.6±0.9	15.6±0.9 <sup>a</sup>	64.0
HP (1 mg/kg)	9.0±0.9 <sup>a</sup>	8.6±0.8 <sup>a</sup>	5.8±0.4 <sup>a</sup>	8.8±0.7	5.6±0.5 <sup>a</sup>	4.0
FL (10 mg/kg)	21.2±0.8 <sup>a</sup>	30.8±2.2 <sup>a</sup>	7.4±0.7 <sup>a</sup>	14.0±0.6	9.6±1.1 <sup>a</sup>	24.0
MS (50 mg/kg)	13.2±1.2 <sup>a</sup>	15.4±1.3 <sup>a</sup>	7.2±0.7 <sup>a</sup>	10.4±0.7	6.4±0.5 <sup>a</sup>	8.0
PCPA (20 mg/kg)	64.8±1.4	68.2±1.0	26.4±1.6	38.2±0.7	28.6±1.5	100.0

Values represent the mean±SEM for six animals per group. <sup>a</sup>p<0.05 compared with control (ANOVA followed by Tukey's post hoc test).

shorten the latency to attacks, suggesting no effect on motivation to fight (Figures 1–2). In the interaction studies, PCPA (20 mg/kg) but not FL (10 mg/kg) or MS (50 mg/kg) significantly (p<0.05) altered the effect of JB (5 mg/kg) on the latency to first attack (Figure 3).

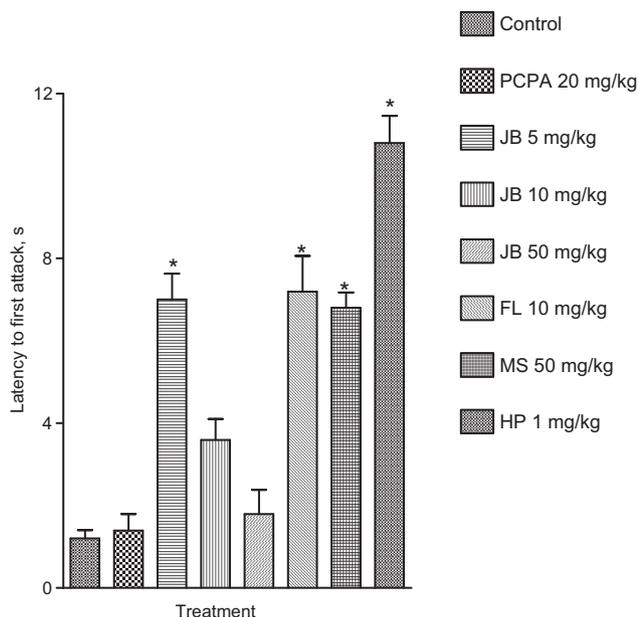
### Effect of JB on defensive behaviors

Table 4 showed that JB (5–50 mg/kg, p.o.) did not impair the defensive behaviors of the intruder animals, as it failed to significantly (p>0.05) alter the number of flights, upright defensive postures and submissive postures in

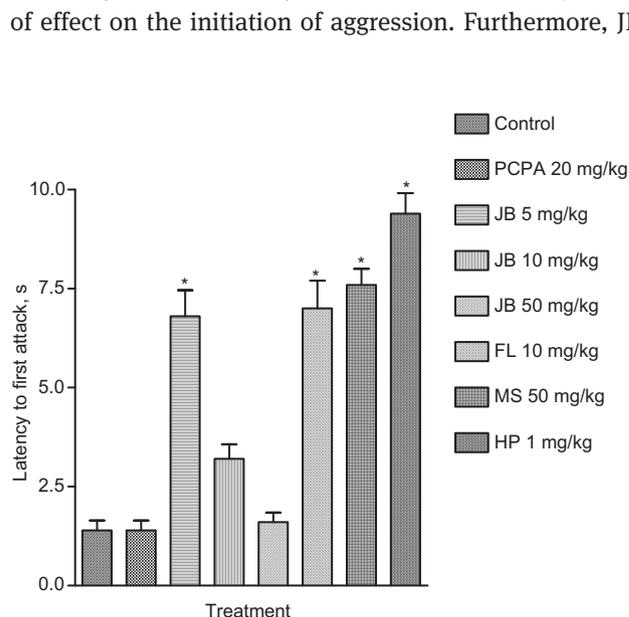
comparison with control. Similarly, FL (10 mg/kg, p.o.), but not HP (1 mg/kg), did not significantly (p>0.05) impair the defensive mechanisms of the intruder mice (Table 3).

## Discussion

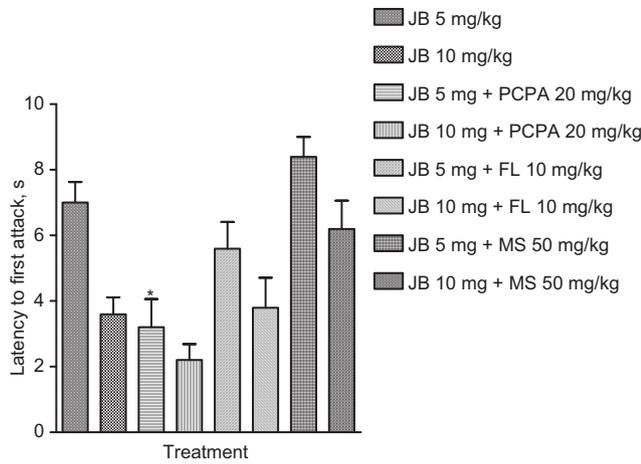
JB was found to reduce aggressive postures, lateral threats, tail rattling, aggressive pursuits and number of attacks, which suggest anti-aggressive property. The intensity of aggressive attack was also reduced, as shown by the decrease in the number of intruder animals with injury. However, at a dose of 10 or 50 mg/kg, it did not significantly alter the latency to first attack, indicating a lack of effect on the initiation of aggression. Furthermore, JB



**Figure 1** Effect of Jobelyn on latency to first attack in resident-intruder aggression paradigm in mice. Each value represents the mean±SEM (n=6 animals per group). \*p<0.05 compared with control (ANOVA followed by Tukey's post hoc test).



**Figure 2** Effect of Jobelyn on latency to first attack in isolation-induced aggression paradigm in mice. Each value represents the mean±SEM (n=6 animals per group). \*p<0.05 compared with JB-treated groups (ANOVA followed by Tukey's post hoc test).



**Figure 3** Effect of serotonergic agents on latency to first attack in resident-intruder aggression paradigm in Jobelyn-pretreated mice. Values represent the mean±SEM for six animals per group. \*p<0.05 compared with control (ANOVA followed by Tukey’s post hoc test).

did not impair the defensive behaviors of the animals, a property that may encourage its development as a therapeutic agent for the treatment of aggression. Aggression in animals possesses many of the characteristic features of violent behavior seen in humans, both in impulsiveness and in pathologies [18–19, 20]. Drugs with anti-aggressive property, such as antipsychotics, reduced offensive aggressive acts but also impaired the defense responses of the organisms [4, 21, 22]. Antipsychotic medications have been used for many years for ameliorating aggressive outbursts especially in patients with psychiatric disorders [4, 21, 22]. However, studies have shown that they lack specific anti-aggressive property [23, 24]. The primary effect of these drugs appears to be related to inhibition of the motivation to engage in a fight rather than the reduction in aggressive performance [4, 24]. In addition, they caused

severe sedation and catalepsy, which further limits their usefulness in the treatment of aggression [4, 24].

Although the neural mechanism that mediates aggressive behavior is yet to be clearly elucidated, reduced levels of 5-HT have been implicated as a major pathological basis of aggression and violent crimes [23, 25]. 5-HT has been shown to play a key role in the initiation and execution of aggression [23, 24]. Thus, research aimed at pharmacological elevation of serotonergic activity, as an approach to the treatment of violent behavior, has gained momentum over the years [4, 21, 22]. Such research efforts had yielded some serotonergic drugs like alnespirone, eltoprazine, anpirtoline, zolmitriptan, and sumatriptan that specifically reduce aggression without impairing other behavioral functions [4, 22]. The results of this study suggest that the effect of JB resembles those of serotonergic agents but may differ from haloperidol-like antipsychotic drugs. Generally, antipsychotic drugs reduce aggression or violent behavior but also impair the defensive behavior, thereby exposing the organisms to more attacks [4, 21, 22, 24]. The finding that JB did not impair the defensive mechanisms of the animals may suggest that its anti-aggressive action differs from those of antipsychotic agents like haloperidol.

Although further studies are required before any firm conclusion could be drawn on how JB reduces aggression, the present data suggest the involvement of a serotonergic pathway. Previous studies had shown that the depletion of serotonin levels by PCPA, an irreversible inhibitor of 5-HT synthesis, heightened aggressive behaviors in animals [26, 27]. Thus, the findings that the effect of JB on aggression was reduced by PCPA support the notion that the serotonergic system might be involved in its anti-aggressive activity. However, FL, a selective 5-HT reuptake inhibitor, did not influence the effect of JB on aggression. This finding suggests that the effect of JB on the 5-HT pathway may not be related to inhibition of the serotonin reuptake system. Both preclinical and clinical studies have shown that FL, an antidepressant drug, attenuated offensive aggression by increasing the brain levels of 5-HT [28, 29]. However, its clinical efficacy in aggression has been compromised by the incidence of severe adverse effects [30, 31].

It has been documented in literature that specific anti-aggressive agents (serenics) activate subtypes of 5-HT receptors to selectively reduce offensive aggression without impairing other behavioral functions [20]. An interaction study between JB and MS, a 5-HT receptor antagonist, was carried out to further investigate the probable mechanism underlying its anti-aggressive effect. MS was found to enhance the anti-aggressive property of JB, suggesting that the effect of JB on aggression might be mediated through 5-HT receptors. MS is primarily an

**Table 4** Effect of Jobelyn on defensive behaviors in mice.

Treatment	Dose, mg/kg	Number of flights	Number of submissive postures	Number of defensive postures
Control	–	27.2±1.6	7.8±0.8	28.2±1.6
JB	5	26.6±2.0	7.6±0.5	27.4±1.2
JB	10	24.2±1.1	7.2±0.7	25.8±1.6
JB	50	23.4±1.4	5.8±0.6	25.2±1.8
FL	10	22.0±1.6	5.6±0.5	24.2±1.1
HP	1	4.2±0.7 <sup>a</sup>	2.4±0.5	7.4±1.3 <sup>a</sup>

Values represent the mean±SEM for six animals per group. <sup>a</sup>p<0.05 compared with control group (ANOVA followed by Tukey’s post hoc test).

antagonist of several subtypes of 5-HT receptors especially the somatodendritic receptors, which function mainly as inhibitory autoreceptors and heteroreceptors [32]. By virtue of antagonizing these somatodendritic receptors, MS disinhibits the release of serotonin in various regions of the brain [32]. This may perhaps account for the marked anti-aggressive effect produced by MS in this study. Previous investigations had shown that pharmacological compounds that activate or antagonize somatodendritic receptor subtypes potently suppress the display of aggressive behavior in various animal species ranging from invertebrates, fish and rodents to primates, including man [21]. However, further studies are necessary to determine which of the 5-HT receptor subtypes are involved in the anti-aggressive effect of JB.

JB had been reported to contain various flavonoids such as polyphenols, proanthocyanidins, anthocyanidins, apigeninidins, luteolinidins, apigenins, luteolins and naringenins as the major phytochemical constituents [6, 7]. Preclinical studies have shown that these compounds exhibit a wide range of pharmacological effects [8–10, 33]. Furthermore, apigenin, luteolin and naringenin in particular have been shown to readily cross the blood brain barrier to exert various CNS activities including anti-amnesia, antidepressant, anti-neuroinflammation,

neuroprotection, and anti-oxidation [9, 10, 33]. However, it is yet to be determined whether these phytochemicals play any role in the anti-aggressive activity of JB.

## Conclusion

This study provides evidence that suggests that JB exhibited anti-aggressive activity, which appears to be mediated through a serotonergic pathway.

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## Conflict of interest statement

**Authors' conflict of interest disclosure:** The authors stated that there are no conflicts of interest regarding the publication of this article.

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