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Comparative Efficacy Study of the Antidepressant Effect of St. John's Wort (Hypericum Perforatum) and Escitalopram in Animal Models

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ABSTRACT

Background: The rise in interest for complementary and alternative therapies reflects a growing inclination towards natural remedies for health management. Despite the proven effectiveness of conventional antidepressant drugs, their association with adverse effects limits their use. The search for alternative drugs with minimal or no adverse effects has necessitated the interest in St. John's Wort (SJW) (*Hypericum perforatum*).
Aim and Objectives: The study aims to compare the effects of SJW with escitalopram in treating depression in animal models.
Materials and Methods: The antidepressant effect of escitalopram (1-3 mg/kg) and SJW (10-30 mg/kg) were evaluated in rats and mice using the forced swim and tail suspension test. Chronic forced swim tests involve repeated acute tests over 7 days. The experiment involved 50 rats and 25 mice. Immobility time was measured and compared using inferential statistical analysis.
Results: Low doses of escitalopram and SJW had similar behavioral effects in the forced swim and tail suspension tests. However, only higher doses of escitalopram and SJW showed significant antidepressant effects compared to the control group. These effects were not sustained after seven days of chronic treatment.
Conclusion: The study demonstrates that SJW and escitalopram have comparable antidepressant effects in behavioral models. In contrast to acute administration, the chronic administration for seven days does not show a significant impact.

INTRODUCTION

Depression is a widespread chronic mental illness that is characterized by sadness, loss of interest, feelings of low self-worth, disturbed sleep, feelings of tiredness, and poor concentration.[1, 2] Depression is different from regular mood changes and feelings about everyday life. It is a complex disorder that takes an enormous toll on the health of an individual.[3] It can occur at any age from childhood to late adult life and has a tremendous cost to the society as it causes severe distress and disruption of life and, if left untreated, can be fatal.[4] Depression can be long-lasting or recurrent, substantially impairing the ability to function at work or school or cope with daily life. At its most severe form, depression can lead to suicide.[2] This condition affects around 320 million people worldwide and 29 million people in Africa.[5]

The pathophysiology of depression remains incompletely understood. However, decreased functioning of monoaminergic neurotransmitters (serotonin, norepinephrine, dopamine, or all of these neurotransmitters) in the brain has traditionally been implicated, with presumed correction of these functional deficits in response to effective antidepressant therapies.[6]

Antidepressants are drugs used in the treatment of depression. These drugs mediate their therapeutic effects by increasing the levels of monoaminergic neurotransmitters in the synaptic junction, thereby alleviating symptoms of depression. Current antidepressant medications that are commonly prescribed for the treatment of Major Depressive Disorder (MDD) fall into one of the following classes; tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), and atypical antidepressants.[7] Escitalopram, although classified as an SSRI, can be further classified as an allosteric serotonin reuptake inhibitor because of its allosteric properties. According to *in vitro* studies, serotonin reuptake transporter (SERT) has at least two binding sites; a primary, high-affinity allosteric site that inhibits serotonin (5-HT) reuptake and a secondary, low-affinity allosteric site that controls the binding of ligands to the primary site. The main and allosteric sites are both occupied in the absence of escitalopram.[8] Escitalopram has been extensively compared with other antidepressants including SSRIs such as paroxetine and sertraline in meta-analyses. An analysis of 10 studies involving a total of 2687 MDD patients up to 2004, showed that escitalopram has a significantly higher overall treatment effect, response rate, and remission rate (compared with all comparators including paroxetine and sertraline).[9]

Although the current antidepressant drugs are effective and well tolerated, patients are non-compliant with these drugs.[10] Premature discontinuation was found to be caused by a number of factors, with adverse effects being the most frequent one.[10] A study showed that 28% of patients stopped taking antidepressants in the first month of treatment and 44% stopped by the third month due to so many factors including the adverse effects of the drugs, no noticeable effect of the drugs within a month of treatment, and continuous use of the drugs even when feeling better.[11] Other studies involving TCAs and SSRIs reported dropout rates of 7% to 44% and 7% to 23%, respectively majorly as a result of adverse effects.[10]

In 45% of studies when herbal drugs were used for the treatment of depression, the primary adverse effects of synthetic antidepressants- headaches, sexual dysfunction, addiction, seizures, and suicide- were minimized.[12] In the treatment of different disorders, including depression, medicinal plants are valuable alternatives to orthodox medicines. Antidepressant effects of SJW have been attributed to its active components, hyperforin and hypericin.[13] Evidences have also shown the therapeutic effects of SJW for different psychiatric conditions, behavioral and mood disorders such as post-traumatic stress disorder (PTSD), attention-deficit hyperactivity disorder (ADHD), anxiety disorders and obsessive-compulsive disorder (OCD).[14]

Considering the increased global interest in the use of herbal medicines and products for treating chronic health conditions[15] and the reported efficacy of SJW for the treatment of depression, the efficacy and safety of this herbal product has not been compared with those of modern antidepressant such as escitalopram. Consequently, this study aimed to compare the efficacy of SJW (*Hypericum perforatum*) and escitalopram in the treatment of depression in animal models.

MATERIALS AND METHODS

Materials and Experimental Procedures

Animals

Experiments were carried out on female Sprague–Dawley albino rats and mice. The rats were weighed at their arrival in the vivarium. The weight of the Rats ranged from 80g-100g and the weight of the mice ranged from 8g-10g. Animals were housed five per cage and kept in a controlled environment maintained at a constant temperature and humidity, with free access to food and water. A 12 h inverted light /dark cycle (7. 00 a. m. lights off, 7. 00 p. m. lights on) was used because rats are more active during the dark phase. All rats were allowed at least one week of habituation to the animal colony before experimental procedures began. At the beginning of the experimental procedures the rats were weighed. The average weight of the rats and mice recorded were 125g and 18.05g, respectively at the initiation of the experimental procedures.

The procedures used in the study were in strict accordance with the guidelines of the National Institute of Health on the use and care of laboratory animals.[16]

Drugs

Escitalopram was obtained from Aurobindo Pharma - Milpharm Ltd (South Ruislip, Middlesex) and St. John's Wort, a processed and packaged extract of *Hypericum perforatum* [aerial], standardized to contain 0.3% Diathrones, measured as Hypericin by UV-Vis testing, was obtained from Puritan's Pride (Oakdale, NY, USA).

Drug regimen

All drugs were freshly prepared before use and administered in a volume of 1ml/kg. The drug doses were estimated based on the base weight and represented in milligrams per kilogram. All substances were administered orally using the gavage technique, based on the following reasons: (1) both the Hypericum extract and hypericin are barely soluble in aqueous solvents and must be administered

as a suspension[17]; (2) the Hypericum extract suspension has a pH of 4-5 (for intraperitoneal injections, solutions should have a pH of 7.0-7.5[17]; and (3) while intraperitoneal injections were contraindicated for chronic application[17], gavage was less stressful for animals than intraperitoneal injection if done correctly.[17] For technique consistency, escitalopram was administered via gavage.

Experimental Procedures

Acute Forced Swim Test

The acute Forced Swim Test (aFST) exists on the concept that when an animal is placed in a container filled with water, it will first try to escape but will gradually demonstrate immobility, which may be interpreted as a sign of behavioral despair. The forced swim stress is, thereafter, a viable animal model of depression that mimics the behavioral despair paradigm. The rats were grouped into five subgroups, each consisting of five animals, and were administered different treatments: oral doses of escitalopram at 1mg/kg and 3mg/kg, oral doses of SWJ at 10mg/kg and 30mg/kg, and a control group receiving an oral dose of 3ml/kg Distilled Water. Each animal was treated one hour before the initiation of the procedure, which was carried out as described by Porsolt *et al.* (1978).[19 18] There were two sessions, 24 hours apart. The first session was the pre-test stage (10 min), and the second session was the test stage (5 min). In order for the rats to get acclimatized to the testing environment, the animals were transported in their home cages at least 30 mins prior to behavioral testing to the waiting room. A 2000 ml beaker (height: 19.3 cm, diameter: 13.1 cm) was used in place of the vertical plexiglass cylinders (height: 40 cm; diameter: 18 cm) used in a previous study.[18] It was filled with tap water at 23±1°C, and the water depth adjusted according to the rat's size, preventing it from touching the bottom of the container with its hind limbs. Each beaker was marked with the animal number for identification later during footage viewing. Each rat was placed in the water-filled cylinder for 10 mins. After 10 mins had elapsed, the rat was removed from the container and wiped with towels until dried. The rat was closely and continuously monitored during recovery. When a rat stayed floating in the water in an upright position, making only slight movements to keep its head above the water, it was considered immobile. Twenty-four hours later, for the second session, the rats again acclimatized to the testing environment and transported to the waiting room. The beakers were again filled with tap water at 23±1°C, and the water depth adjusted, based on the rat's size. Each beaker was marked with the animal number. The video camera was turned on, and the rat placed in the water-filled beaker for 5 mins. After 5 mins, the camera was turned off, the rat removed from the beaker and wiped with towels until dried. The rat was closely and continuously monitored during recovery.

Chronic Forced Swim Test

The chronic Forced Swim Test (cFST) exists on the same concept described in the aFST. However, majority of depression disorders in humans are caused by chronic stress, not acute stress. This animal model of depression therefore closely resembles the development of human depression. The cFST is induced by repeating the forced swim test as described in the acute forced swim test for 7 days.

The rats were grouped into five subgroups, each consisting of five animals, and administered different treatments: oral doses of escitalopram at 1mg/kg and 3mg/kg, oral doses of SJW at 10mg/kg and 30mg/kg, and a control group receiving an oral dose of 3ml/kg distilled water. Each animal was treated one hour before the initiation of the procedure, which was carried out as described in a previous study for 7 days.[18]

Tail Suspension test

The Tail Suspension Test (TST) operates under the premise that an animal suspended by its tail with a tape, in such a position that it cannot escape or hold on to nearby surfaces, would attempt to escape at first, but will eventually show signs of immobility that could be interpreted as a sign of behavioral despair.

The mice were grouped into five subgroups, each consisting of five animals, and administered different treatments: oral doses of escitalopram at 1mg/kg and 3mg/kg, oral doses of SJW at 10mg/kg and 30mg/kg, and a control group receiving an oral dose of 3ml/kg distilled water. Each animal was treated an hour before the initiation of the procedure, which was carried out as described in a previous study.[19] In order for the rats to get acclimatized to the testing environment, the animals were transported in their home cages at least 30 minutes prior to behavioral testing to the waiting room. For the test, the mice are suspended on the edge of a rod 40 cm above the table top by adhesive tape placed approximately 1 cm from the tip of the tail. The mice were placed approximately 30 cm away from the nearest object to avoid climbing. The duration of immobility was recorded for a period of 6 mins with 1 min for acclimatization and the duration of immobility was measured within 5 mins. Mice are considered immobile when they hang passively and completely motionless. The video camera was turned on before suspending each mouse. After 6 mins, the camera was turned off, and the mice brought down and placed back in their cages. The mice were closely and continuously monitored during recovery from stress.

Data Analysis

Statistical analysis of the data was carried out using a Graphpad statistical software, version 8.0.2 for windows (Graphpad Software, Inc La Jolla, CA, USA). Data were expressed as Mean ± Standard Error of Mean (SEM) and were represented as bar charts on each graph. The time obtained for each experimental procedure were compared using one-way Analysis of variance (ANOVA), followed by post-hoc Tukey's test.

RESULT

Acute Forced Swim Test

The activities of acute pre-treatment with SJW and Escitalopram in the forced swim test are shown in Table 1.

Acute pre-treatment with escitalopram (1 mg/kg and 3 mg/kg) induced a dose-dependent decrease in immobility time (Table 1). At 3 mg/kg reduction of immobility time was statistically significant when compared with the control group (150.8 ± 6.4 seconds vs. 195.8 ± 9.4 seconds, **p< 0.01), whereas, 1 mg/kg of escitalopram produced a less pronounced reduction in immobility time (174.4 ± 6.2 seconds) compared with the control group (195.8 ± 9.4 seconds), which was not statistically significant (p= 0.149).

Acute pre-treatment with SJW (10 mg/kg and 30 mg/kg), like escitalopram, shows a dose-dependent decrease in immobility time (Table 1). There was a statistically significant reduction in immobility time at 30 mg/kg of SJW compared with the control (146.2 ± 8.2 seconds vs. 195.8 ± 9.4 seconds, **p= 0.003), whereas, 10 mg/kg of SJW produced a less pronounced reduction in immobility time compared to the control group, which was not statistically significant (173.2 ± 7.2 seconds vs. 195.8 ± 9.4 seconds, p = 0.173).

Table 1: Effect of acute pre-treatment of escitalopram and SJW on immobility time for rats undergoing acute forced swim test

Treatment group	Dose and route of administration	Immobility time (seconds)	*p* value
Control (distilled water)	3 ml/kg, *p.o*	195.8 ± 9.4	-
Escitalopram (ESC)	1 mg/kg, *p.o*	174.4 ± 6.2	0.149
Escitalopram (ESC)	3 mg/kg, *p.o*	150.8 ± 6.4	0.003**
H. perforatum (SJW)	10 mg/kg, *p.o*	173.2 ± 7.2	0.173
H. perforatum (SJW)	30 mg/kg, *p.o*	146.2 ± 8.4	0.003**

Note: The values of immobility time in seconds are expressed as Mean ± SEM.

***p*-value was statistically significant when the test groups were compared with the control using one-way ANOVA test, followed by post-hoc Tukey's test.

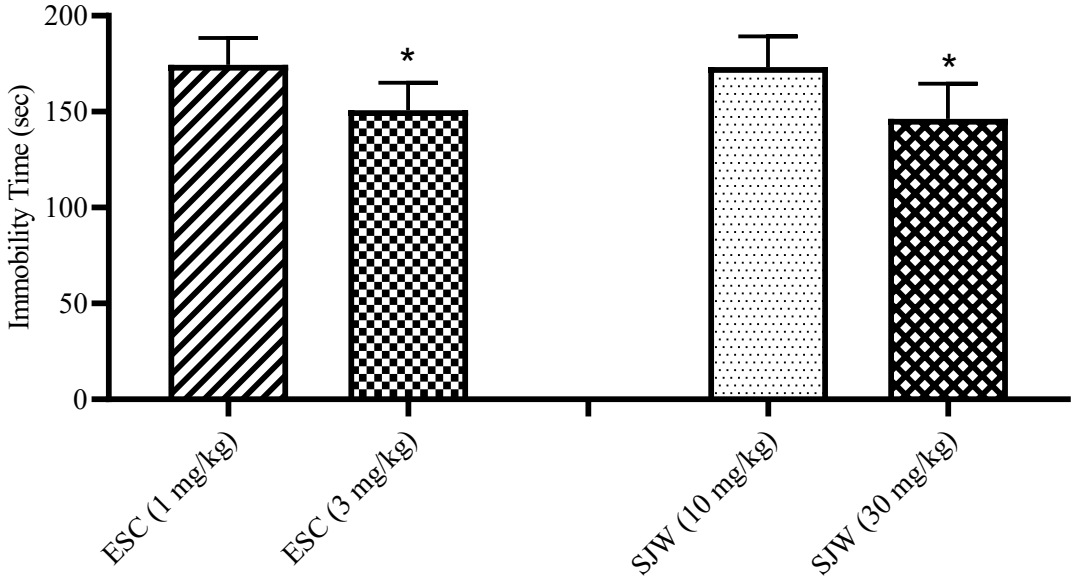

Figure 1: Comparing the effects of acute pre-treatment with low and high doses of escitalopram as well as low and high doses of SJW on the immobility time in acute forced swimming model depression in rats

Each column represents the Mean ± SEM for five animals per group (n=5). There was a statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg and at a low dose of 1 mg/kg (*p =0.030). There was also a statistically significant difference in the height of the bar charts for SJW at a high dose of 30 mg/kg and at a low dose of 10 mg/kg (*p =0.038)

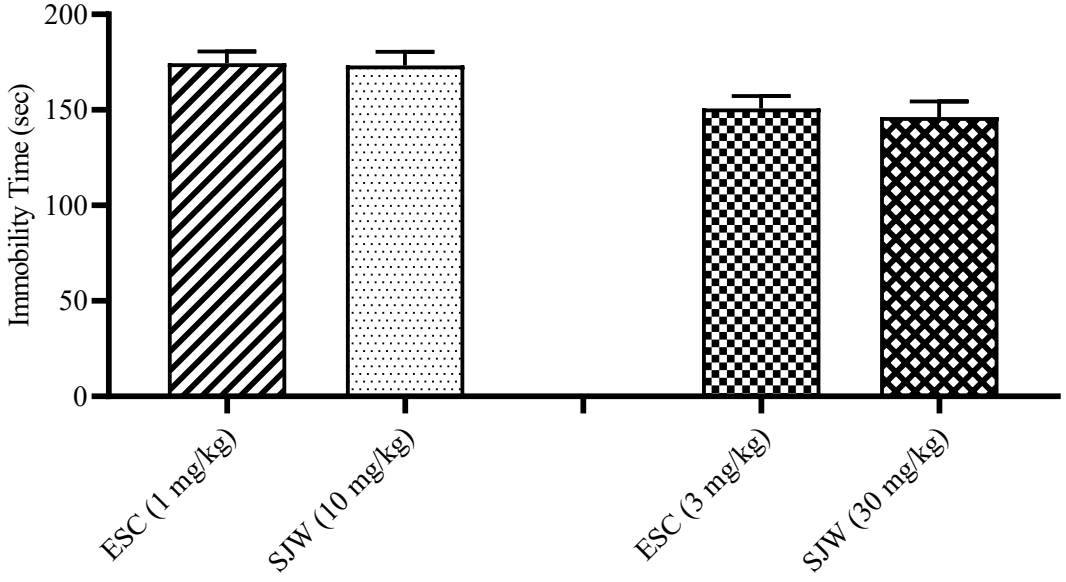

Figure 2: Comparing the effects of acute pre-treatment with low doses of escitalopram and SJW as well as high doses of escitalopram and SJW on the immobility time in acute forced swimming model depression in rats

Each column represents the Mean ± SEM for five animals per group (n=5). There was no statistically significant difference in the height of the bar charts for escitalopram at a low dose of 1 mg/kg and SJW at a low dose of 10 mg/kg (p = 0.903). There was also no statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg and SJW at a high dose of 30 mg/kg (p = 0.670)

Chronic Forced Swim Test

The activity of acute and repeated treatment of escitalopram and SJW on repeated exposure to stress (forced swimming) for 7 days are shown in Table 2. Data for Day 7 were compared with those for Day 1 for each treatment. Furthermore, data for the control were compared with those for each treatment at Day 7.

Acute (Day 1) and chronic (Day 7) pre-treatment with escitalopram (1mg/kg and 3mg/kg) and SJW (10mg/kg and 30mg/kg) induced a slight decrease in immobility time when the data were compared (Table 2). There was no statistically significant reduction in immobility time on Day 7 compared with Day 1 for the control and all treatment doses. However, when data for the control group and various treatment groups were compared at Day 7, there was statistically significant reduction in the immobility time from 191.8 ± 9.1 seconds for control to 146.0 ± 10.1 seconds for 3 mg/kg escitalopram (p= 0.006). Similar statistically significant reduction in the immobility time from 191.8 ± 9.1 seconds for control to 135.6 ± 10.6 seconds for 30 mg/kg SJW (p= 0.002) was observed (Table 2).

Table 2: Effect of acute and repeated pre-treatment of escitalopram and *H. perforatum* (SJW) on immobility time in chronic forced swim test in rats

Treatment	Dose and route of administration	Immobility time (second)		[a]p value	[b]p value
		Day 1	**Day 7**		
Control (distilled water)	3 ml/kg; *p.o*	198.4 ± 8.4	191.8 ± 9.1	0.992	
Escitalopram (ESC)	1 mg/kg; *p.o*	176.4 ± 5.5	171.2 ± 5.4	0.997	0.480
Escitalopram (ESC)	3 mg/kg; *p.o*	153.6 ± 8.7	146.0 ± 10.1	0.984	*0.006
H. perforatum (SJW)	10 mg/kg; *p.o*	173.2 ± 8.3	165.8 ± 9.1	0.992	0.353
H. perforatum (SJW)	30 mg/kg; *p.o*	141.8 ± 8.6	135.6 ± 10.6	0.996	*0.002

Note: The values of immobility time in seconds are expressed as Mean ± SEM. [a]p-value compares the mean ± SEM value at Day 1 to mean ± SEM at Day 7 for each treatment. [b]p-value compares the mean ± SEM value of the control with the mean ± SEM for each treatment at Day 7. *p-value was statistically significant when the test groups were compared with the control using one-way ANOVA test, followed by post-hoc Tukey's test.

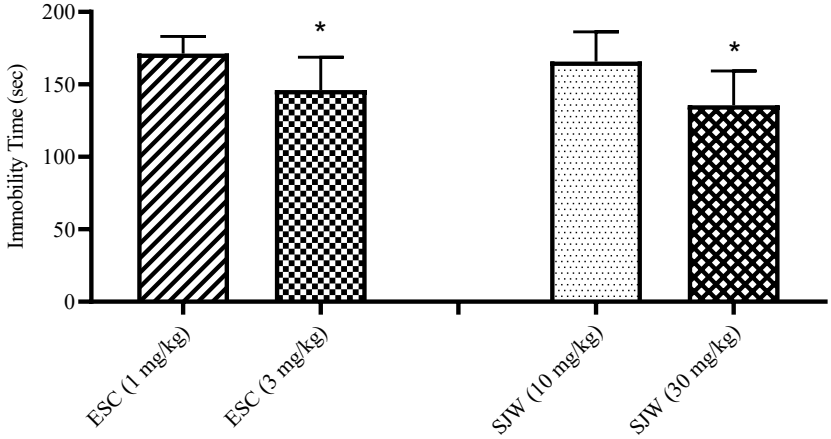

Figure 3: Comparing the effects of repeated pre-treatment with low and high doses of escitalopram as well as low and high doses of SJW on the immobility time in chronic forced swim test model depression in rats. Each column represents the Mean ± SEM for five animals per group (n=5). There was a statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg and at a low dose of 1 mg/kg (*p =0.039). There was also a statistically significant difference in the height of the bar charts for SJW at a high dose of 30 mg/kg and at a low dose of 10 mg/kg (*p =0.025)

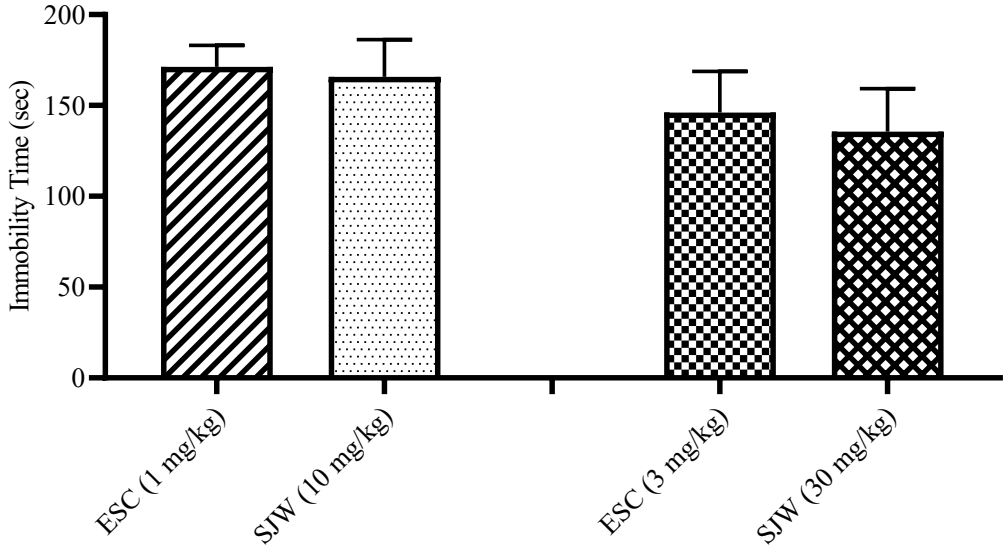

Figure 4: Comparing the effects of chronic pre-treatment with low doses of escitalopram and SJW as well as high doses of escitalopram and SJW on the immobility time in chronic forced swim test model depression in rats. Each column represents the Mean ± SEM for five animals per group (n=5). There was no statistically significant difference in the height of the bar charts for escitalopram at a low dose of 1 mg/kg and SJW at a low dose of 10 mg/kg (p = 0.974). There was also no statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg and SJW at a high dose of 30 mg/kg (p = 0.847)

Tail Suspension Test

The activities of acute pre-treatment with SJW and escitalopram in the tail suspension test are shown in Table 3. Acute pre-treatment with escitalopram (1 mg/kg and 3 mg/kg) induced a dose-dependent decrease in immobility time (Table 3). At 3 mg/kg reduction of immobility time was statistically significant when compared with the control group (216.2 ± 5.4 seconds *vs*162.6 ± 10.3 seconds, p= 0.004), whereas, 1 mg/kg of escitalopram produced a less pronounced reduction in immobility time (189.6 ± 11.1 seconds) compared with the control group (216.2 ± 5.4 seconds), which was not statistically significant (p= 0.148). The decrease in immobility time was similar to that in the forced swim test.

Acute pre-treatment with SJW (10 mg/kg and 30 mg/kg), like escitalopram, shows a dose-dependent decrease in immobility time (Table 3). There was a statistically significant reduction in immobility time at 30 mg/kg of SJW compared with the control (146.2 ± 8.2 seconds vs. 195.8 ± 9.4 seconds, $^{**}p< 0.01$), whereas, 10 mg/kg of SJW produced a less pronounced reduction in immobility time compared with the control group, which was not statistically significant (173.2 ± 7.2 seconds vs. 195.8 ± 9.4 seconds, p= 0.173).

Table 3: Effect of acute pre-treatment of Escitalopram and *H. perforatum* (SJW) on immobility time in tail suspension test in mice

Treatment	Dose and Route of Administration	Immobility time (sec)	*p value*
Control (Distilled water)	3 ml/kg; *p.o*	216.2 ± 5.4	-
Escitalopram (ESC)	1 mg/kg; *p.o*	189.6 ± 11.1	0.148
Escitalopram (ESC)	3 mg/kg; *p.o*	162.6 ± 10.3	0.004**
H. perforatum (SJW)	10 mg/kg; *p.o*	185.0 ± 9.7	0.043*
H. perforatum (SJW)	30 mg/kg; *p.o*	160.0 ± 8.4	0.001***

Note: The values of immobility time in seconds are expressed as Mean ± SEM.
. *p< 0.05, **p<0.01, ***p<0.001 was statistically significant when the test groups were compared with the control using one-way ANOVA test, followed by post-hoc Tukey's test.

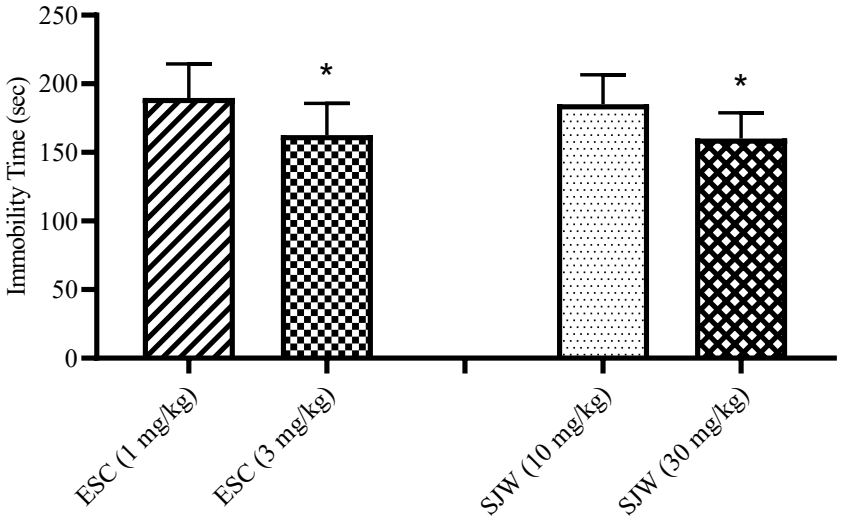

Figure 5: Effects of acute pre-treatment with high and low doses of escitalopram as well as high and low doses of SJW on the immobility time in tail suspension test in mice. Each column represents the Mean ± SEM for five animals per group (n=5). There was a statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg compared with low dose of 1 mg/kg (p =0.040). There was a similar trend at a high dose of SJW (30 mg/kg) compared to its low dose (10 mg/kg) (p =0.046).

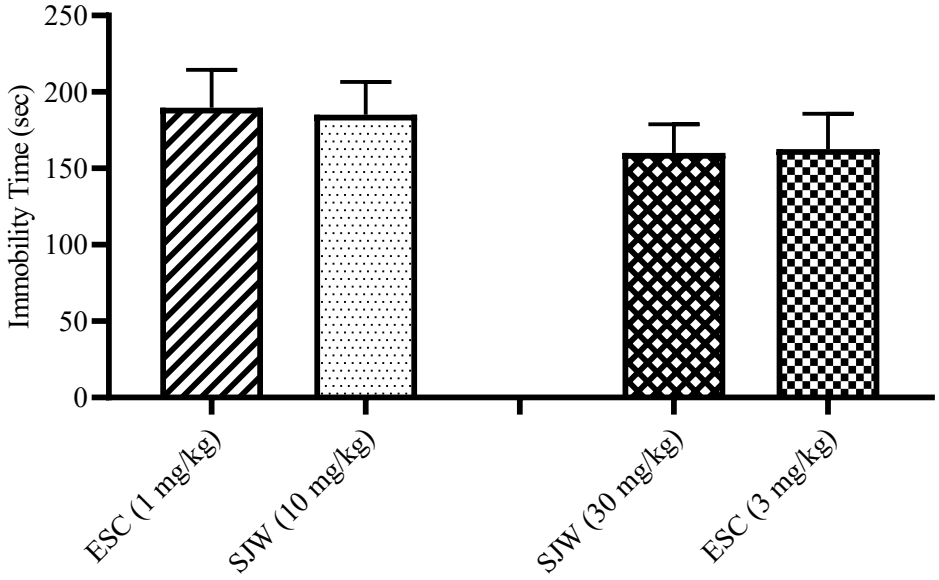

Figure 6: Effects of acute pre-treatment with low doses of escitalopram and SJW on the immobility time in tail suspension test in mice. Each column represents the Mean ± SEM for five animals per group (n=5). There was no statistically significant difference in the height of the bar charts for escitalopram at a low dose of 1 mg/kg compared with SJW at a low dose of 10 mg/kg (p = 0.763). There was a similar trend of no statistically significant difference in the height of the bar charts for escitalopram at a high dose of 3 mg/kg compared with SJW at a high dose of 30 mg/kg (p = 0.850).

DISCUSSION

The results from this study shows that oral administration of high doses of escitalopram and SJW are effective in producing significant anti-depressant effects in a dose-dependent manner, evidenced by a statistically significant decrease in the immobility time in acute forced swim test for rats. Similar findings have been reported in a study evaluating the antidepressant effects of an extract of *Capparis thonningii* Schum and imipramine; a tricyclic antidepressant (TCA).[20]

Our results are also in tandem with the findings from another study evaluating the antidepressant and anxiolytic effects of escitalopram in rats.[21] Using the forced swim test and the elevated plus-maze test in rats, Kaminska & Rogoz (2016) demonstrated that escitalopram at doses of 2.5 or 5 mg/kg evoked dose dependent antidepressant-like effect in the forced swim test, which was similar to our findings. Unfortunately, the low dose of 1 mg/kg escitalopram was not evaluated in the comparative study.[22] [21] However, these authors demonstrated that risperidone, at low doses (0.05 or 0.1 mg/kg), enhanced the antidepressant activity of 1 mg/kg escitalopram by increasing the swimming time and decreasing the immobility time in the studied rats. This suggests that at 1 mg/kg the antidepressant effect of escitalopram is unnoticeable and insignificant in rats. Escitalopram, being an SSRI, has a significant selectivity and dosage-dependent inhibitory effects on the human serotonin transport system; thus, making it a valuable and recommended treatment option for individuals with major depressive disorder.[22]

SJW has been reported to act by biochemical mechanisms similar to the TCAs or SSRIs.[24] [23] Using the forced swim test, some researchers reported that 30-90 mg/kg of *H. perforatum* extract (SJW) caused a dose dependent reduction in immobility time in rats with maximal effect being observed at 90 mg/kg.[24] [23] Although the rats in our study were administered 10 and 30 mg/kg of SJW orally, the high dose of 30 mg/kg produced similar antidepressant effects seen in ta previous study where the animals were injected SJW intraperitoneally.[23] This suggests that the antidepressant effect of SJW is independent of route of administration. In another study evaluating the antidepressant effect of SJW in rats, using an acute form of escape deficit induced by an unavoidable stress, reported that escape deficit significantly reverted following treatment with 250, 500, 1000, and 1500 mg/kg of SJW.[24] Even though the doses of SJW administered to the rats in this study are far higher than the doses use in our study, similar results were obtained at 30 mg/kg of SJW. It is understandable that hydro-alcoholic extract of *H. perforatum* used in the comparative study may likely contain little active principle(s) with a potent antidepressant activity; thus accounting for the high doses of the extract used in the study.[24] In contrast, we used the already processed and packaged capsule form of SJW that was free of non-active ingredients;

thus explaining the low dose of 10-30 mg/kg administered to animals in our study.

In a systematic review of SJW for major depressive disorder (MDD) in humans, it was reported that SJW monotherapy for mild and moderate depression is superior to placebo in improving depression symptoms but not significantly different from other antidepressant medications. This further lends credence to the antidepressant activity of SJW demonstrated in our study.[25]

The tail suspension test is an alternative animal model for assessing acute effect of antidepressant drugs in animals. Findings from this test are often similar to that of the forced swim test. We observed a statistically significantly reduced immobility time for mice administered 3 mg/kg escitalopram compared with the control group. However, at 1 mg/kg dose of escitalopram, the immobility time did not statistically significantly differ from that of the control. These findings were similar to those observed in the forced swim test. While the former test involved the use of rats, the latter involved mice as the animal model. A recent study determined the effect of simultaneous testing of two mice in the tail suspension test and forced swim test and observed that the environment of these behavioral experiments investigating depression-like behavior in mice could cause a difference in depression-like behavior.[31 30] These results suggested the importance of describing in detail the experimental method used for such behavioral testing. However, this subtle difference in the results of tail suspension test and forced swim test did not undermine the similarity in the immobility time observed in our studies testing the acute antidepressant effects of 1-3 mg/kg of escitalopram and 10-30 mg/kg of SJW.

Our study demonstrated a statistically significant difference in the immobility time for pre-treated mice with 1 mg/kg and 3 mg/kg of escitalopram in the tail suspension test. Similar findings were observed when comparing the immobility time for pre-treated mice with 10 mg/kg and 30 mg/kg of SJW in the tail suspension test. These findings are similar to the results of other studies involving higher doses of escitalopram (2.5-5 mg/kg)[21] and SJW (30-90mg/kg)[23] or (250-1500 mg/kg).[24] These findings underscore the significance of increasing the doses of antidepressant drugs to achieve a significant clinical effect in patients with major mood disorders when unresponsive to low doses. The doses of both escitalopram (1-3 mg/kg) and SJW (10-30 mg/kg) administered to the rats in our study are too low compare to the doses required to give noticeable clinical effects in human. An early study had shown a significant correlation between dosage at which antidepressants are effective clinically and which produce behavioral effects in the forced swim test.[26]

We also observed no statistically significant difference in the immobility time of pre-treated mice with 3 mg/kg escitalopram and 30 mg/kg of SJW in the tail suspension test. Considering both drugs to have similar SSRIs mechanism of action, their respective doses are considered to have similar efficacy. A previous double-blind randomized study comparing the antidepressant effects of SJW extract and Sertraline, an SSRIs, observed similar effects in the treatment of mild to moderate depression [27] Another randomized controlled trial study had failed to demonstrate the efficacy of SJW in moderately severe MDD possibly due to low assay sensitivity of the trial.[28] The study, however, acknowledged the efficacy of SJW based on its ability to obviate symptoms of depression in the patients.

The chronic forced swim test in rats demonstrated no statistically significant difference in the Immobility time for days 1 and 7 following pretreatment with 1-3 mg/kg of escitalopram or 10-30 mg/kg of SJW. Although earlier studies have examined the effects of antidepressant drugs in the forced swim test with chronic treatment protocols spanning 7-21 days, statistically significant effects were observed after ≥2 weeks of treatment.[29, 30] However, we did not treat the rats beyond 7 days in our study, thus; explaining why no significant effectiveness of 3mg/kg of escitalopram and 30 mg/kg of SJW was observed in our chronic treatment study. During a 5-min forced swimming testing period, after chronic administration of a SSR, fluoxetine, at various doses of 1, 2, and 5 mg/kg for 14 days, a statistically significant decrease in immobility time was observed at 5 mg/kg dose compared to the control group.[31] The short duration of chronic treatment and use of low doses of escitalopram and SJW in our study may further explain the contrast between our findings and those from previous studies,[32, 33] Although antidepressant drugs given to animals can change their behavior in the forced swim test when given acutely or subacutely, clinical folklore indicates that antidepressants produce therapeutic effects in human depressed patients only after chronic administration for several weeks.[33] This inconsistency between laboratory findings and clinical practice is perhaps a major limitation of the forced swim test's validity as a model of depression.

CONCLUSION

Low doses of escitalopram and SJW produced similar dose dependent behavioral patterns in the acute treatment forced swim test and tail suspension test at 3 mg/kg and 30 mg/kg, respectively, but no such observation after chronic administration for 7 days. The results strengthen the validity of the forced swim test and tail immersion test as a behavioral screen for antidepressant drugs. The efficacy of escitalopram

and SJW as antidepressants is comparable at 3mg/kg and 30 mg/kg, respectively. Further studies for chronic treatment beyond 7 days are required to validate our present findings.

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