Original Article

Antiaggressive activity of hyperforin: A preclinical study

Navneet Kumar, Gulam Mohammed Husain, Paras Nath Singh, Vikas Kumar*

Neuropharmacology Laboratory, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, India.

ABSTRACT: The aim of present study was to investigate the *in vivo* antiaggressive activity of hyperforin using defensive and offensive behavioral models in rodents. Adult male rats and mice were used for the present study. Animals were divided into three groups, with 6 animals in each. Lorazepam was used as standard antiaggressive agent. Animals were treated once daily, for seven consecutive days. Hyperforin (10 mg/kg, *i.p.*) was injected in a volume of 10 mL/kg for seven consecutive days. Standard group was treated with lorazepam (2.5 mg/kg, *i.p.*). The control group was treated with equal volume of vehicle (0.3% carboxy methyl cellulose suspension, *i.p.*). Animals were screened for aggressive behavior before dividing them into groups. At the end of 7 days, experiments were performed. Antiaggressive activity was evaluated using following validated models of aggression *viz.* foot shock-induced aggression, isolation-induced aggression, resident-intruder aggression and water competition test. Hyperforin treatment significantly ($p < 0.001$) reduced various aggressive parameters *viz.* latency to first attack and number of fights in isolation induced aggression, resident intruder aggression and foot shock induced aggression tests. In water competition test, hyperforin treatment significantly ($p < 0.001$) reduced the duration of water consumption and frequency of water spout possession. We conclude that hyperforin, the major lipophilic compound contained in extracts of *Hypericum perforatum*, is thus responsible for the antiaggressive activity, suggesting the therapeutic potential of hyperforin as an antiaggressive agent.

Keywords: Aggression, hyperforin, foot-shock, isolation-induced, resident-intruder

**Address correspondence to:*
Dr. Vikas Kumar, Reader in Pharmacology, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi 221 005, India.
e-mail: vikas.phe@itbhu.ac.in

1. Introduction

Aggression is a significant public health problem that has received limited attention. Many psychiatric disorders (*e.g.*, personality disorders, schizophrenia and bipolar disorder) are characterized by impulsive aggressive behavior, which often brings patients with psychiatric disorders to the attention of medical and forensic systems (*1*). Human aggression is defined as behavior directed towards another individual carried out with the proximate intent to cause harm. Pharmacological treatment of aggression poses several challenges. Although the agents that have been used successfully in the clinic or in trials encompass nearly the full range of psychotropic medications, from antidepressants and neuroleptics to mood stabilizers and even β-blockers, there is a huge need for psychotropic drugs, specifically influencing aggression, without interfering with other important modalities. The drugs used clinically as antiaggressive are not at all specific for aggression but induces sedation, motor disturbances or other unwanted effects (*2*).

Recent studies have expanded the list of neurotransmitters, hormones, cytokines, enzymes, growth factors, and signaling molecules that influence aggression (*3*). Nevertheless, the prevalence of aggressive and violent behavior today is sufficient to make it a social problem worthy of attention around the world. The behavioral biology of mouse aggression offers insights to understanding the neurobiological and molecular mechanisms mediating behavior in social conflict (*4*).

There is a growing increase in the popularity of herbal medicines, and one of the most popular herbal remedies is the perennial herb, St. John's wort (SJW), consisting of the leaves and the flowering top of *Hypericum perforatum* L. (Clusiaceae). SJW contains numerous biologically active constituents *viz.* naphtodianthrone derivatives, phloroglucinol derivatives (*e.g.* hyperforin), flavonoids, tannins, procyanidines, essential oils, phenylpropanes, amino acids, xanthones and other hydrosoluble compounds (*5*). Hyperforin was isolated in 1975 by Bystrov and co-workers (*6*). SJW has been used to fight against infections and for the treatment of respiratory

and inflammatory diseases, peptic ulcers and skin wounds (*7*), it inhibits proliferation of peripheral blood mononuclear cells and tumor cells, and induces apoptosis of tumor cells (*8-10*). It has been used for the treatment of neuralgia, anxiety, neurosis and depression (*11*). We have earlier reported the efficacy of hyperforin and standardized extract of SJW in various neurobiological disorders (*12-22*). Recently, we have investigated antiaggressive activity of SJW extract standardized to contain 3% hyperforin (*23*). This later investigation has prompted us to further elucidate the role of hyperforin in the observed antiaggressive activity.

2. Materials and Methods

2.1. *Animals*

Adult male Charles Foster rats and male Wistar mice, were obtained from the Central Animal House, Institute of Medical Sciences, Banaras Hindu University, and were randomly distributed into different experimental groups. The animals were housed in groups of six in polypropylene cages at an ambient temperature of 25 ± 1°C and 45-55% relative humidity, with a 12:12 h light/dark cycle. They were provided with commercial food pellets and water ad libitum. Experiments were conducted between 09:00 and 14:00 h. Animals were acclimatized to laboratory conditions for at least one week before using them for experiments and were subjected only once to the experimental conditions. Principles of laboratory animal care (NIH publication number 85-23, revised 1985) guidelines were followed.

2.2. *Drugs and chemicals*

Hyperforin (99.9% pure) was procured from Dr. Willmar Schwabe, GmbH & Co. Karlsruhe, Germany. Lorazepam (Intas, Ahmadabad, India) was used as standard antiaggressive agent in all the experiments.

2.3. *Drug treatments*

Animals were treated once daily, for seven consecutive days. Animals were divided into three groups. Group I was treated intraperitonially with equal volume of 0.3% carboxy methyl cellulose (CMC) suspension. Group II was treated with lorazepam (2.5 mg/kg, *i.p.*). Group III was treated with hyperforin (10 mg/kg, *i.p.*). Animals were screened for aggressive behavior before dividing them into groups. A fresh solution of hyperforin was prepared everyday immediately before treatment. Hyperforin was suspended in 1% dimethylsulfoxide (DMSO) that contained 0.3% CMC. Hyperforin was injected *i.p.* in a volume of 10 mL/kg. At the end of 7 days, experiments were performed.

2.4. *Models of aggression*

A battery of four rodent models often used to detect potential effects of therapeutically used anti-depressants and anxiolytics on aggression and violence was chosen to screen the effects of hyperforin. Potential effects of agents on defensive (foot shock-induced aggression and water consumption tests) as well as offensive (isolation-induced and resident-intruder aggression tests) aggressive behavior have been detected and quantified by the battery of behavioral models chosen.

2.4.1. *Foot shock-induced aggression*

Male mice of Wistar strain weighing 20-30 g were used. Mice were treated with vehicle, hyperforin or lorazepam for seven consecutive days. On day seven, 1 h after the last treatment, all pairs of mice were subjected to foot shock by placing them in a box with a grid floor consisting of steel rods with a distance of 6 mm. A constant current of 0.6 mA was supplied to the grid floor by a shocker with an associated scrambler. During 3 min observation period, every 5 sec a 60-Hz current was delivered for 5 sec. Each pair of mice was dosed and tested without previous exposure. The total number of fights was recorded for each pair. The fighting behavior consisted of leaping, running, rearing and facing each other with some attempt to attack by hitting, biting or boxing (*24,25*). Behavioral parameters quantified in this test were leaping, running, rearing, facing each other and total number of fighting bouts.

2.4.2. *Isolation-induced aggression*

Male mice of Wistar strain weighing 20-30 g were used. Mice were kept isolated in small cages for a period of 6 weeks. Prior to the administration of the test drug, the aggressive behavior of the isolated mouse was assessed against a male mouse (similar in weight to that of isolated mouse, and accustomed to live in a group) into the cage of an isolated mouse for 5 min. Immediately, the isolated mouse started to attack the "intruder". The aggressive behavior of the isolated mouse was characterized by hitting the tail on the bottom of the cage, screaming and biting. Isolated mice not exhibiting aggressive behavior were excluded from the test. One day after the initial trial, isolated animals were distributed into three groups (6 in each) and were treated with vehicle, hyperforin or lorazepam for seven consecutive days. One hour after the last dose, aggressive behavior of isolated mouse against a male mouse was evaluated again for 5 min (*25-27*). Aggressive behavior related parameters assessed during this test were latency to first attack, screaming, pursuit frequency, tail rattle, aggressive posture and total number of fighting bouts.

2.4.3. *Resident-intruder aggression*

Resident male rats (400 ± 20 g) were tested in their home cages for aggression against a smaller (200 ± 20 g) male intruder. Before the start of the experiments, each resident male rat was kept in pair with one female rat in a polypropylene cage for 15 days, and they were randomly divided into three groups (6 pair in each). Drug treatment was started 16th day onward, and only male rats of each pair were administered with vehicle, hyperforin or lorazepam for seven consecutive days. Resident female was removed from the cage 30 min prior to the start of the test. One hour after the last treatment, a male intruder (~200 g) was placed in the territorial cage of the resident male, and behavior of the resident male was observed for the next 15 min. During this period, the time until the first attack (in seconds), number of attacks, and duration of each attack (in seconds) were recorded by a blind observer (*25*).

2.4.4. *Water competition test*

Two male rats of equal body weight (200 ± 20 g) were paired and housed in one cage for 6 days. After 6 days, the animals were deprived of water for 23 h, and then a water bottle was introduced with a shielded spout so that only one animal of a pair can drink at a time. Duration and frequency of spout possession and water consumption of dominant rat were recorded for 5 min (day 1 of experiment) and the aggressive animal of the pairs was marked for identification (test 1). Animals were then allowed another 55 min for water consumption and again deprived of water for next 23 h. The same procedure was repeated on next day (test 2). At the end of this, aggressive rat was administered with either drugs or vehicle for seven consecutive days. Frequency and time in seconds of spout possession of same rat (dominant) were again recorded for 5 min as mentioned above on the sixth and seventh day (test 3 and 4, respectively). Treatment effects were assessed by comparing the values before drug treatment with the values obtained after the drug treatments. Duration of water consumption in this test is considered to be a more specific parameter for evaluating effects of agents on aggressiveness of more dominant rats (*25*,*27*).

2.5. *Statistical analysis*

All values are expressed as mean ± SEM. Statistical significance between control and treatment groups was analysed by one way analysis of variance (ANOVA) followed by Students Neuman-Keuls post hoc analyses. Statistical analysis was performed using the software Graphpad prism version 5. Statistical significance between same treatment groups was analysed by Student's *t*-test and *p* values less than 0.05 were considered statistically significant.

3. Results

3.1. *Foot shock induced aggression*

Hyperforin significantly reduced the rearing and leaping behavior ($p < 0.001$). Running behavior in response to foot-shock was also inhibited by hyperforin treatment ($p < 0.01$). Tendency to face each other and number of fights were also significantly reduced by hyperforin ($p < 0.01$). Effect of lorazepam in this model was qualitatively similar to those of hyperforin (Figure 1).

3.2. *Isolation-induced aggression*

Hyperforin extended latency period to first attack and the number of fighting episodes ($p < 0.001$). Number of aggressive postures, number of screamings and tail rattle frequency were also significantly reduced by hyperforin ($p < 0.001$). Qualitatively, these effects of hyperforin (10 mg/kg) were identical to that of the lorazepam (2.5 mg/kg) (Figure 2).

3.3. *Resident-intruder aggression*

Hyperforin treatment prolonged the latency period of first attack ($p < 0.001$) and reduced the total duration and mean number of fights ($p < 0.001$). Mean numbers of lateral threats and aggressive grooming were also lowered in the hyperforin treated group as compared to control group ($p < 0.001$). The observed effects of lorazepam in this model were qualitatively similar to those of hyperforin (Figure 3).

3.4. *Water competition test*

In control group rats, duration of water consumption of the animals did not change significantly over the four different test days (Table 1), indicating that a stable relationship of water consumption and aggressive

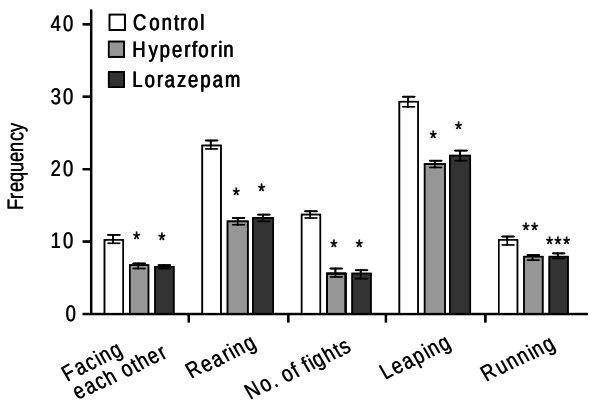

Figure 1. Effect of hyperforin on foot shock induced aggressive behavior. Values are given as mean ± SEM ($n = 6$). * $p < 0.001$, ** $p < 0.01$, *** $p < 0.05$ compared to control.

behavior had been established in each pair. Hyperforin treatment significantly ($p < 0.001$) reduced the duration of water intake by the dominant rats. Similar relationship was obtained during frequency of water spout possession (Table 2).

4. Discussion

The behavioral data reported here presents significant antiaggressive activity of hyperforin (10 mg/kg) in rodents, and the effect was qualitatively comparable to that of lorazepam (2.5 mg/kg). Various antidepressant drugs have been reported to be effective in the treatment of aggression (*28*,*29*). Hyperforin has been identified as one of the main components of SJW extracts responsible for its antidepressant effects

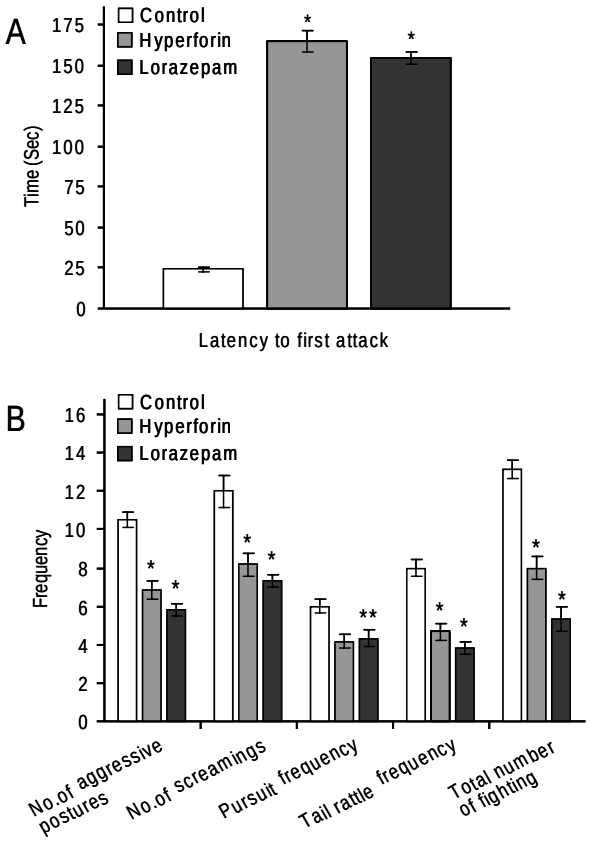

Figure 2. Effect of hyperforin on isolation induced aggressive behavior. Values are given as mean ± SEM ($n = 6$). * $p < 0.001$, ** $p < 0.01$ compared to control.

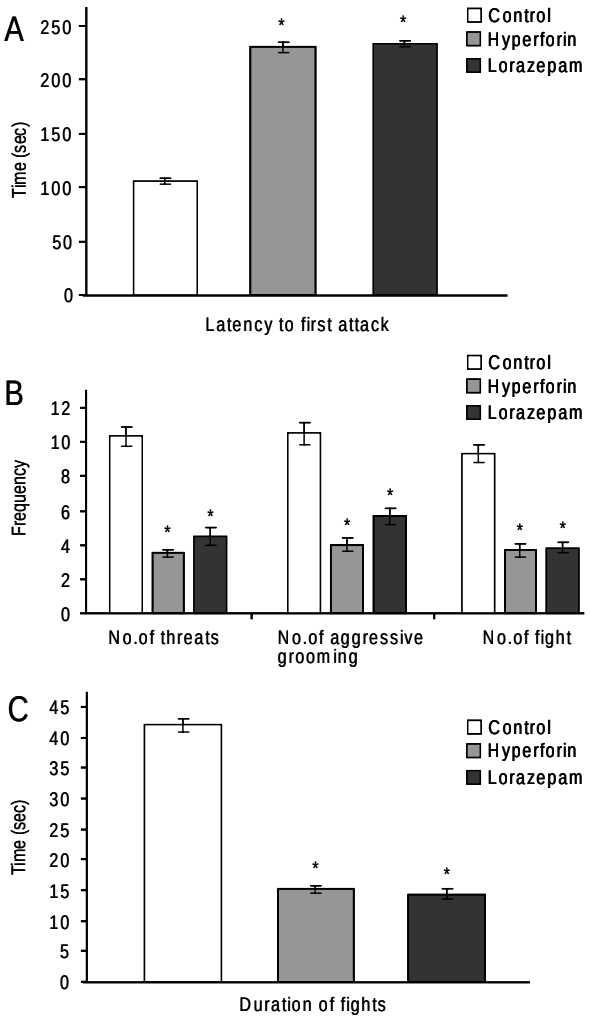

Figure 3. Effect of hyperforin on resident intruder aggressive behavior. Values are given as mean ± SEM ($n = 6$). * $p < 0.001$ compared to control.

Table 1. Effect of hyperforin on duration of water consumption

Treatment	Test 1	Test 2	Average 1	Test 3	Test 4	Average 2	Difference
Control	138.16 ± 2.18	139.83 ± 2.1	139.0 ± 2.12	146.0 ± 2.01	146.33 ± 2.75	146.16 ± 2.32	7.16 ± 1.28
Hyperforin (10 mg/kg)	140.0 ± 3.20	140.66 ± 2.14	140.33 ± 2.64	129.16 ± 2.33	125.66 ± 2.41	127.41 ± 2.27	-12.91 ± 1.59*
Lorazepam (2.5 mg/kg)	139.66 ± 3.16	142.16 ± 3.16	141.0 ± 3.09	123.16 ± 1.99	119.16 ± 2.16	121.16 ± 2.05	-19.83 ± 1.24*

Values represent mean ± SEM ($n = 6$). Average 1 indicates mean of tests 1 and 2; Average 2 indicates mean of tests 3 and 4; Difference indicates Average 2 – Average 1. * $p < 0.001$, compared to control.

Table 2. Effect of hyperforin on frequency of water spout possession

Treatment	Test 1	Test 2	Average 1	Test 3	Test 4	Average 2	Difference
Control	13.33 ± 0.42	13.16 ± 0.70	13.25 ± 0.35	13.66 ± 0.55	14.66 ± 0.55	14.16 ± 0.16	0.91 ± 0.23
Hyperforin (10 mg/kg)	15.66 ± 1.22	15.33 ± 1.14	15.5 ± 1.16	10.33 ± 0.66	9.33 ± 0.61	9.83 ± 0.60	-5.66 ± 0.71*
Lorazepam (2.5 mg/kg)	15.33 ± 1.02	16.0 ± 1.06	15.66 ± 0.92	9.33 ± 0.55	9.0 ± 0.73	9.16 ± 0.61	-6.5 ± 0.69*

Values represent mean ± SEM ($n = 6$). Average 1 indicates mean of tests 1 and 2; Average 2 indicates mean of tests 3 and 4; Difference indicates Average 2 – Average 1. * $p < 0.001$, compared to control.

(*30-34*). Therefore, observed antiaggressive activity of hyperforin adds a new potential use in the wide spectrum of hyperforin for the treatment of neurological disorders.

Aggression is associated with low cerebrospinal fluid concentrations of the serotonin (5-HT) metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in humans and nonhuman primates, and reduced 5-HT level or turnover in the brain of laboratory animals (*35*). Brain levels of gamma-aminobutyric acid (GABA) and glutamic acid decarboxylase in the striatum and the olfactory bulbs are low in mice and rats that exhibited aggressive behavior (*36*,*37*). Pharmacological strategies of increasing 5-HT levels, such as the use of 5-HT precursors and 5-HT reuptake inhibitors are able to reduce aggressive behavior in rodents (*38-41*). Likewise, increased GABAergic transmission is therapeutically beneficial in aggression (*e.g.* benzodiazepines) (*42*). Hyperforin is a neurotransmitter reuptake inhibitor, affecting the synaptosomal uptake of serotonin, dopamine, noradrenalin, glutamate and GABA with similar efficiencies (*34*). Therefore, increased serotonergic transmission due to reuptake inhibition may be responsible for observed antiaggressive activity of hyperforin.

The findings of this study are consonant with our earlier investigation (*23*) and further elucidate that hyperforin may be potentially responsible for the observed antiaggressive activity.

Acknowledgement

The authors are thankful to Dr. Michael Noeldner, Senior Scientist, Pharmacological Division, Dr. Willmar Schwabe, Gmbh & Co. KG, Karlsruhe, Germany for providing gift sample of hyperforin.

References

1. Hollander E, Tracy KA, Swann AC, Coccaro EF, McElroy SL, Wozniak P, Sommerville KW, Nemeroff CB. Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. Neuropsychopharmacology. 2003; 28:1186-1197.
2. Roz N, Mazur Y, Hirshfeld A, Rehavi M. Inhibition of vesicular uptake of monoamines by hyperforin. Life Sci. 2002; 71:2227-2237.
3. Nelson RJ, Chiavegatto S. Molecular basis of aggression. Trends Neurosci. 2001; 24:713-719.
4. Miczek KA. Aggressive and social stress responses in genetically modified mice: from horizontal to vertical strategy. Psychopharmacology (Berl). 1999; 147:17-19.
5. Greeson JM, Sanford B, Monti DA. St. John's wort (*Hypericum perforatum*): a review of the current pharmacological, toxicological, and clinical literature. Psychopharmacology (Berl). 2001; 153:402-414.
6. Bystrov NS, Chernov BK, Dobrynin VN, Kolosov MN. The structure of hyperforin. Tetrahedron Lett. 1975; 32:2791-2794.
7. Di Carlo G, Borrelli F, Ernst E, Izzo AA. St John's wort: prozac from the plant kingdom. Trends Pharmacol Sci. 2001; 22:292-297.
8. Schempp CM, Kirkin V, Simon-Haarhaus B, Kersten A, Kiss J, Termeer CC, Gilb B, Kaufmann T, Borner C, Sleeman JP, Simon JC. Inhibition of tumour cell growth by hyperforin, a novel anticancer drug from St. John's wort that acts by induction of apoptosis. Oncogene. 2002; 21:1242-1250.
9. Hostanska K, Reichling J, Bommer S, Weber M, Saller R. Hyperforin a constituent of St John's wort (*Hypericum perforatum* L.) extract induces apoptosis by triggering activation of caspases and with hypericin synergistically exerts cytotoxicity towards human malignant cell lines. Eur J Pharm Biopharm. 2003; 56:121-132.
10. Donà M, Dell'Aica I, Pezzato E, Sartor L, Calabrese F, Della Barbera M, Donella-Deana A, Appendino G, Borsarini A, Caniato R, Garbisa S. Hyperforin inhibits cancer invasion and metastasis. Cancer Res. 2004; 64:6225-6232.
11. Bilia AR, Gallori S, Vincieri FF. St. John's wort and depression: efficacy, safety and tolerability-an update. Life Sci. 2002; 70:3077-3096.
12. Kumar V, Mdzinarishvili A, Kiewert C, Abbruscato T, Bickel U, Schyf CJ, Klein J. NMDA receptor-antagonistic properties of hyperforin, a constituent of St. John's wort. J Pharmacol Sci. 2006; 102:47-54.
13. Kumar V. Potential medicinal plants for CNS disorders-an overview. Phytother Res. 2006; 20:1023-1035.
14. Kumar V. Agrawala SK, Bhattacharya SK. Behavioural studies on *Hypericum perforatum* formulations. Phytomedica. 2004; 5:19-30.
15. Kumar V, Singh PN, Bhattacharya SK. Neuropsy chopharmacological studies on Indian *Hypericum perforatum* Linn. In: Medicinal and Aromatic Plants-Industrial Profile. Volume Genus Hypericum, edited by E. Ernst. First edition. Taylor & Francis, London and simultaneously published by Taylor & Francis Inc., New York, USA and Canada. 2003; pp. 179-226.
16. Kumar V, Khanna VK, Seth PK, Singh PN, Bhattacharya SK. Brain neurotransmitter receptor binding and nootropic studies on Indian *Hypericum perforatum* Linn. Phytother Res. 2002; 16:210-216.
17. Kumar V, Singh PN, Bhattacharya SK. Anti-stress activity of Indian *Hypericum perforatum* Linn. Indian J Exp Biol. 2001; 39:344-349.
18. Kumar V, Singh PN, Bhattacharya SK. Anti-inflammatory and analgesic activity of Indian *Hypericum perforatum* L. Indian J Exp Biol. 2001; 39:339-343.
19. Kumar V, Singh PN, Bhattacharya SK. Neurochemical studies on Indian *Hypericum perforatum* Linn. Indian J Exp Biol. 2001; 39:334-338.
20. Kumar V, Singh PN, Muruganandam AV, Bhattacharya SK. Effect of Indian *Hypericum perforatum* Linn on animal models of cognitive dysfunction. J Ethnopharmacol. 2000; 72:119-128.
21. Kumar V, Jaiswal AK, Singh PN, Bhattacharya SK. Anxiolytic activity of Indian *Hypericum perforatum* Linn: an experimental study. Indian J Exp Biol. 2000; 38:36-41.
22. Kumar V, Singh PN, Jaiswal AK, Bhattacharya SK. Antidepressant activity of Indian *Hypericum perforatum* Linn in rodents. Indian J Exp Biol. 1999; 37:1171-1176.
23. Husain GM, Chatterjee SS, Singh PN, Kumar V. Antiaggressive activity of standardized extract of Indian

Hypericum perforatum L. Pharmacologyonline. 2009; 1:432-444.
24. Jain K, Barar FSK. Central cholinergic involvement in Clonidine and shock-induced aggression, and its modification by nitrazepam, haloperidol and propranolol: an experimental study in albino mice. Indian J Pharmacol. 1985; 17:34-41.
25. Vogel HG. Drug Discovery and Evaluation: Pharmacological Assays. 2nd ed. Springer-Verlag: Berlin Heidelberg. 2002; pp. 425-430.
26. Plummer HK, Holt I. Effect of alprazolam and triazolam on isolation induced aggression in rats. Ohio J Sci. 1987; 87:107-111.
27. Muehlenkamp F, Luciont A, Vogel WH. Effects of selective serotonergic agonists on aggressive behaviour in rats. Pharmacol Biochem Behav. 1995; 50:671-674.
28. Bond AJ. Antidepressant treatments and human aggression. Eur J Pharmacol. 2005; 526:218-225.
29. Alevizos V. Pharmacotherapy of aggression. Ann Gen Psychiatry. 2006; 5 (Suppl 1):S62.
30. Chatterjee SS, Bhattacharya SK, Wonnemann M, Singer A, Muller WE. Hyperforin as a possible antidepressant component of Hypericum extracts. Life Sci. 1998; 63:499-510.
31. Laakmann G, Schule C, Baghai T, Kieser M. St. John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. Pharmacopsychiatry. 1998; 31:54-59.
32. Briskin DP. Medicinal plants and phytomedicines. Linking plant biochemistry and physiology to human health. Plant Physiol. 2000; 124:507-514.
33. Di Carlo G, Borrelli F, Ernst E, Izzo AA. St John's wort: prozac from the plant kingdom. Trends Pharmacol Sci. 2001; 22:292-297.
34. Muller WE. Current St John's wort research from mode of action to clinical efficacy. Pharmacol Res. 2003; 47:101-109.
35. Lesch KP, Merschdorf U. Impulsivity, aggression, and serotonin: a molecular psychobiological perspective. Behav Sci Law. 2001; 18:581-604.
36. Clement J, Simler S, Ciesielski L, Mandel P, Cabib S, Puglisi-Allegra S. Age-dependent changes of brain GABA levels, turnover rates and shock-induced aggressive behavior in inbred strains of mice. Pharmacol Biochem Behav. 1987; 26:83-88.
37. Guillot PV, Chapouthier G. Intermale aggression, GAD activity in the olfactory bulbs and Y chromosome effect in seven inbred mouse strains. Behav Brain Res. 1998; 90:203-206.
38. Olivier B, Mos J, van Oorschot R, Hen R. Serotonin receptors and animal models of aggressive behavior. Pharmacopsychiatry. 1995; 28:80-90.
39. Miczek KA, Hussain S, Faccidomo S. Alcohol-heightened aggression in mice: attenuation by 5-HT1A receptor agonists. Psychopharmacology (Berl). 1998; 139:160-168.
40. Fish EW, Faccidomo S, Miczek KA. Aggression heightened by alcohol or social instigation in mice: reduction by the 5-HT (1B) receptor agonist CP-94,253. Psychopharmacol. 1999; 146:391-399.
41. Lyons WE, Mamounas LA, Ricaurte GA, Coppola V, Reid SW, Bora SH, Wihler C, Koliatsos VE, Tessarollo L. Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. Proc Natl Acad Sci U S A. 1999; 96:15239-15244.
42. DiMascio A. The effects of benzodiazepines on aggression: reduced or increased? Psychopharmacologia. 1973; 30:95-102.

(*Received May 13, 2009; Accepted June 16, 2009*)