ANTIAGGRESSIVE ACTIVITY OF STANDARDISED EXTRACT OF INDIAN *Hypericum perforatum* L.

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Summary

The present study was undertaken to evaluate *in vivo* anti-aggressive potential of standardised extract of Indian *Hypericum perforatum* (IHp) by using defensive and offensive behavioural models in rodents. Standardised extract of IHp was evaluated for its potential effects against defensive or offensive aggressive behaviour of rodents.

IHp extract was orally administered at two dose levels (100 and 200 mg/kg of body weight) once daily for three consecutive days, lorazepam (2.5 mg/kg, p.o.), was used as standard anti-aggressive agent. Control group animals were given equal volume of vehicle (0.3 % carboxy methyl cellulose). Anti-aggressive activity was evaluated using following validated models of aggression viz. foot shock-induced aggression, isolation-induced aggression, resident-intruder aggression, water competition test and apomorphine induced aggression in rodents.

IHp extract has demonstrated dose dependant anti-aggressive activity in the aforementioned validated models of aggression.

IHp at both dose levels (100 and 200 mg/kg) have shown promising anti-aggressive activity qualitatively comparable to that of lorazepam.

Key words: St. John's Wort; *Hypericum perforatum*; Aggression; Stress; Foot shock; Isolation.

Introduction

Like for most, if not all, traditionally known medicinal herbs, diverse medicinal uses of different types concoctions obtainable from *Hypericum perforatum* L. (Clusiaceae), has been known since long [1]. More recent observations on bio-activities of different types of extracts of this herb, popularly called St. John's Wort (SJW), indicate that they possess wound healing, diuretic, antibiotic, antiviral, central nervous function modulating, as well as diverse other therapeutically interesting pharmacological properties.

However, by far a vast majority of preclinical and clinical studies reported during more recent decades have focused mainly on antidepressant like activities of hydro-alcoholic extracts of the herb. Taken together, the results of these efforts clearly demonstrate the efficacy and safety of hydro-alcoholic SJW-extracts (SJWEs) for the treatment of mild to moderately severe symptoms of depression, and that their adverse effects are much lower than those of most therapeutically used antidepressants and other known psycho-active drugs [2-7]. Although several similarities between preclinical activity profiles of some commercialised SJWEs and conventionally known antidepressants and anxiolytics have repeatedly been demonstrated, it has now also become apparent that neither modes of actions, nor activity profiles of SJWEs in behavioural models are like those of any therapeutically used drug. However, definite statements on their mechanisms of actions involved in their diverse therapeutically interesting bio-activities are not yet possible. Similar is the case also for their active components.

Hypericin and hyperforin are structurally unique chemo-taxonomic markers of the herb, and their diverse therapeutically interesting bio-activities have also been widely described. Amongst them hyperforin is quantitatively the major secondary metabolite of the herb. However, antidepressant like activities of SJWEs observed in animal models and clinical trials are neither quantitatively, nor qualitatively, dependant on their hyperforin, or hypericin, contents only. In addition, available information on their behavioural activity profiles in animal models reveal that unlike conventionally known antidepressants, hyperforin enriched extracts possess anxiolytic and cognitive function improving potentials as well [8-11]. Thus, for therapeutic purposes, classification of SJWEs and hyperforin as antidepressants only seems no longer very justifiable. Consequently, efforts are now being made in our laboratories and elsewhere, to better define their more appropriate therapeutic potentials as psychoactive agents.

Preliminary observations in our laboratories leading eventually to the identification of cognitive function modulating effects of SJWEs and hyperforin [12, 13] indicated that some of their effects on animal behaviour could be due to their possible beneficial effects against uncontrollable stress. Since animals in most behavioural models used to date for evaluation of their neuronal function modulating activities are subjected to stress situations, their potential ability to enable them better cope with such situations could as well explain their antidepressants like, anxiolytic and other activities. If such would indeed be the case, some other stress induced behaviour should also be modulated by anti-depressive treatment regimen with SJWEs. Aggression is one such behaviour, and several pharmacological models are now available for evaluating anti-aggressive potentials of antidepressants and other agents. Consequently, a study was designed to assess potential anti-aggressive activity of a hydro-alcoholic extract of Indian variety of *Hypericum perforatum* (IHpE).

Materials and Methods

Animals: Adult Charles Foster rats and Wistar mice, of either sex, 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 (unless stated otherwise) in polypropylene cages at an ambient temperature of $25^0C \pm 1^0C$ and 45-55 % relative humidity, with a 12:12 h light/dark cycle. Unless stated otherwise, 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.

Drugs and Chemicals: The extract (50% ethanolic extract; standardised to contain more than 3% hyperforin, HPLC) of Indian *Hypericum perforatum* was supplied by Indian Herbs Research & Supply Co. Ltd., Saharanpur, UP, India. This extract was similar to those used in earlier reports from our laboratories. Like in other analogous studies in our laboratories, lorazepam (Intas Pharmaceutical Ltd., Ahmedabad) was always used as a reference standard for all experiments. Apomorphine (Sandoz) was used to induce aggressive behaviour in rats. Solution of apomorphine was prepared freshly in 0.1% sodium metabisulphite solution. All reagents and chemicals used were of analytical grade.

Drug Treatment: The extract (IHpE) was orally administered as suspension in 0.3 % carboxy methyl cellulose (CMC), at the doses of 100 and 200 mg/kg, once daily for three consecutive days. Control animals were treated with equal volume of vehicle (0.3% CMC suspension), whereas the reference standard group was treated with lorazepam (2.5 mg/kg, p.o.). Potential effects of the treatments were always assessed one hour after such treatments. Choices of the IHpE doses and treatment regimen were based on our earlier observations made with this extract in other rodent behavioural models used to evaluate its antidepressant like and cognitive-function modulating activities.

Experimental Methods: A battery of five 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 IHpE. Potential effects of agents on defensive (foot shock-induced aggression and water consumption tests) as well as offensive (isolation-induced, resident-intruder and apomorphine-induced aggression tests) aggressive behaviour have been detected and quantified by the battery of behavioural models chosen.

1. Foot shock-induced aggression: Four groups of male mice (weighing 25 ± 5g), each consisting of 6 pairs of animals, were treated with vehicle, IHpE (100 or 200 mg/kg) or lorazepam for three consecutive days. On day three, 1 hour after the last oral treatment, all pairs of mice were subjected to foot shock by placing them 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 minute observation period, every 5 seconds a 60-Hz current was delivered for 5 seconds. Each pair of mice was dosed and tested without previous exposure. The total number of fights was recorded for each pair. The fighting behaviour consisted of vocalization, leaping, running, rearing and facing each other with some attempt to attack by hitting, biting or boxing [14, 15]. Behavioural parameters quantified in this test were vocalization, leaping, running, rearing, facing each other and total number of fighting bouts.

2. Isolation-induced aggression: Male mice (with initial body weight of 25 ± 5 g) were kept isolated in small cages for a period of 6 weeks. Prior to the administration of the test drug, the aggressive behaviour 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 minutes. Immediately the isolated mouse started to attack the “intruder”. The aggressive behaviour of the isolated mouse was characterized by hitting the tail on the bottom of the cage, screaming and biting. Isolated mice not exhibiting aggressive behaviour

were excluded from the test. One day after the initial trial, isolated animals were distributed into four groups (6 in each) and were treated with vehicle, IHpE (100 or 200 mg/kg) or lorazepam for three consecutive days. One hour after the last dose, aggressive behaviour of isolated mouse against a male mouse was evaluated again for 5 minutes [15-17]. Aggressive behaviour related parameters assessed during this test were latency to first attack, screaming, pursuit frequency, tail rattle, aggressive posture and total number of fighting bouts. Other behavioural parameters quantified during the test were rearing, grooming and sniffing.

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 4 groups (6 pair in each). Drug treatment was started 16th day onward, and only male rats of each pair were administered with vehicle, IHpE (100 or 200 mg/kg) or lorazepam for three consecutive. Resident female was removed from the cage 30 min prior to the start of the test. One hour after the last oral treatment, a male intruder (~200 g) was placed in the territorial cage of the resident male, and behaviour of the resident male was observed for the next 15 minutes. 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 [15]. Motor activity of each resident animal was assessed by a second observer in each of three 5-minute period and a single numerical score was assigned to each rat, for each period. Scoring was based on a five-point scale (0- 4); 0 indicating lack of movement and 4 indicating continuous motor activity. The three scores from each of the periods were summed, yielding a score in the range of 0-12 for each resident animal [18]. The numbers of sniffing and rearing during the observation period was also recorded by the second observer.

4. Apomorphine-induced aggression: Male rats (200 ± 20 g) were housed singly and treated with apomorphine (1.0 mg/kg s.c.). After apomorphine administrations, two rats were immediately tested for aggressiveness according to the procedure described below. Through out the study the same animals were paired with each other. Daily apomorphine treatments lasted for 15 days, during which aggressiveness was scored five times (on the first, third, sixth, ninth and twelfth days). Thereafter, non-aggressive animals (rats whose behaviour did not become aggressive during 12 days) were excluded from further experiment. The apomorphine pre-treatment was considered appropriate for the experiment when the score of the aggressive behaviour of the apomorphine treated group was higher than 1.5 [19]. During screening of animals for aggressive behaviour 20% of animals had to be excluded. Selected animals were randomly divided into 4 groups (6 pair in each) and treated with vehicle, IHpE (100 or 200 mg/kg) or lorazepam from day 13 to day 15. During this period, all animals were simultaneously injected apomorphine (1.0 mg/kg s.c.) one hour after oral treatment. On the 15th day, aggressive behaviour of each pair of all the groups was observed 1 h after the last oral treatment and immediately after the injection of apomorphine.

Aggressive behaviour was assessed in specially designed cages with transparent plastic sidewalls (35 × 35 × 55 cm, length × width × height) and stainless steel floor, covered with wooden chips. Immediately after s.c. injection of apomorphine, the animals were put pair wise to the test cage and observed for the time of the latency (the time before the first attack or the first aggressive posture) and the intensity of aggressive behaviour. During 15 min observation period the intensity of aggressive behaviour was scored [20, 21] on a 0-3 point scale (0- no aggressive manifestations; 1- intermittent mild aggressive posture or attack toward other rat, no vocalizations; 2- intermittent intensive upright aggressive posture or

attack or boxing with other rat, vocalizations, but no biting or continuous fighting; 3-continuous fighting or attempts to bite the opponent rat, loud vocalizations). In case of the development of the highest score of aggressive behaviour, the test was terminated to avoid injuries. Such was the case in two pairs of the control group only.

5. 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 hours, 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). Animals were then allowed another 55 min for water consumption and again deprived of water for next 23 h. On day 2 rats were treated with vehicle, IHpE (100 or 200 mg/kg) or lorazepam and then allowed another 55 min for water consumption, which followed water deprivation for the next 23 h. This schedule was repeated on day 3 and day 4. On day 4, one hr after the last drug treatment, duration and frequency of spout possession and water consumption of same rat (dominant) were again recorded for 5 min as mentioned above [15, 17]. 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 [17].

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 Tukey-Kramer multiple comparisons test. Statistical significance between same treatment groups was analysed by Student's t-test, and p values less than 0.05 ($p < 0.05$) were considered statistically significant. GraphPad InStat software (version 3.06) was used for all statistical analysis.

Results

Table1 summarises the results of the foot shock-induced aggression test conducted in mice. Mean number of fights were dose dependently reduced in the IHpE treated groups. The effect of the higher dose of the extract tested was identical to that observed in the lorazepam treated group. Except for vocalisation and rearing, all other aggressive behaviour related parameters in the treated groups were significantly suppressed in a similar manner. However, in comparison to the lorazepam group slightly more vocalisations and lesser rearing episodes occurred in the higher dose IHpE treated group. These results indicate that the extract possesses anti-aggressive activity and that in this respect its activity profile is not identical to that of the reference drug lorazepam used in this study.

Table–1: Effects of IHpE and lorazepam on aggressive behaviour in the foot shock-induced aggression test. Each value represents the mean (± SEM) for 6 pairs of rats in each group.

Treatment (Dose)	Vocalization (No.)	Leaping (No.)	Running (No.)	Facing each other (No.)	Rearing (No.)	No. of fighting bouts
Vehicle	134.33±1.99	32.67 ±1.65	10.67 ±0.71	10.5 ±0.76	24.33 ±1.40	12.33 ±0.84
IHpE (100 mg/kg)	141±1.5	25.33 ±0.99**	8.17 ±0.6*	7.67 ±0.67*	17.5 ±1.43**	8.33 ±0.76**
IHpE (200 mg/kg)	146.5±1.67**	21.5 ±1.46***	6.83 ±0.6**	6.67 ±0.67**	7 ±0.58*** ††	4.83±0.6*** †
Lorazepam (2.5 mg/kg)	138±2.3	24 ±1.59**	8 ±0.58*	6.66 ±0.71**	17 ±1.46**	4.5 ±0.56***

*= p <0.05, ** = p <0.01, *** = p <0.001 compared to vehicle
†=p <0.05, ††= p <0.01 compared to IHpE 100 mg/kg

Almost analogous was also the case in the isolation-induced aggression test in mice, the results of which are presented in Table 2. IHpE dose dependently inhibited various aggressive behavioural parameters like: pursuit frequency, aggressive postures, tail rattle frequency and number of fighting bouts. Both doses of IHpE extended latency period to first attack, and the number of fighting episodes. Quantitatively, these effects of lorazepam (2.5 mg/kg) were almost identical to that of the higher IHpE dose (200 mg/kg). However, the effects of lorazepam on other parameters quantified were somewhat more pronounced than those in the higher dose IHpE treated group. Neither IHpE nor lorazepam treatment had any significant effect on non-aggressive behaviour of isolated mice quantified during the experiments (data not shown).

Aggressive behaviour related parameters quantified in the rat resident-intruder aggression test are summarised in Table 3. IHpE treatments dose dependently prolonged the latency period of first attack, and reduced the total duration and mean number of fights. As compared to the control group, mean numbers of lateral threats and aggressive grooming were also lower in the extract treated groups. Qualitatively, the observed effects of lorazepam in this model were again similar to those of the extract, and quantitatively the effects of the higher extract dose were again comparable to that of lorazepam. There was no significant effect of the extract, or of lorazepam, on the non-aggressive behavioural parameters quantified simultaneously during this test (data not shown).

Table–2: Effects of IHpE and lorazepam on various aggressive parameters in isolation-induced aggression test. Each value represents mean (± SEM) for 6 animals in group.

Behavioural Parameters	Vehicle	IHpE 100 mg/kg	IHpE 200 mg/kg	Lorazepam 2.5 mg/kg
Latency to first attack (sec)	7.57 ± 2.03	123.86 ±16.01*	162.71 ± 36.9**	154.71 ± 39.7**
Screaming (No.)	26.14 ± 2.82	20.57 ± 3.06	26.0 ± 3.26	15.86 ± 2.82
Pursuit frequency (No.)	8.86 ± 0.51	6.29 ± 0.68*	5.57 ± .65**	4.14 ± 0.26***
Aggressive-Postures (No.)	12.0 ± 0.65	9.43 ± 0.53*	8.29 ± 0.68**	5.57 ± 0.37***
Tail rattle frequency (No.)	14.14 ± 0.59	11.29 ± 0.68**	8.43 ± 0.48*** ††	7.71 ± 0.42***
Total No. of fighting bouts	17.0 ± 0.93	12.29 ± 1.12**	7.14 ± 1.12*** ††	6.71 ± 0.52***

*= p <0.05, ** = p <0.01, *** = p <0.001 compared to vehicle
†=p <0.05, ††= p <0.01 compared to IHpE 100 mg/kg

Table–3: Effects of IHpE and lorazepam on aggression related behaviour in the resident-intruder aggression test. Each value represents mean (± SEM) for 6 pairs of rats in each group.

Treatment (Dose)	Latency to first attack (sec)	No. of lateral threats	No. of aggressive grooming	Total duration of fighting (sec)	No. of fighting bouts
Vehicle	107.33 ± 0.9	10 ± 1.0	10.83 ± 0.79	36 ± 2.84	12.17 ±0.87
IHpE (100 mg/kg)	170.83 ± 11.1**	6.67 ± 0.56*	7.87 ± 0.67*	24.67 ± 2.07**	8.17 ±0.79**
IHpE (200 mg/kg)	236.67 ± 13.9*** ††	5.5 ± 0.76**	4.33 ± 0.49***†	18.17 ± 1.81***	5 ±0.77*** †
Lorazepam (2.5 mg/kg)	239.83 ± 13.2***	4.17 ± 0.60***	5.82 ± 0.74***	14.83 ± 1.7***	4.83 ±0.6***

*= p <0.05, ** = p <0.01, *** = p <0.001 compared to vehicle;
†=p <0.05, ††= p <0.01 compared to IHpE 100 mg/kg

The results of the apomorphine-induced aggression test (Table 4), revealed that IHpE pretreatment significantly prolonged the latency period till first attack in a dose dependant manner, and mean aggressive scores of the extract treated groups were significantly lower than that of the control group ($p < 0.05$, $p < 0.01$ for IHpE 100 and 200 mg/kg, respectively). The observed effects of lorazepam on aggressive score ($p < 0.001$ vs. control) in this test was more pronounced than that of the higher extract dose.

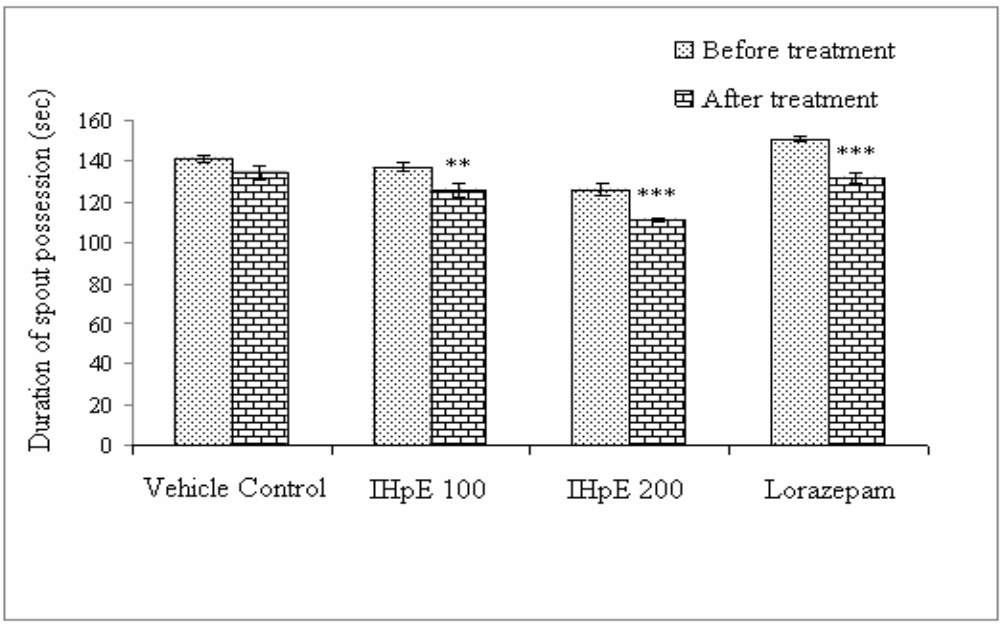
Table–4: Effects of IHpE and lorazepam on apomorphine-induced aggression. Each value represents the mean (± SEM) of 6 pairs in each group.

Treatment (Dose)	Latency to first attack (min)	Intensity of aggression (score)
Vehicle	5 ± 0.37	2.5 ± 0.22
IHpE (100 mg/kg)	8.33 ± 0.49**	1.33 ± 0.21*
IHpE (200 mg/kg)	12.5 ± 0.76*** †	1.00 ± 0.36**
Lorazepam (2.5 mg/kg)	11 ± 0.89***	0.83 ± 0.3***

*= p <0.05, ** = p <0.01, *** = p <0.001 compared to vehicle
†= p <0.01 compared to IHpE 100 mg/kg

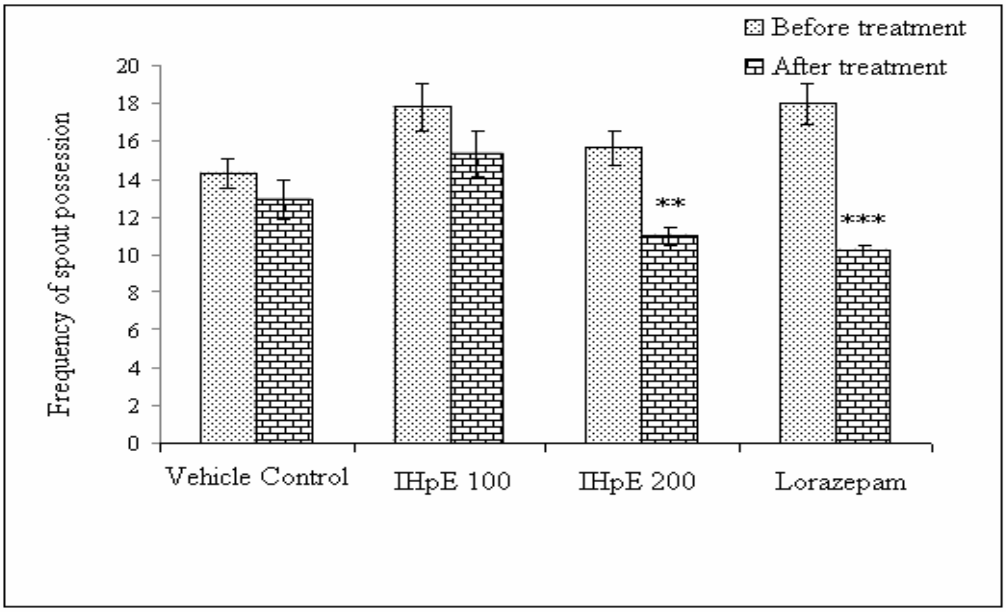
In water consumption test, IHpE dose dependently reduced the duration of water intake by the dominant rat (Figure 1), and similar was also the case for the frequency of spout possession (Figure 2). However, both quantified parameters were statistically significantly reduced in the higher dose IHpE and lorazepam groups only.

Figure-1: Effects of IHpE and lorazepam on duration of water consumption by the dominant rat in water competition test. Data represents the mean (± SEM) for 6 animals in each group.



**= p < 0.01, ***= p < 0.001 compared to 'before treatment'

Figure-2: Effects of IHpE and lorazepam on frequency of spout possession by the dominant rat in water competition test. Data represents the mean (± SEM) for 6 animals in each group.



**= $p < 0.01$, ***= $p < 0.001$ compared to 'before treatment'

Discussion

Ultimate goal of the described experiments was to verify whether effective anti-depressive, anxiolytic, and cognitive function modulating treatment regimen established for IHpE could also modify aggressive behaviour of rodents. Choices of the doses and treatment regimen of the extract for these experiments were, therefore, based on earlier findings in our laboratories revealing therapeutically interesting effects of the extract in animal models for depression [4], anxiety [8] and cognitive dysfunctions [12]. Clear dose dependant anti-aggressive activity of the extract was observed in all five experimental models used in this study, and in this respect the effects of its 200 mg/kg dose was qualitatively and quantitatively comparable to that of 2.5 mg/kg of lorazepam. Although beneficial effects of both IHpE and lorazepam against defensive as well as offensive aggressive behaviour were apparent, presented observations did also indicate some differences in their behavioural activity profiles. Thus, these observations revealed yet another therapeutically interesting bio-activity of IHpE. In addition, they add further experimental evidences to the conviction that such extracts represent a novel class of psychoactive agent with a uniquely broad spectrum of bio-activities useful for treating patients with diverse types of co-morbid mental health conditions.

Aggression and violence are significant public health problems [22] that have received only limited attention of neurologists interested in identifying novel psychotherapeutics. Many neurological disorders (e.g. personality disorders, schizophrenia, bipolar disorder etc.) are characterized by impulsive aggressive behaviour [23], and aggressive behaviour is also often encountered in demented patients [24]. Despite considerable progress, therapeutic possibilities for controlling or coping with, pathological aggressive behaviour remain far from being satisfactory.

Most currently recommended therapeutics for the control of aggression are antidepressants, anxiolytics, and cognitive function modulators, and more recently some anticonvulsants and other psychoactive agents have also been identified as potential anti-aggressive therapeutics. Although diverse mechanisms have been proposed for their modes of actions, definitive statements on the pharmacological targets involved in their observed anti-aggressive activities remain difficult. Thus, for example, although neurotransmitter re-uptake inhibition is widely accepted as the mode of action of antidepressants, their suppressive effects in rodent models of aggression disappear after their repeated daily doses [25]. A recent critical analysis of available information on the effects of some anti-depressants on aggression and violence in patients conclude actually that they aggravate violence and aggression in patients [26]. Based on available information on the modes of actions and behavioural activity profiles of diverse other psychotherapeutic, it is often concluded that close interactions of different neurotransmitter systems ultimately dictate their ultimate therapeutic potentials and activity profiles [22, 25, 27, 28].

Literature now available on IHpE and other SJWEs reveal that such extracts can modulate numerous neurotransmitter systems of different brain regions in a unique manner [29-32]. In this respect some of its reported effects are quite analogous to those of some psychotherapeutics often therapeutically recommended for controlling aggression. However, like other antidepressants and psycho-therapeutic drugs, no very definitive statements can yet be made on pharmacological targets involved in the observed anti-aggressive and other activities of IHpE. It must be pointed out though, that repeated daily doses of tri-cyclic and other (so-called “second generation”) antidepressants actually increase aggressive behaviour in rodents [25], whereas clear anti-aggressive effects of IHpE was apparent in all models after daily administration of its anti-depressive doses. Consequently, it seems reasonable to assume that unlike other conventionally known antidepressants, the pharmacological target(s) involved in the antidepressant like efficacy of IHpE could also be involved in its observed anti-aggressive effects. It has been pointed out indeed that unlike other antidepressants, therapeutically used SJWEs actually stimulates neuronal acetylcholine release also; and that this effect of the extract is observed in rats after its pharmacological doses much lower than those used in other neurotransmitter studies [11]. Therefore, efforts to clarify the role of cholinergic mechanisms in the observed behavioural activity profile of IHpE could be a starting point for defining its modes and targets of actions.

Although many questions concerning active principles of IHpE and their modes of actions still remain to be defined, till now observed behavioural activity profile in rodent models strongly suggest its unique psychotherapeutic potentials for helping patients suffering from diverse co-morbid mental health problems. It is now well recognised that in a vast majority of mentally ill patients with varying degrees of cognitive defects, aggression, anxiety and depression are often encountered. At present, for therapeutic management of such patients diverse combinations of different types of psychotherapeutics are often used. More often than not such practices are restricted by adverse effect potentials of known psychotherapeutics, and therapeutic demands of numerous patients are not properly met with by diverse combination therapies. Unfortunately, despite such a situation, most drug discovery projects still continue to concentrate efforts for the search of better, safer and more potent and specific leads and potential drugs for each of these co-morbid conditions. This is mainly because our current knowledge on aetiology, pathogenesis and progression of such co-morbid conditions is not precise enough for rationally developing or identifying potential therapeutics useful for combating the complications inherent in multiple ongoing mental health conditions.

In view of the situation, and the fact that adverse effect potentials of SJWEs are negligible in comparison to various other drugs and their combinations, appropriate clinical trials with such extracts in patients with multi-morbid neurological problems seem to be an urgent necessity. Such efforts are not only necessary for evaluating therapeutic relevance of preclinical findings and predictions, but also could eventually be useful for more rational search of novel pharmacological targets suitable for drug discovery purposes.

Till now, all properly controlled clinical trials with SJWEs were conducted in patient suffering from mild to moderately severe depression. Ultimate goal of such studies was to evaluate their antidepressant like efficacy; whereupon only a few of them attempted to evaluate other psychotherapeutic potentials of such extracts in depressed patients (for review see Volz, 2005) [33]. Although the results of such efforts have been instrumental in triggering the interest of many in therapeutic potentials and commercial possibilities offered by the herb, they are of limited value for better evaluation of the appropriate psychotherapeutic potentials of the herb, or for identifying the pharmacological targets involved in diverse therapeutically interesting bio-activities of its extractable components.

The present study constitute a part of a project directed to experimentally verify the possibility that therapeutically used SJWEs could be due to their beneficial actions for coping with neurological disorders triggered by stress. Reported observations strongly suggest that such could indeed be the case, and that efforts to identify and characterise their active constituents in terms of their potential “anti-stress” or “stress alleviating” activities could be a better way to answer many therapy relevant open questions on such extracts. Consequently, we are now concentrating our efforts to better characterise such therapeutic potentials of IHpE, and to test whether it could also be useful for treatment of psychiatric disorders often associated with stress induced metabolic disorders.

Conclusion

Reported observations reveal yet another therapeutically interesting activity of IHpE, and add experimental evidences to the conviction that such extracts could be pharmacologically better defined as stress alleviating agents. Therefore, further studies to properly characterize them for such activities and to identify their active anti-aggressive constituents seems warrantable.

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