INVOLVEMENT OF MONOAMINERGIC SYSTEM IN ANTIDEPRESSANT- LIKE ACTIVITY OF *GLYCYRRHIZA GLABRA* ROOT EXTRACTS IN RAT

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Summary

Objective: To study the antidepressant activity of ethanol and aqueous extracts of *Glycyrrhiza glabra* in albino rats.
Materials and methods: The antidepressant effect of the ethanol and aqueous extracts of *Glycyrrhiza glabra* root was evaluated, after administration once in a day for 14 successive days at the dose level 100, 200 and 400 mg/kg, p.o, using force swim test (FST) and tail suspension test (TST) in albino rats. Further the effect of the extract, on rat spontaneous locomotion and brain monoamine oxidase (MAO) activity was evaluated using photoactometer and spectrophotometer respectively.
Results: Administration of both ethanol and aqueous extract of *Glycyrrhiza glabra* root for 14 successive days, shows a dose dependant and significant (p<0.01) decrease in immobility in FST and TST. In both the paradigms, the percentage reduction in immobility was more in ethanol extract at dose level of 400 mg/kg, p.o than the aqueous extracts. There was no increase in spontaneous locomotion activity observed in ethanol extract at 400 mg/kg, rather than shows decrease in locomotion, signifies that the extract showing antidepressant and having no CNS stimulant effect. Further, the ethanol extract at 400 mg/kg administered for 14 successive days to rat decreases the brain MAO-A and MAO-B activities as compared to control. The percentage inhibition of MAO-A was more compared to MAO-B activity.
Discussion and conclusion: These findings demonstrate that *Glycyrrhiza glabra* showed significant antidepressant-like activity probably by inhibiting MAO and subsequent increase in the brain monoamines. Therefore it can be a potent candidate for the management of depression.

Key words: Antidepressant effect; force swim test; tail suspension test; monoamine oxidase; locomotor activity; *Glycyrrhiza glabra*.

Introduction

Depression is a heterogeneous disorder that affects a person's mood, physical health and behavior. Patient with major depression have symptoms that reflect changes in brain neurotransmitter, especially norepinephrine (NE), serotonin (5-HT) and dopamine (DA)(1). Depression may range from vary mild condition, to severe depression (psychotic depression) accompanied by hallucinations and delusions. According to World Health Organization estimation, 121 million people world wide suffer from depression. The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effect on cardiovascular system have suggested that it will be the second leading cause of death by the year 2020 (2). An estimated 5.8% of men and 9.5% of women experience the depressive episodes in their lifetime (3). Although, several classes of antidepressants are currently being used, due to clinical limitations and adverse effects there is critical interest in development of efficient and safe drugs for treatment of depression (4). Plant sources such as *Withania somnifera* (5), *Bacopa monniera* (6) and St. John's wort extract (7) have been reported to have antidepressant activity and can be effective therapeutic alternatives for treatment of depression.

Glycyrrhiza glabra L. (Family: Leguminosae) is a perennial herb native to the Mediterranean region, Middle East and now widely cultivated throughout Europe (8). The most important bioactive components of *Glycyrrhiza glabra* root are glycyrrhizin, glycyrrhetinic acid (GA), liquiritin, liquiritigenin and glabridin (9). Most of the pharmacological activities shown by glycyrrhiza extract are attributed to its aglycone saponins, 18β-glycyrrhetinic acid. Glycyrrhetinic acid has a semisteroidal structure and its synthetic derivative, carbenoxolone has been used for peptic ulcer treatment (10). It also shows various CNS activities like anticonvulsant activity in rat and mice (11), memory improvement activity in mice (12), and antidepressant effect of glabridin, an isoflavans of *Glycyrrhiza glabra* (13). The aim of this study was to evaluate the antidepressant activity of ethanol and aqueous extract of *Glycyrrhiza glabra* using force swim test (FST) and tail suspension test (TST) and to explore the possible underlying mechanisms of antidepressant-like activity.

Materials and Methods

Selection and collection of plant material

The plant *Glycyrrhiza glabra* was selected for the present study was based on the presence of active constituents like saponin glycolsides and flavonoids. The powdered root of *Glycyrrhiza glabra* was procured from the Yucca enterprises, Mumbai in the year 2007.

Preparation of crude ethanol and aqueous extract of *Glycyrrhiza glabra*

The crude ethanol and aqueous extract of *G*lycyrrhiza *glabra* was prepared by macerating dried powdered root with respective solvent for 24 h. The macerated powdered roots were then extracted in a soxhelet extractor for 36 h, 1-2 cycles per hour. The crude extracts were evaporated to dryness using a rotary evaporator and a yield of 77 g (15.4%w/w) for aqueous and 80 g (16%w/w) for ethanol extract was obtained. The resultant extract was then stored in a freeze for further investigation (14). Fresh solutions of each extracts of *Glycyrrhiza glabra* were prepared in each day of the experiment by reconstituting the weighed quantity of the crude extract in a minimum amount of distilled water for oral administration.

Experimental animal

Albino rats of 150 to 200 g were procured from Gosh enterprise, Kolkata and were maintained in the college animal house with temperature (25 ± 1°C) on a 12 h light/dark cycle,

with free access to standard pellet diet and water for seven days for acclimatization. Experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC), Roland institute of pharmaceutical sciences, Berhampur, Odisha (India) (Regd no.926/ab/06/CPCSEA dated 22.02.2006). Four sets of animals were used in the study for forced swim test (FST), tail suspension test (TST), locomotor activity and biochemical measurement of MAO. Each set of animal was further divided into groups according to the treatment, consisting of six animals each selected randomly.

Drugs and Chemicals

Imipramine was used as the standard drug, were procured from Sigma Chemicals Co., USA. Serotonin (5-HT), EDTA, benzylamine, thiobarbituric acid (Hi Media Laboratories, Mumbai, India); Copper sulphate, sodium hydroxide (Ranchem, Mumbai) were used in the present study. Distilled water was used as a vehicle.

Determination of maximum tolerated dose

Maximum tolerated dose was determined as per OECD-423 guidelines (acute toxic class method) (15). Female albino rats (n = 3 per step) selected by random sampling technique. The rats were kept fasting for overnight providing with water, then the extracts (ethanol and aqueous) were administered orally at the dose level of 5 mg/kg body weight (volume should not exceed 2 ml/100 g body weight) by intra gastric tube, food my be withheld for further 3-4 h and observed once in every 30 minutes during the first 24 h and daily thereafter, for a total of 14 days for any mortality. If mortality was observed for 2-3 animals, then the dose administered was assigned as toxic dose. If mortality was not observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed the procedure was repeated for further higher dose such as 50, 300, 1000 and 2000mg/kg body weight. After the completion of acute toxicological studies the dose of each extract were chosen randomly as 100, 200 and 400 mg/kg body weight.

Forced Swim Test (FST)

Forced swim test, the most frequently used behavioral model for screening antidepressant-like activity in rats, was first proposed by Porsolt *et al*., 1978(16). Rats were moved from the animal house to laboratory in their own cages and allowed to adapt to the laboratory conditions for 1-2 h. Rats were forced to swim in an open cylindrical container (diameter 20 cm, height 45 cm), containing 38 cm of water at 25 ± 1°C. All the rats were divided into five different groups. The rats were tested in two sessions: an initial 15 min training session latter after 24 h by a 6 min test session. Following the training session rats were removed from the cylinder, towel dried and then returned to the home cage for testing 24 h latter. The rats were treated with ethanol and aqueous extracts in different doses (100, 200 and 400 mg/kg, p.o.) as test, imipramine (15 mg/kg, p.o.) as standard and distilled water (10 ml/kg, p.o.) as control group, once a day for 14 successive days. On 14^{th} day, after 1 and 5 h of treatment, each rat was forced to swim for a period of six min test. After an initial period of two min period of vigorous activity, each animal assumed a typical immobile posture. A rat was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs, necessary to keep its head above the water. The total duration of immobility was recorded during the next four min of the total test duration of six min by a blind observer (17).

Tail Suspension Test (TST)

The tail suspension test uses the uncontrollable, inescapable stressor of tail suspension to elicit immobility (16). The rats were treated with ethanol and aqueous extracts in different doses (100, 200 and 400 mg/kg, p.o.) as test drug, imipramine (15 mg/kg, p.o.) as standard

drug and distilled water (10 ml/kg, p.o.) as control, once a day for 14 successive days. Rats were moved from the animal house to laboratory in their own cages and allowed to adapt to the laboratory conditions for 1-2 h. On day 14th, 1 h after treatment, each rat was individually suspended to the age of a table, 50 cm above the floor, by adhesive tape placed approximately 1 cm from the tip of the tail. The total period of immobility was recorded manually for six minutes. Animals were considered to be immobile when it didn't show any body movement, hung passively and completely motionless (18).

Measurements of Locomotor Activity

The effect ethanol extract (400 mg/kg, p.o.) of *Glycyrrhiza glabra* root administered for 14 successive days to rat were studied for locomotor performance in 15 minutes, using photoactometer (INCO, Ambala, India) to rule out the CNS stimulant effect of the extract. The difference in the mean locomotor activity scores were compared between the distilled water treated rat and extract treated rat on 14th day after treatment.

Biochemical Estimation of MAO-A and MAO-B

On 14th day, rats were sacrificed after six min exposure to FST, the brain samples were collected immediately on an ice plate. The collected brain samples were washed with cold 0.25 M sucrose, 0.1 M Tris, 0.02 M EDTA buffer (pH 7.4) and weighed. The whole procedure of brain isolation was completed with in five minutes (19). The rat brain mitochondrial fraction was prepared following the procedure of Schurr and Livne, 1976(20). The MAO activity was accessed using spectrophotometer (19, 21). Briefly, the buffer washed brain sample was homogenized in 9 volumes of cold 0.25 M sucrose, 0.1 M Tris, 0.02 M EDTA buffer (pH7.4) and centrifuged twice at 800 g for 10 min at 4°C in cooling centrifuge (Remi Instruments, Mumbai). The pellets were discarded and the supernatant was then centrifuged at 12000 g for 20 min. The precipitates were washed twice with about 100 ml of sucrose-Tris-EDTA buffer and suspended in 9 volumes of cold sodium phosphate buffer (10 mM, pH 7.4, containing 320 mM sucrose) and mingled well at 4°C for 20 min. The mixture was then centrifuged at 15000 g for 30 min at 4°C and the pellets were re-suspended in cold sodium phosphate buffer. The protein concentration was estimated by Lowry method using bovine serum albumin (22).

For estimating MAO-A activity, 2.75 ml sodium phosphate buffer (100 mM, pH 7.4) and 100 µl of 4 mM 5-hydroxytryptamine were mixed in a quartz cuvette which was then placed in double beam spectrophotometer (Systronics 2230, Bengaluru, India). This was followed by the addition of 150 µl solution of mitochondrial fraction to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 280 nm for 5 min against the blank containing sodium phosphate buffer and 5-hydroxytryptamine.

For estimating MAO-B activity, 2.75 ml sodium phosphate buffer (100 mM, pH 7.4) and 100 µl of 0.1 M benzylamine were mixed in a quartz cuvette which was then placed in double beam spectrophotometer (Systronics 2230, Bengaluru, India). This was followed by the addition of 150 µl solution of mitochondrial fraction to initiate the enzymatic reaction and the change in absorbance was recorded at wavelength of 249 nm for 5 min against the blank containing sodium phosphate buffer and benzylamine.

Both MAO-A and MAO-B values were expressed as Unit/g protein. Specific activity was expressed as the number of units of activity per gram of protein. The enzyme protein was measured by the method of Lowry *et al*., 1951(22).

Statistical Analysis

All the results are expressed as mean ± standard error of mean (SEM). Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test as post hoc test using the software prism, version 5.00 for windows. The level of statistical significance considered was $p< 0.05$, when compared with the control group.

Results

Maximum Tolerated Dose

Both the ethanol and aqueous extract of *Glycyrrhiza glabra* root has not shown any sign of toxicity and mortality up to the dose of 1000 mg/kg body weight. The dose selected for antidepressant activity was 100, 200 and 400 mg/kg.

Effects of Ethanol and Aqueous Extracts of *Glycyrrhiza glabra* on Immobility Periods in FST and TST

Compared to distilled water treated group, chronic administration for 14 successive days of both ethanol and aqueous extract of *Glycyrrhiza glabra* at dose level of 100, 200 and 400 mg/kg, p.o. shows dose dependent and significant ($p<0.01$) decrease in duration of immobility time in both FST and TST. Also in FST all the extracts shows an inhibition of immobility time up to 5 h. Among the three doses 400 mg/kg of both the ethanol and aqueous extract decrease the immobility period to a greatest extent. Imipramine (15mg/kg, p.o.) on chronic administration for 14 successive days also significantly ($p< 0.01$) decreased the immobility period in both FST and TST as compared to distilled water treatment (Table 1 and 2).

The percentage reductions of immobility of ethanol extract (400 mg/kg, p.o) in FST at 1 and 5 h was 47 and 49% respectively and imipramine (15 mg/kg, p.o) showing a percentage reductions of immobility of 66 and 70% respectively (Table1). Where as in TST ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o) and imipramine (15 mg/kg, p.o) shows percentage reductions in immobility of 54 and 62% respectively (Table 2). The percentage reductions in immobility by ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o) was more in TST than FST and was comparable with standard drug imipramine (15 mg/kg, p.o) (Table1 and 2).

Effect on Locomotor Activity

There was no significant increase in ambulatory movement observed between the distilled water and ethanol extract treated group. The ambulatory movement of the rats treated with distilled water for 14 successive days was 208 ± 5.5, and ethanol extract of *Glycyrrhiza glabra* (400mg/kg, p.o.) administered for 14 successive days shows an ambulatory movement of 141 ± 4.5. This implies that the ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o) shows a decrease in ambulatory movement, so the extract was not showing a CNS stimulant effect (Table not shown).

Effect of Ethanol Extract of *Glycyrrhiza glabra* on Rat Brain MAO

The effect of ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o) and imipramine (15 mg/kg, p.o) administered for 14 successive days on MAO-A and MAO-B activities of rat whole brain were shown in Table 3 and 4. The MAO-A and MAO-B activities in distilled water treated group were 28.06 ± 3.33 and 31.05 ± 3.20 U/g proteins respectively. Oral administration of ethanol extract of *Glycyrrhiza glabra* at the dose of 400 mg/kg significantly ($p<0.01$ and $p<0.05$) inhibited both MAO-A and MAO-B activity. Imipramine at the dose of 15 mg/kg showed a significant ($p<0.01$) decrease in MAO-A and MAO-B activity as

compared to distilled water treated group. The percentage inhibition of MAO-A and MAO-B activities by the ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o) was 57 and 39% respectively; this implies that the extract showed more MAO-A inhibiting activity than the MAO-B and the efficacy of the extract was comparable to imipramine (Table 3 and 4).

Table 1

Effect of ethanol and aqueous extracts of *Glycyrrhiza glabra* on immobility period of rats in forced swim test (FST)

Treatment for 14 days (n=6)	**Dose (Kg^{-1}) (p.o.)**	**Duration of immobility(sec) mean ± SEM**		**Percentage decrease in immobility**	
		1h	**5h**	**1h**	**5h**
DW	10 ml	171.5 ± 4.79	174.8 ± 3.59	0	0
Imipramine	15 mg	57 ± 2.93**	52.33 ± 2.13**	**66**	**70**
EEGG	100 mg	141.33 ± 3.29**	136.83 ± 4**	18	22
EEGG	200 mg	110.83 ± 2.94**	118.16 ± 2.73**	35	32
EEGG	400 mg	90.16 ± 3.43**	88.83 ± 5.37**	**47**	**49**
AEGG	100 mg	148 ± 2.38**	147.66 ± 1.38**	14	15
AEGG	200 mg	123.5 ± 4.12**	122.66 ± 1.83**	28	30
AEGG	400 mg	97.66 ± 1.08**	97.16 ± 3.85**	**43**	**44**

DW = Distilled water; EEGG = Ethanol extract of *Glycyrrhiza* glabra; AEGG = Aqueous extract of *Glycyrrhiza glabra*; Values are mean ± SEM (n=6); Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's multiple comparison test, ***p*< 0.01 as compared to distilled water treated group.

Table 2

Effects of ethanol and aqueous extracts of *Glycyrrhiza glabra* on immobility period of rats in tail suspension test (TST)

Treatment for 14 days (n=6)	Dose(Kg^{-1}) (p.o.)	Duration of immobility (sec) mean ± SEM	Percentage decrease in immobility
DW	10 ml	186.5 ± 4.79	0
Imipramine	15 mg	71 ± 3.75**	**62**
EEGG	100 mg	136.83 ± 7.71**	27
EEGG	200 mg	113.5 ± 3.63**	39
EEGG	400 mg	85.16 ± 1.62**	**54**
AEGG	100 mg	152.5 ± 6.80**	18
AEGG	200 mg	144.33 ± 7.45**	22
AEGG	400 mg	122.16 ± 3.93**	**34**

DW = Distilled water; EEGG = Ethanol extract of *Glycyrrhiza* glabra; AEGG = Aqueous extract of *Glycyrrhiza glabra*; Values are mean ± SEM (n=6); Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's multiple comparison test, ** $p < 0.01$ as compared to distilled water treated group

Table 3

Effect of ethanol extract of *Glycyrrhiza glabra* on rat brain monoamine oxidase-A (MAO-A) activity

Group No (n=6)	Treatment for 14 days	Dose (Kg^{-1}) (p.o.)	MAO-A activity U/g protein (mean ± SEM)	Percentage inhibition (%)
I	DW	10 ml	28.06 ± 3.33	0
II	Imipramine	15 mg	11.03 ± 2.41**	61
III	EEGG	400 mg	12.16 ± 2.33**	**57**

DW = Distilled water; EEGG = Ethanol extract of *Glycyrrhiza* glabra; Values are mean ± SEM (n=6); Statistical analysis was carried out by one way ANOVA followed by Dunnett's multiple comparison test, ** $p < 0.01$ as compared to distilled water treated group

Table 4

Effect of ethanol extract of *Glycyrrhiza glabra* on rat brain monoamine oxidase-B (MAO-B) activity

Group No (n=6)	Treatment for 14 days	Dose (Kg^{-1})	MAO-B activity U/g protein (mean ± SEM)	Percentage inhibition (%)
I	DW	10 ml	31.05 ± 3.20	0
II	Imipramine	15 mg	14.04 ± 2.18**	55
III	EEGG	400 mg	19.08 ± 3.12*	**39**

DW = Distilled water; EEGG = Ethanol extract of *Glycyrrhiza* glabra; Values are mean ± SEM (n=6); Statistical analysis of data was carried out by one way ANOVA followed by Dunnett's multiple comparison test, * $p< 0.05$ and ** $p< 0.01$ as compared to distilled water treated group.

Discussion

It has been widely accepted that affective states, such as mood, are mainly regulated by serotonin and norepinephrine (23). The antidepressant drugs have been designed to interfere with the action of these neurotransmitters (24, 25). There is an increasing interest to evaluate antidepressant effect of herbs, since treatment of depression with conventional antidepressant (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors) provides a complete remission just for 50% of the individuals (26). The forced swim test (FST) and tail suspension test (TST) are widely used model for screening of antidepressants. The immobility behavior displayed in rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorder in humans. These models are widely employed in rodents to predict antidepressant potential by decrease of immobility period produced by several different classes of antidepressant drugs (16, 27).

In the present study, ethanol and aqueous extract of *Glycyrrhiza glabra* pretreatment for 14 days in the doses of 100, 200 and 400 mg/kg, (p.o) was evaluated for antidepressant activity in the most commonly used paradigms of models of depression namely, the force swim test and tail suspension test. Both ethanol and aqueous extracts (100, 200 and 400 mg/kg, p.o.) produced a dose dependant and significant ($p< 0.01$) anti-depressant-like effect in FST as well as in TST. So, the escape-directed behaviors and with minimal immobile posture showed by *Glycyrrhiza glabra* treated rats may be due to its attenuating effect in endogenous depression. This was in agreement with Dhingra and Sharma (2006), they reported that aqueous extract of *Glycyrrhiza glabra* at a dose of 150 mg/kg significantly reduced the immobility times of mice in FST and TST (28).

It has been argued that the TST is less stress full than FST and has a greater pharmacological sensitivity (29). The FST shows a strong sensitivity to monoamine alterations and is sensitive to monoaminergic manipulations (30). Remarkably, TST detects the anti-immobility effect of a wide array of antidepressants, including tricyclic antidepressants (TCA),

selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOIs) (27). The percentage inhibition of immobility in FST and TST by ethanol extract of *Glycyrrhiza glabra* (400 mg/kg, p.o.) was maximum i.e. 49% and 54% respectively in comparison to aqueous extract, where as standard drug imipramine shows a percentage inhibition of 70 and 62% respectively (Table 1 and 2). The ethanol extracts shows decrease in immobility in both the model of depression and a greater percentage of inhibition in TST than FST. So, the ethanol extract of *Glycyrrhiza glabra* showing antidepressant activity could involve one of the mechanisms of the established as described above.

It has been reported that psycho-stimulants which are clinically ineffective as antidepressants, however show antidepressant like effects in FST (31). To discount the possibility of false positive, ethanol extract of *Glycyrrhiza glabra* (400 mg/kg) was evaluated for its spontaneous motor activity using actophotometer. Ethanol extract of *Glycyrrhiza glabra* did not increase spontaneous motor activity in rat but had anti-immobility effect. It is of interest to note that several established antidepressants decrease locomotor activity (32). It conform the assumption that the anti-depressant like effect of ethanol extract of *Glycyrrhiza glabra* is seemed to be the real antidepressant like activity of the extract, not a false positive.

MAO is an important enzyme in the metabolism of a wide range of monoamine neurotransmitters, including norepinephrine, dopamine, and 5-hydroxytryptamine. MAO exist in two forms, A and B. MAO-A is more important than MAO-B in the metabolism of the major neurotransmitter monoamines. MAO-A inhibitors have been accepted to treat depression (33, 34). MAO-A preferentially metabolize epinephrine, norepinephrine and serotonin. MAO-B metabolizes phenylethylamine. Dopamine is metabolized by both MAO-A and MAO-B (35). Inhibitors of monoamine oxidase enzyme cause an increase in the content of neuronal monoamines, thus increasing neuronal monoaminergic activity (36). The present study revealed that ethanol extract of *Glycyrrhiza glabra* (400mg/kg, p.o.) administered for 14 successive days inhibits both MAO-A and MAO-B enzyme significantly as compared to control group. The percentage inhibition of MAO-A was more than the MAO-B as MAO-A inhibitors have been accepted to treat depression (33,34). Inhibition of MAO-A increases the brain norepinephrine and serotonin, whereas dopamine is metabolized by both MAO-A and MAO-B (35). As ethanol extract of *Glycyrrhiza glabra* decreases duration of immobility in both FST and TST paradigm and also inhibits the MAO activity, preferentially more MAO-A activity so the antidepressant effect of *Glycyrrhiza glabra* might be due to increase in norepinephrine, serotonin and dopamine level in the rat brain.

Conclusion

In conclusion, the extract of *Glycyrrhiza glabra* root showed significant antidepressant-like activity probably by inhibiting MAO activity, prefentially MAO-A activity. The antidepressant-like action was comparable to imipramine. Hence, *Glycyrrhiza glabra* root extract may have potential therapeutic value for the management of depressive disorder.

Acknowledgement

The authors were thankful to Dr. M. E. Bhanoji Rao, Principal and the management, Roland Institute of Pharmaceutical Sciences, Berhampur, Odisha (India) for their encouragement and providing the necessary facilities to carry out this research work.

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