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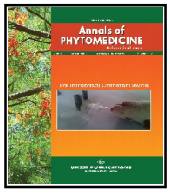

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Development of microemulsions of Jyotishmati oil for the treatment of Parkinson's disease *via* intranasal route: Pharmacodynamic evaluation in rats

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Abstract

Jyotishmati herb has been used to treat neurological disorders in Ayurveda for thousands of years. *Celastrus paniculatus* Willd. is its scientific name, and it is also known as Malkangani. In the current study, nasal microemulsions of Jyotishmati oil were developed and tested for pharmacodynamic activity in rats. Microemulsions were formulated by phase titration method. The optimized microemulsion was comprised of oil (Jyotishmati oil), Smix (Tween 80: PEG 400; 1:1) and water in the proportion of 5:65:30. The mean globule size, PDI and zeta potential of optimized formulation (F5) were 72.8 nm, 0.176 ± 0.10, 25.6 ± 1.3 mV, respectively. *Ex vivo* permeation studies on porcine nasal mucosa were carried out utilize Franz diffusion cells. The steady-state flux of Jyotishmati oil and Jyotishmati oil microemulsion F5 were 165 µg/cm^2/h and 301 µg/cm^2/h, respectively. Antiparkinsonism activity was evaluated on disease induced rats by administering rotenone 3 mg/kg intraperitoneal route for 11 days. From 12th day to 24th day (13 days) treatment was given. Optimized ME (F5) formulation intranasal treated group showed significant increase in rat body weight (79%), locomotor activity by photoactometer (78%) and grip strength on rotarod (98%) compared to oral route (13% weight, 20% locomotor activity and 33% grip strength). Brain homogenates from the optimized formulation group demonstrated a significant decrease in levels of lipid peroxides, nitric oxide and total protein as well as a significant increase in reduced glutathione (p<0.0001) in comparison to group treated with pure oil orally. Hence, we conclude that intranasal route could improve significantly brain bioavailability of antiparkinson's drugs especially when given as microemulsions.

1. Introduction

Herbal medicinal plants play an important role in traditional systems of medicine such as Ayurveda, Siddha and Unani. Herbal medicines are becoming increasingly popular due to their low side effects and their efficiency. *Celastrus panniculatus* Willd. is an important drug in the Ayurvedic system of medicine, belonging to the family "Celastraceae" also known as "Jyotishmati". Jyotishmati oil (Jyo oil) is valued in Ayurvedic medicine for its beneficial properties against neurological disorder due to the presence of various bioactive compounds such as phytosterols, tocopherols.

Nasal therapy has long been used in the Indian Ayurvedic system. Nasya karma, one of Ayurveda's panchakarmas is a process in which the drug is administered through the nostrils. The nasal route is one of the promising non-invasive methods for drug delivery to the brain that avoids the blood-brain barrier (BBB) by using the trigeminal nerve and olfactory neuroepithelium. Some neurological diseases, such as Parkinson's disease and epilepsy, are treated using this pathway (Vinay *et al.*, 2018).

Parkinsonism disease, the second most common progressive neuro degenerative disorder characterized by rigidity, tremor, postural instability and bradykinesia, is the most significant clinical challenge. It primarily affects dopamine-producing (dopaminergic) neurons in the substantianigra, a region of the brain. Jyotismati oil was long been known to attenuate brain function and studies have demonstrated the versatile roles of these novel phytochemicals as natural acetylcholinesterase inhibitors and neuroprotectants and exhibited their efficacy in the management of neurological or memory impairment, dementia, Parkinson's and Alzheimer's disease. The main objective of this study is to create a Jyotishmati oil microemulsion for nasal delivery to the brain in order to increase bioavailability, therapeutic efficacy and prevent gastrointestinal side effects when treating Parkinson's disease (Dorsey *et al.*, 2018).

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2. Materials and Methods

Jyotishmati oil was obtained from Chemiloids, Vijayawada, India. Labrasol was from Gattefosse Pvt. Ltd. (Mumbai, India). Propylene glycol,Tween 80, Polyethylene glycol 400 and Tween 20, were procured from S.D Fine Chemicals (Mumbai, India). The remaining chemicals were all analytical reagent grade.

2.1 Animals

Male Wistar rats, weighing between 220-250 g were procured from Sainadh agencies, Hyderabad. Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and Institutional Animal Ethics Committee (IAEC), approves the animal study vide 04/IAEC/UCPSc/KU/2022 CPCSEA 2018-2023. The animals were kept in a standard laboratory setting.

2.2 UV spectrophotometric measurement

To make a stock solution (1 mg/ml), Jyotishmati oil was dissolved in methanol. Diluting the stock solution with PBS pH 6.4, yielded

various concentrations (10 to 100 µg/ml) of Jyotishmati oil. At 254 nm, the absorbance of the sample was measured and a calibration curve for Jyotishmati oil was plotted (Bhanumathy *et al.,* 2010).

2.3 Solubility studies

Jyotishmati oil's solubility in various surfactants and co-surfactants was assessed using the equilibrium solubility method by adding extra Jyotishmati oil to a glass vial with a screw cap that contained solvent. The mixture was shaken in a water bath at room temperature, the sample was collected, the supernatant was filtered through a membrane filter and the filtrate was appropriately diluted with methanol before the drug content was determined using UV spectroscopy (Syed and Peh, 2014).

2.4 Construction of pseudoternary phase diagrams

Chemix software was used to create pseudoternary phase diagrams at various surfactant and co-surfactant ratios (1:1, 1:2, 2:1 and 3:1). A homogeneous mixture of oil and surfactant was diluted with water drop-by-drop until it became turbid. The amount of water added was noted. Water, Smix and oil (drug) made up the phase diagrams components. A phase diagram with a significant microemulsion region was deemed ideal **(**Zhang *et al*., 2004).

2.5 Preparation of microemulsion

Aqueous phase titration was used to prepare microemulsions. A precisely weighed amount of drug (Jyo oil) was dissolved in Smix, and the required amount of water was added, vortexed to produce a homogeneous microemulsion (Ramesh *et al*., 2010).

2.6 Characterization of microemulsion

The developed microemulsion was characterized for mean globule size, PDI, zeta potential, *ex vivo* permeation studies and pharmacodynamic studies.

2.6.1 PDI (polydispersity index), zeta potential, pH, mean globule size

PDI, zeta potential, and globule size of the sample were all measured using a zeta sizer and the pH of the formulation was assessed using a digital pH metre (Nano-ZS 90, Malvern instruments Ltd., UK).

2.7 *Ex vivo* permeation studies or estimation of steady state flux

On the experiment day, a porcine nose was obtained from a nearby slaughterhouse and dipped into Krebs bicarbonate ringer's solution. In order to mount the nasal mucosa on a vertical Franz diffusion cell device, the nasal mucosa was carefully isolated with a scalpel blade and blunt forceps, free of adherent tissues. After reloading the receptor compartment with fresh buffer and giving it 30 min to settle, the formulation was put in the donor compartment. A fresh batch of buffer was added to the 2 ml samples every hour. The samples were looked at a wavelength of 254 nm using the UV method. The total volume of Jyotishmati oil permeated at different time intervals was calculated using the formula given below (He *et al.*, 2010):

$$Q - [C_n V + \Sigma C_i S]_{i=1}^{n-1}$$

where,

Q = Cumulative amount of drug permeated

ΣCiS = Sum of drug concentration of sample (1 to n-1)

i = 1 multiplied with sample volume (S)

V = Volume of franz diffusion cell,

Cn = Concentration of drug (µg/ml) in nth sample interval

2.8 Analysis of permeation data

For each formulation, a graph was produced between the cumulative amount of Jyotishmati oil penetrated through the nasal mucosa (g) and time (h). The formulation flux (g/cm^2/h) at steady state was calculated by dividing the slope of the linear component of the curve by the effective mucosal area. The permeability coefficient (Kp) was determined by dividing the steady-state flux by the initial concentration of Jyotishmati oil in the formulation. The enhancement ratio was calculated by dividing the formulation's steady state flux by the drug solution's steady state flux.

Table 1: Pharmacodynamic study protocol

Group	Induction-rotenone (3 mg/kg)	Treatment (route)	Jyotishmati oil (dose)
I-Normal control	-	-	-
II-Positive control	I.P (11 days)	-	-
III- Jyotishmati oil	I.P (11 days)	Oral (13 days)	50 mg/kg
IV-Jyotishmati oil	I.P (11 days)	Nasal (13 days)	50 mg/kg
V-Jyotishmati oil ME	I.P (11 days)	Nasal (13 days)	50 mg/kg

Note: Group II to V were administered 3 mg/kg consecutive days. Above treatments were administered by respective route from 12th day to 24th day.

2.9 *In vivo* evaluation of optimized formulation

Jyotishmati oil and optimized formulation, Jyotishmati oil (F5) ME were evaluated for antiparkinsonism activity in a rat model in comparison to the oral route Table1 (Lowry *et al*., 2012).

2.10 Procedure for intranasal administration

Impel Neuropharma's rat nasal catheter, version 2.1, was used to give the formulations intranasally (Figure 1). The rat intranasal catheter device (ICD) was developed specifically to deliver drugs

to the rat nasal cavity's olfactory region, enabling direct nose-to-brain medication delivery by avoiding the blood-brain barrier. Its purpose is to facilitate the placement of the catheter tube for the delivery of drugs from the nose to the brain. When it was time to dose, the catheter tube was linked to the hamilton syringe. The therapies were given to sedated rats.

Figure 1: Rat intranasal catheter device.

2.11 Antiparkinsonism activity (Pharmacodynamic study)

Male Wistar rats weighing 300 to 350 g were placed into five groups of six rats each. Parkinsonism disease was developed in rats in this work by injecting rotenone at a dose of 3 mg/kg intraperitoneally daily for 11 days. Parkinson's disease induction and development were observed using criteria such as weight changes, photoactometer activity evaluation and grip strength by rotarod test on days 1st and 12th, before to daily treatment and during treatment (15th,18th, 21stand 24th). Rats were sacrificed by cervical dislocation on the 24th day. To estimate biochemical parameters like lipid peroxidation, reduced glutathione (GSH), total protein and nitric oxide level, the brain was separated, washed twice with saline, wiped with a soft tissue, weighed and stored at –20^{o}C (Oetz *et al*., 2005).

2.12 Behavioural parameters assessment

2.12.1 Training of rats

Male Wistar rats were trained for three days prior to the evaluation of behavioural measures such as the photoactometer and rotarod test.

2.12.2 Body weight monitoring

Rats in each group were weighed on days 1st, 12th and during therapy (15th, 18th and 24th day).

2.12.3 Locomotoractivity

Rat locomotor activity was monitored using a digital photoactometer (IC 1121, Dolphin V.R. Pharmacy Instruments Pvt Ltd., Mumbai, India). For 1 min, rats were acclimatized within the activity box. Locomotor activity and the number of counts displayed by the equipment in 5 min were recorded.

2.12.4 Rotarod test

The rats were placed on the rod and their time spent there was recorded. For 3 min, the rotarod was rotated at a steady speed of 15 rpm. The mean duration of stay on the rod was calculated after three trials**.**

2.13 Estimation of biochemical parameters

2.13.1 Brain homogenate preparation

The isolated brain was homogenized in a buffer of pH 7.4 0.1 M Tris-HCl buffer. After centrifuging the homogenate at 10,000 rpm for 10 min, the supernatant was analysed for biochemical parameters such as reduced glutathione, total protein, lipid peroxidation, and nitric oxide content (Green *et al*.,1982).

3. Results

3.1 Calibration curve of Jyotishmati oil

The Jyotishmati oil calibration curve in PBS pH 6.4 and methanol displayed good linearity with a correlation coefficient value of 0.999.

3.2 Solubility studies

The solubility of Jyotishmati oil in various surfactants and cosurfactants were shown in Figure.2. Tween 80, PEG 400 have the highest solubility for Jyotishmati oil. According to their ability to solubilize, Tween 80, PEG 400 were chosen as cosurfactants and surfactants, respectively.

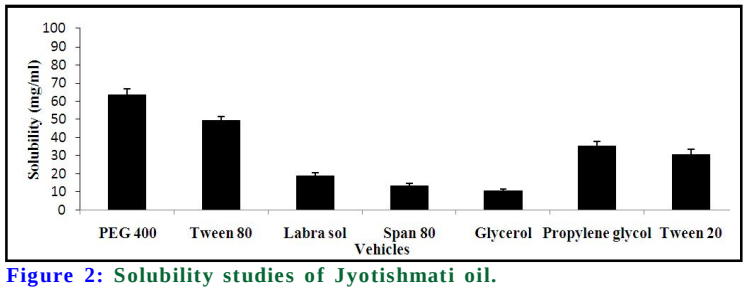


Figure 2: Solubility studies of Jyotishmati oil.

3.3 Pseudoternary phase diagrams

Figure 3 depicted Tween 80 and PEG 400 (Smix) in various ratios (Smix 1:1, 2:1, 3:1, and 1:2). The microemulsion region is indicated by the shaded region in the ternary phase diagram. The maximum isotropic region was found at a Tween 80: PEG 400 ratio of 1:1. As a result, a 1:1 ratio of Tween 80 and PEG 400 was chosen for the formulation of microemulsions.

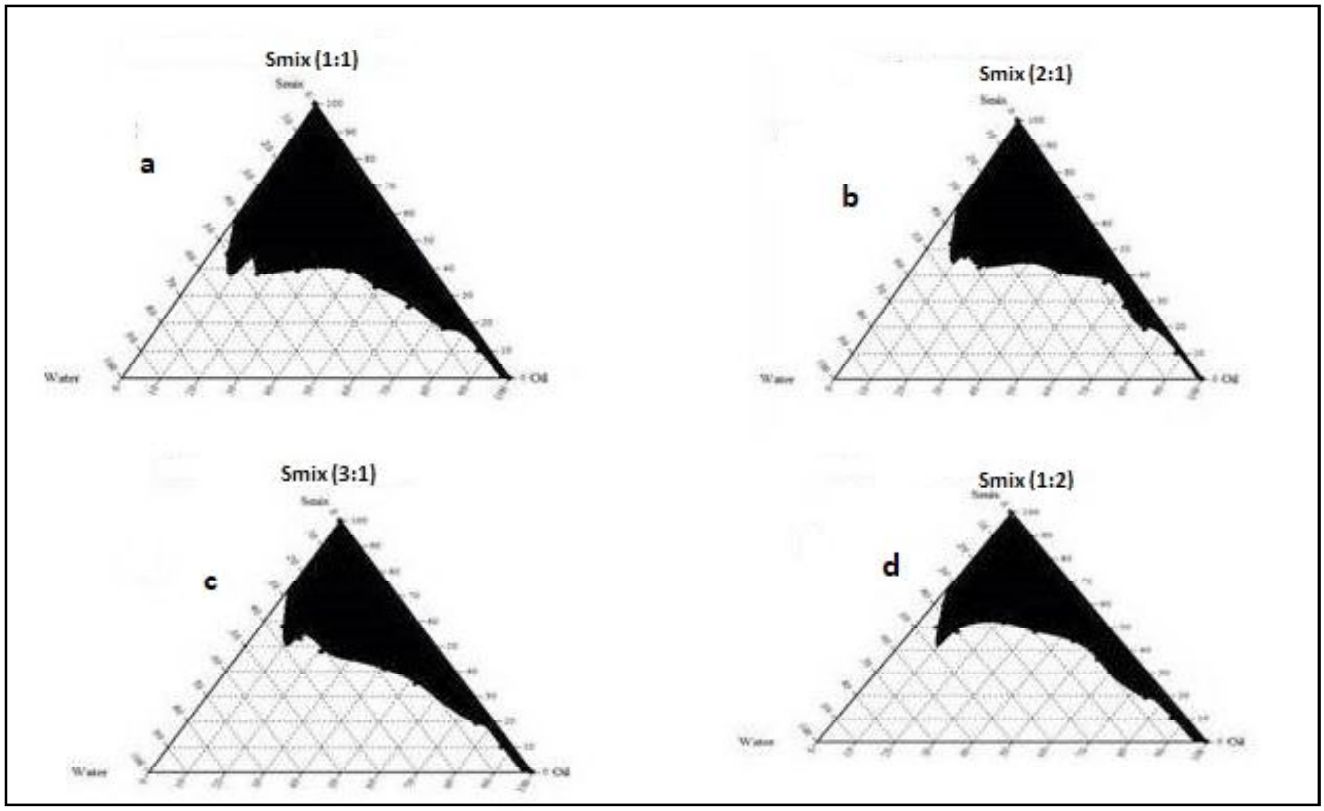


Figure 3: Pseudoternary phase diagrams composed of oil (Jyotishmati oil), Smix (Tween 80, PEG400) and water.

3.4 Characterization of microemulsion

3.4.1 Mean globule size, polydispersity index (PDI) and zeta potential

Formulations were diluted 100 times in distilled water and the mean globule size, PDI and zeta potential were measured. The improved formulation (F5) was found to have mean globule sizes of 72.8 nm, PDIs of 0.176 and zeta potentials of –25.6 mV. A PDI value less than 0.2 denotes homogenous globule size distribution (Table 2).

3.4.2 Visual inspection

The microemulsion was observed for clarity, homogeneity and phase separation. All the ME formulations were visually clear and transparent.

Table 2: Composition and characterization of formulations

Formulation	oil (Drug)	Smix	water	size (nm)	zeta potential (mV)	PDI
F1	5	45	50	146 ± 2.3	– 25.3 ± 0.05	0.342 ± 1.87
F2	5	50	45	138 ± 6.3	– 27.4 ± 0.11	0.267 ± 3.20
F3	5	55	40	125 ± 3.4	– 22.4 ± 0.45	0.238 ± 0.98
F4	5	60	35	92 ± 1.8	– 28.9 ± 0.32	0.225 ± 6.67
F5	5	65	30	72.8 ± 4.4	– 32.6 ± 1.3	0.165 ± 0.43
F6	5	70	25	176 ± 5.2	– 29.5 ± 2.31	0.264 ± 2.31

Note: Data presented as mean ± SD, (n = 3), Oil (Jyotismati oil), Smix (Tween 80: PEG400).

3.5 *Ex vivo* permeation studies

The *ex-vivo* permeation profiles of Jyotishmati oil microemulsion formulations are shown in Figure 4. The optimised formulation (F5) had a steady-state flux value of 302.13 g/cm^2/h. Optimized formulation (F5) outperformed Jyotishmati pure oil significantly at 165.21.32 g/cm^2/h. When compared to Jyotishmati pure oil, the enhancement ratio of F5 was 1.82 times higher.

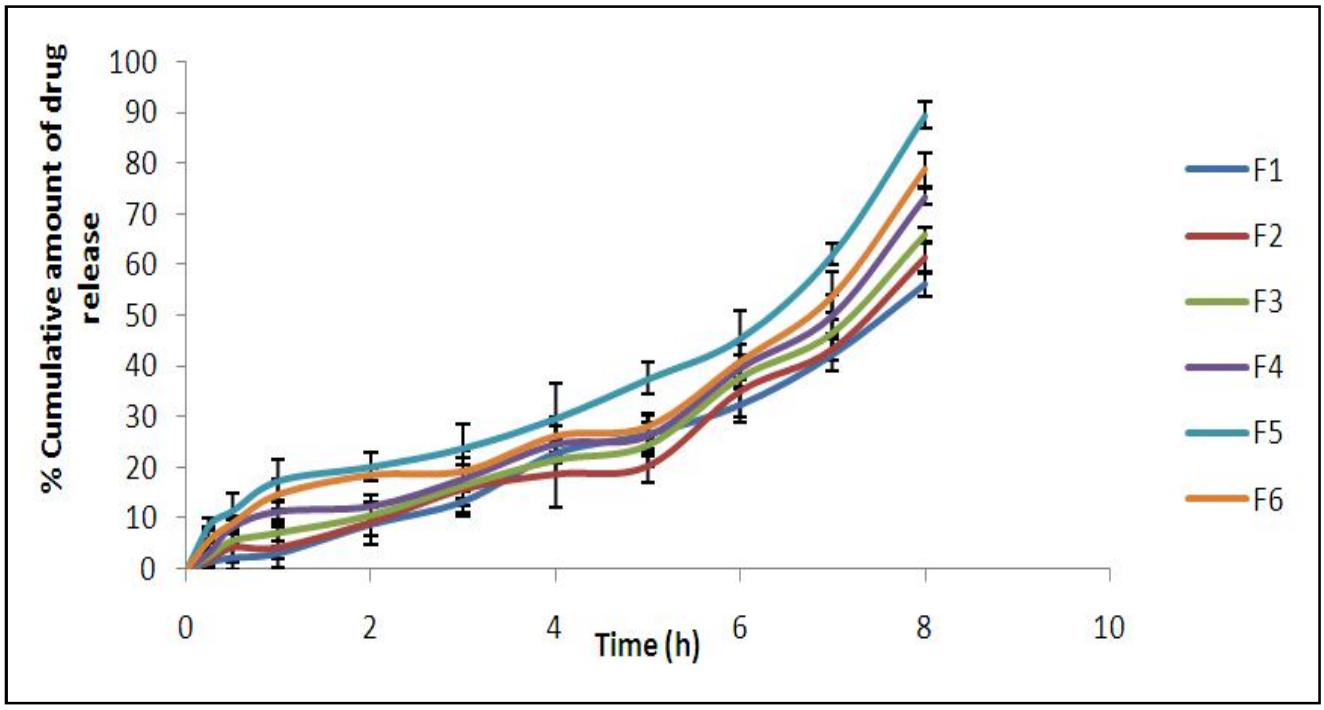


Figure 4: ***Ex vivo*** **permeation profiles of Jyotishmati oil microemulsions.**

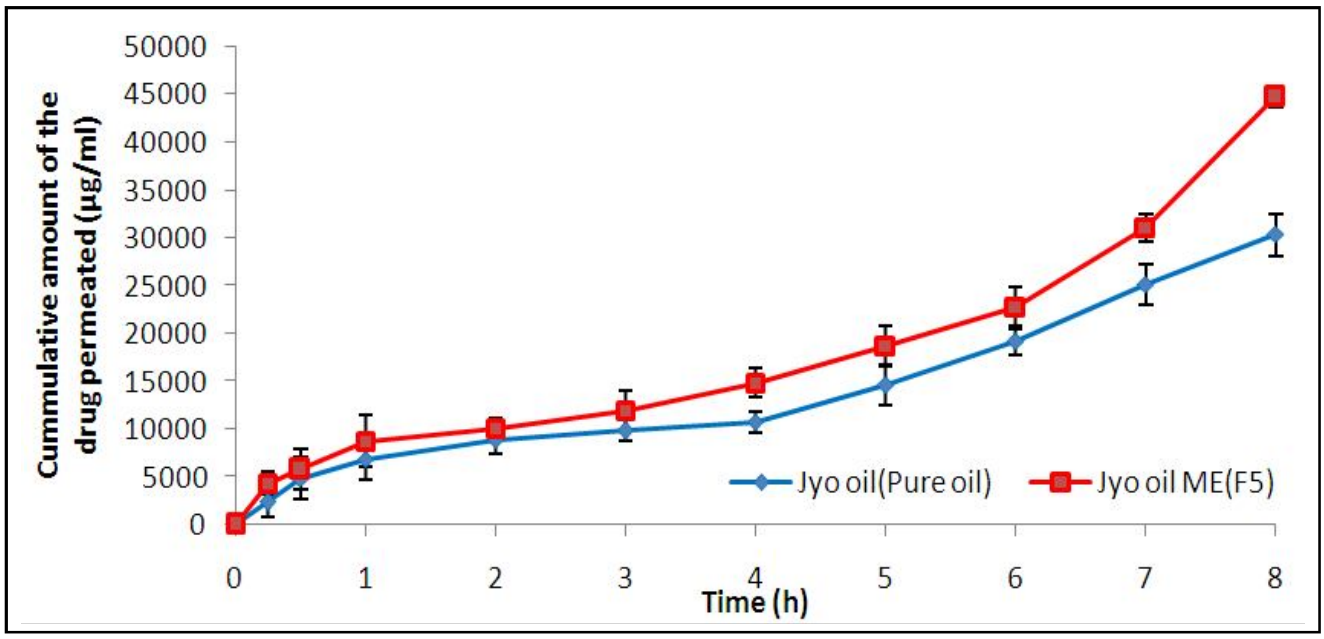


Figure 5: ***Ex vivo*** **permeation profiles of Jyotishmati oil and Jyotishmati microemulsion F5 (mean ± SD n=3).**

3.6 Pharmacodynamic study

The behavioural characteristics were estimated using a rotenone-induced rat model. The change in body weight, grip strength and locomotor activity were plotted as bar graphs and displayed in Figures 6,7, 8. The control group was regarded to be 100% in all behavioral measures. Graph pad Prism (viewing mode) 8.0.1 was used for statistical comparisons.

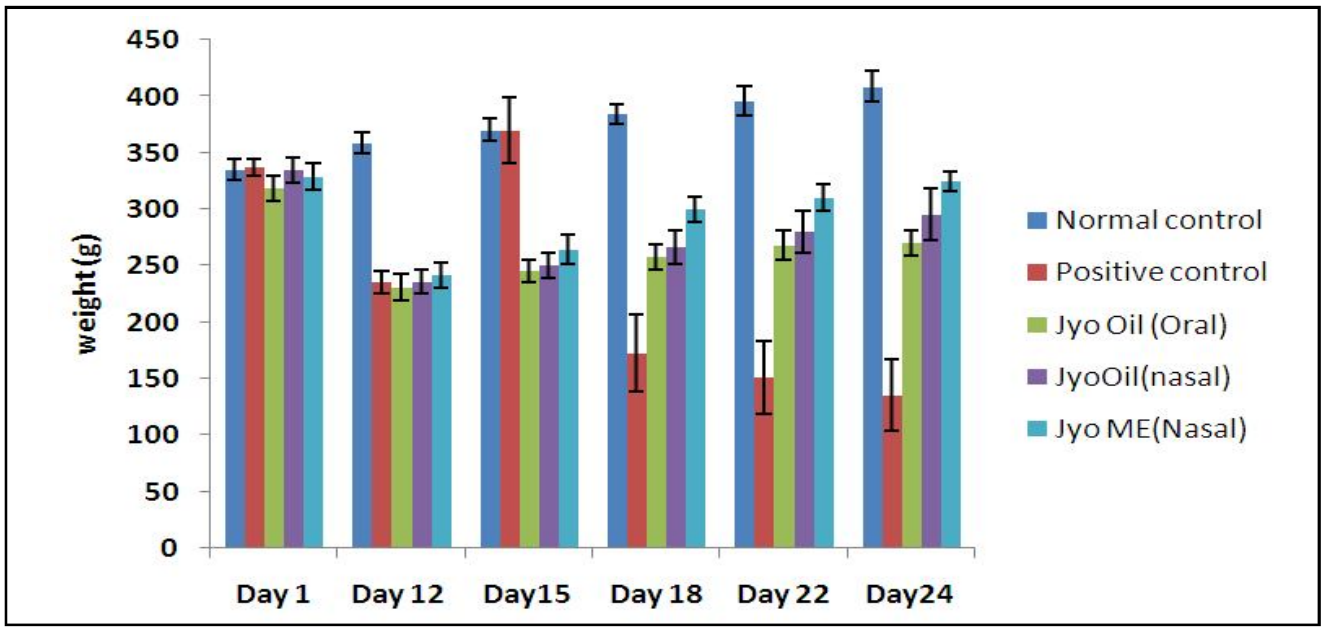


Figure 6: Body weight before rotenone induction (1st day), after induction (12th day), during treatment period (15th,18th, 22ndand 24th day). Values were measured in grams. Each value represents Mean ± SD, n = 6.

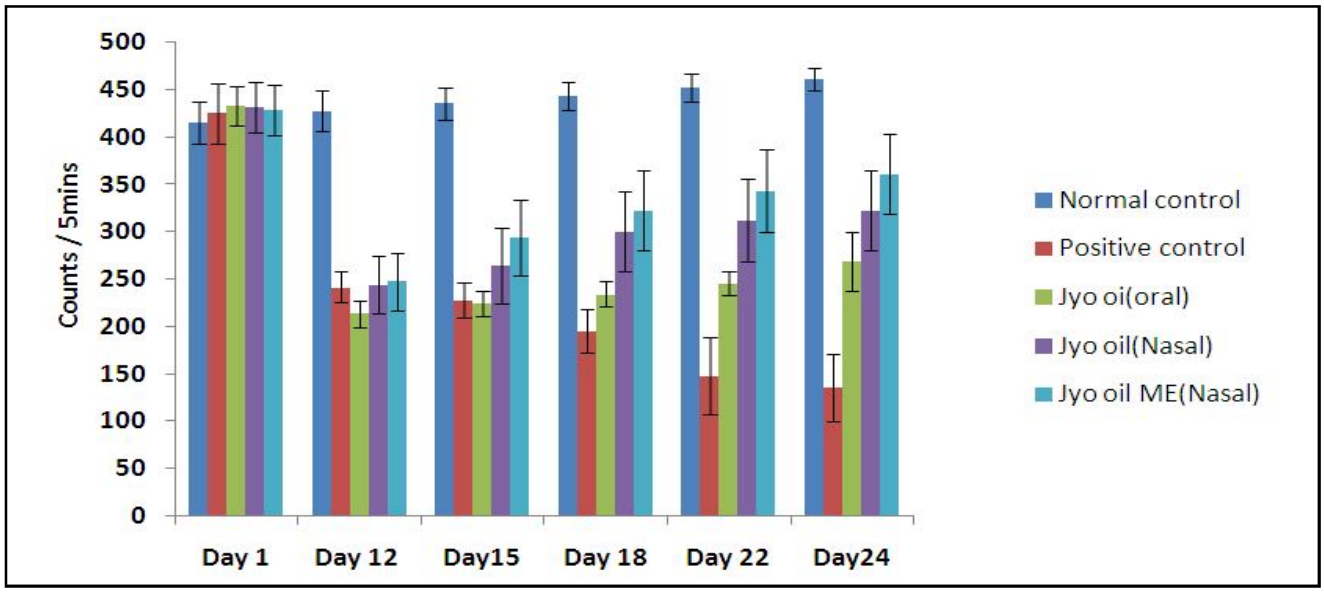


Figure 7: Number of counts in 5 min in photoactometer, before rotenone induction (1st day), after induction (12th day), during treatment period (15th, 18th, 22nd and 24th day). Each value represents Mean ± SD, n = 6.

Mean body weight of rats: Body weight in the Jyothismati oil ME treated group was restored to 79%, pure oil nasal to 72% and pure oil oral to 66% when compared to the control group.

Locomotors activity: All treatment groups were compared to the positive control group, Jyo oil ME treated group locomotor activity was restored to 78%, pure oil nasal to 70%, and pure oil oral to 58%.

Grip strength of rat on rotarod: Grip strength on a rotarod was restored to 98% in the Jyotismati oil ME treated group, 84% in the pure oil nasal group and 65% in the pure oil oral group, when all treatment groups were compared to the control group.

3.7 Estimation of biochemical parameters

After 13 days of treatment, the biochemical parameters reduced glutathione, nitric oxide, lipid peroxidation and total protein levels in all groups were estimated were shown Table.3.

3.7.1 Reduced GSH level

In this study, we found that the positive control dramatically reduced GSH levels in the brain by 0.270 ± 004 moles/g. Therapy with Jyotishmati oil ME (F5) at 0.450 ± 02 moles/g successfully prevented this rotenone-mediated decline in GSH level and restored it to 66%, but oral treatment could only restore it to 30%.

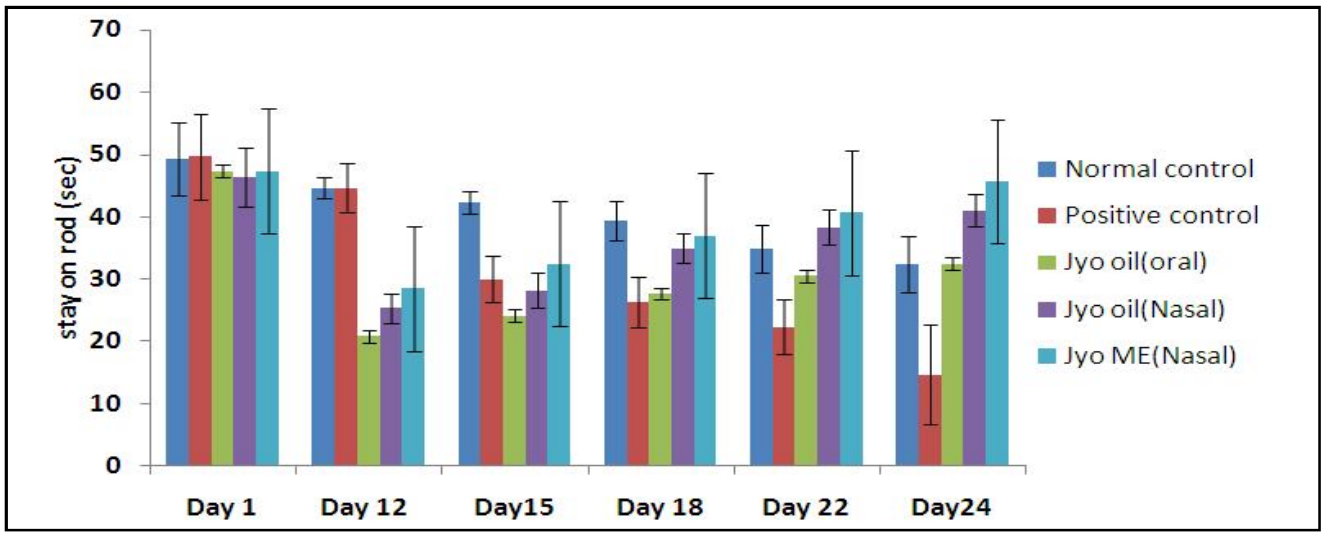


Figure 8 : Duration of stay on rotarod before rotenone induction (1st day), after induction (12th day), during treatment period (15th,18th, 22nd and 24th day). Each value represents Mean ± SD, n = 6.

3.7.2 Total protein levels

Total protein levels in the positive control group increased significantly from 77.16 ± 11.7 µg/g to1375 ± 22 µg/g. Jyotismati oil ME (F5) treatment lowered total protein to 457 ± 58 µg/g, Jyo oil nasal to 848.67 ± 29.4 µg/g and Jyotismati oil oral to 999.17 ± 41.2 µg/g.

3.7.3 Nitric oxide levels

Nitric oxide levels in positive control group were increased to 14.54 ± 0.52 µg/g than that of normal control group 1.58 ± 0.2µg/g. Treatment with Jyotismati oil ME (F5) was 6.86 ± 0.1µg/g, Jyotismati oil nasal was 9.41 ± 0.45µg/g and Jyotismati oil oral was 11.31 ± 0.31 µg/g, showed decreased levels of nitric oxide in the brain which found to be significant.

3.7.4 Lipid peroxidation levels

MDA levels in the positive control were substantially higher (8.13 ± 0.633 nM/g). Treatment with Jyotismati oil ME (F5) was 3.580 ±15 nM/g, Jyotismati oil nasal was 4.410 ± 24 nM/g, and Jyotismati oil oral was 6.130 ± 37, showed significant reductions in MDA levels in the brain.

Based on the above data, we may conclude that rotenone induction resulted in significant alterations in GSH, nitric oxide, total protein and lipid peroxidation. The formulas' efficacy was ranked in the following order: Jyo oil ME (F5)> Jyo oil (Nasal)> Jyo oil>Jyo oil (oral).

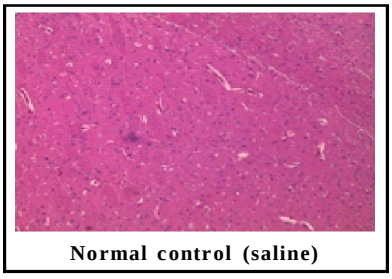
Table 3: Biochemical parameters estimation

Biochemical parameter	Normal control	Positive control	Jyo oil (oral)	Jyo oil (nasal)	Jyooil ME (F5) (nasal)
Reduced GSH (µM/g)	0.68 ± 0.03	0.21 ± 0.04	0.29 ± 0.02	0.34 ± 0.05	0.45 ± 0.02
Lipid peroxidation (nM/g)	1.54 ± 0.13	8.13 ± 0.63	6.31 ± 0.37	4.41 ± 0.24	3.58 ± 0.5
Nitric oxide (µg/g)	1.58 ± 0.2	14.54 ± 0.52	11.31 ± 0.13	9.41 ± 0.45	6.86 ± 0.34
Total protein (µg/g)	77.16 ± 11.7	1375 ± 22	999.17 ± 41.2	848.67 ± 29.4	457.58 ± 53.7

Note: % value calculated by considering normal control as 100%, All values expressed as Mean ± SD (n = 4). ***p<0.0001, **p<0.001,*p<0.01 significant compared to positive control.

3.8 Histopathology of the rat midbrain and substantianigra region

The histopathology of the midbrain and substantianigra regions of the rat brain before and after 13 days of treatment were shown in Figure 9. The midbrain region was identified and thin slices were cut using a microtome. Hematoxylin and eosin staining was performed after cleaning the slides (H&E). The morphology of the brain was studied using a light microscope. Rotenone-induced neuronal necrosis and lesions were seen in the positive control group. The groups treated with pure oil oral and pure oil nasal showed mild lesions, whereas the groups treated with the optimised formulation showed no lesions, indicating clear recovery from Parkinson's disease.



Normal control (saline)

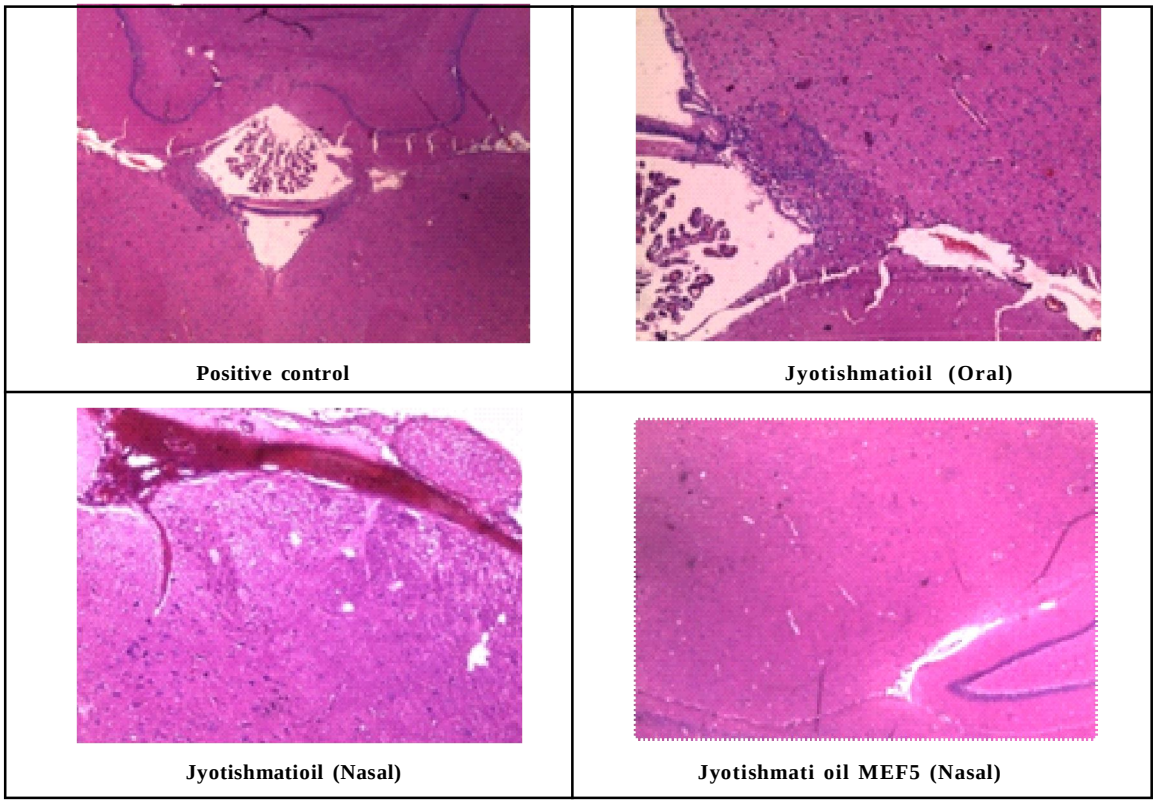


Figure 9: Histopathology of substantianigra region in rat mid brain treatment with formulation for 13 days.

4. Discussion

One of the most prevalent age-related neurodegenerative disorder is Parkinson's disease (PD). The nasal route is one of the promising non-invasive methods for drug delivery to the brain that avoids the blood-brain barrier (BBB) by trigeminal nerve and olfactory neuro -epithelium (Eskandari *et al.*, 2011). Jyotishmati oil is extracted from seeds, it contains alkaloids, sterols and bright coloring substance. Celapanine, celapanigine, celapagine, celastrine and paniculatine are some of the important alkaloids reported in jyothishmati oil. The oil contains oleic acid as main fatty acid, together with linoleic acid , palmitic acid and stearic acid (Dwivedi Maurya, 2018). It has been studied for a variety of pharmacological activities, such as antidepressant, antiparkinson's, anti- Alzheimer's, neuroprotective, antioxidant, anti-inflammatory, analgesic, immunomodulatory and antiarthritic activities by administering *via* oral route, transdermal route (Anjaneyulu *et al*., 2020). In a case study, a male Parkinson's patients treated with Jyotishmati taila at a dose of four drops per nostril for seven days, along with other Ayurveda drugs given orally showed a noticeable recovery (Divya, 2013).

Though, Jyotishmati oil was studied by administering *via* oral route, no study reported antiparkinsons activity *via* intranasal route. For the first time, we are reporting enhanced Antiparkinson's activity for Jyothishmathi oil microemulsions given by nasal route. The microemulsion is selected due to its advantages like enhanced absorption, bioavailability, permeability and stability. Micro-emulsion of Jyotishmati oil showed significantly high pharmacodynamic activity (p<0.0001) compared to pure oil by oral route. The activity of Jyotishmati oil in the microemulsion form was further enhanced due to high permeability *via* nasal mucosa owing to their nanosized globule

5. Conclusion

In the current study, we developed intranasal microemulsions of Jyotismati oil and analysed for pharmacodynamic activity in comparison to oral administration. Optimized Jyotishmati micro emulsion formulation showed significantly high antiparkinson effect in rat model when compared to Jyotishmati oil administered by oral and nasal route. Jyo oil ME (F5) formulation flux was 1.82 times of pure oil. Optimized microemulsion treated group showed substantial increase in rat grip strength, body weight and locomotor activity. Brain homogenates of optimized formulation group showed substantial reduction in levels of nitric oxide lipid peroxides and total protein and significant increase in reduced glutathione (p<0.0001) compared to plain oil treated by oral. Hence, we conclude that intranasal route could improve significantly brain bioavailability of Jyotishmati oil especially as microemulsion formulation.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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