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MODULATION OF DOPAMINERGIC NEUROTRANSMISSION AND MOTOR FUNCTION BY AQUEOUS EXTRACT OF *CURCUMA LONGA* IN HALOPERIDOL INDUCED CATATONIA IN MICE.

Pharmacology

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ABSTRACT

OBJECTIVE: The present study was attempted to evaluate the protective effect of *Curcuma longa* on dopaminergic neurotransmission and motor function in haloperidol induced catatonia in mice.

METHODS: Rigidity and dyskinesia are the common symptoms of Parkinson's disease and the most prevalent adverse extrapyramidal signs during the course of drug therapy associated with significant morbidity, economic and social burden. So the search for better agents in the place of conventional drugs continues. Catatonia induced by these drugs in animals has been used as a model for the extrapyramidal side effects associated with antipsychotic agents in human beings. Mice were allocated to 5 groups, each group containing 6 animals. The 1st group of 6 mice was treated with vehicle and rest of the groups was treated with haloperidol. The 3rd, 4th and 5th groups of mice were pretreated with the aqueous extract of *Curcuma longa* 50mg, 100mg and 200mg/kg of body weight respectively. The locomotor activity (LMA) and catatonia scoring of all animals were measured by using actophotometer and Morpurgo scoring method respectively on 8th and 15th day.

RESULTS: The effect of aqueous extract of *Curcuma longa* on haloperidol induced catatonia tested by LMA and Morpurgo scoring showed the reduction in latency by increase in LMA after 4 hours on 15th day and reduction in rigidity by reduction in Morpurgo scoring after 4 hours on 15th day.

CONCLUSION: The results suggest that aqueous extract of *Curcuma longa* has a protective effect against haloperidol-induced catatonia, indicating that it could be used as an adjuvant to prevent drug-induced extrapyramidal side effects.

KEYWORDS

Catatonia, extrapyramidal signs, Parkinson's disease, rigidity

INTRODUCTION:

The Parkinson's disease (PD) is one of the common neurodegenerative disorders which can also be induced by administration of antipsychotic drugs while treating positive symptoms of schizophrenia.[1]There have been suggestions that the Parkinsonism effects, frequently observed with phenothiazines which have been conventionally used in Psychiatry for several decades. The motor disorders like dyskinesia, rigidity and tremors can also result from chronic administration of neuroleptic drugs.[2] The neuroleptic drug induced neurological disorders may not be improved by the supplement of dopamine due to chronic blockade of dopamine D_2 receptors by the neuroleptic drugs like phenothiazine compounds. The hypothesis of dopamine receptor super sensitivity proposes that antipsychotic drug treatment causes hypersensitization of dopamine D_2 receptors.[3] There is no single laboratory model to evaluate parkinsonism and in which a proper evaluation of antiparkinsonian activity can be carried out. However, there is a positive correlation between catatonia in the laboratory animals and the extrapyramidal symptoms produced by neuroleptics in humans.[4] Hence, Morpurgo described a direct method to screen the drugs affecting dopamine receptors. He induced catatonia which is a state of neurogenic motor immobility and behavioural abnormality manifestations with stupor.[5] The occurrence and irreversibility of this neurological disorder with motor immobility in neuroleptic drug induced parkinsonism has been considered as a major clinical issue in the treatment of schizophrenic patients.[6]It has been claimed that with prolonged treatment in Parkinson's disease with anticholinergic drugs loses efficacy but there is no information concerning the effects of prolonged treatment in drug-induced Parkinsonism. The search for new drugs is needed to avoid such side effects while treating schizophrenia.

Natural products have received considerable attention by the researchers who work on reverse pharmacology. The traditional medicine practised in our country the leaves, stems, roots, flowers, fruits and seeds are being used as alternative and complementary therapy. Resvertarol, curcumin, ginsenoside, polyphenols and triptolides are derived from herbs and are used to treat various neurological diseases and disorders. Flavinoids, alkaloids and isoprenoids are the phytochemical constituents of herbal products which contain complex active therapeutic components. Therefore, it is frequently difficult to determine which component(s) of the herb(s) has more biological activity. The spice turmeric, which is one of the common commodities used in cooking by Indians derived from the root of the plant *Curcuma longa* has long been described as a treatment for several diseases inAyurvedic and traditional Chinese medicine for thousands of years. *Curcuma longa* (CL) belongs to the family Zingiberaceae and is cultivated in the countries of Southeast Asia. The active constituents of turmeric are the flavonoid curcumin (diferuloylmethane) and various volatile oils, including tumerone, atlantone, and zingiberone. Other constituents include sugars, proteins, and resins. The best-researched active constituent is curcumin, which comprises 0.3-5.4% of raw turmeric.[7] Bioactive derivatives of plants such as flavonoids, stilbenoids and alkaloids possess potent anti-oxidative and anti-inflammatory properties that improve the mitochondrial function and serve as cognitive enhancers. The aqueous extract of *Curcuma longa* being a herbal product has flavonoid as a bioactive derivative and italso has the tendency of passing through blood brain barrier (BBB), which may prove effective in treating drug induced PD and related neuropsychiatry disorders.

MATERIALS AND METHODS:

The adult Swiss albino mice weighing 25 – 30g were sourced from the institutional central animal house. The animals were divided randomly into five groups containing 6 in each group housed in five different polypropylene cages (32.5 × 21 × 14) cm and (24 × 14 × 12) cm lined with raw husk (renewed after 48 h). The cages were given different colour coding to carry out the experimental process blind. Animals were maintained in the cages under controlled lighting conditions (12hlight/12hdark regime), relative humidity (50±5%) and temperature (37±2ºC). Animals were maintained in the cages under controlled lighting conditions (12hlight/12h dark regime), relative humidity (50±5%) and temperature (37±2ºC). They were fed with mice pellets and provided *ad libitum* access to water. The study was approved by the Institutional Animal Ethics Committee and all the experiments were performed as per the Committee for the purpose of control and supervision on experiments on animals (CPCSEA) guidelines. Actophotometer and other instruments necessary in Morpurgo method were used in the department of pharmacology for this study. The formulations in the syringes were given different numbers by a faculty in the department of pharmacology to blind the procedure with the intervention.The 1st group of 6 mice was treated with vehicle and rest of the groups was treated with haloperidol. The 3rd, 4th and 5th groups of mice were pretreated with the aqueous extract of *Curcumalonga* 50mg, 100mg and 200mg/kg of body weight respectively 50mins before the administration of haloperidol.The intensity of catatonia was assessed by the locomotor activity tested in actophotometer on 8th and 15th day prior and at 2hrs, 4hrs, 6hrs and 22 hrs after the administration of drugs. Haloperidol was administered to induce catatonia in the dosage of 1mg/kg of body weight/day/animal intraperitoneally for 15 days.[4] The assessment was done as per Morpurgo scoring (Table 3) method on 8th and 15th day at 2hrs, 4 hrs , 6hrs and 22 hours of the last dosage.

STATISTICAL METHOD:

All the results are expressed as mean ± SEM. Data were analyzed by using One-way analysis ANOVA and Kruskal-Wallis followed by Post hoc test Dunn test with Bonferroni correction. Analysis was done using SPSS 11 software. $p<0.05$ was considered as statistically significant.

RESULTS

In this study the data are presented as mean ± SEM. Mean differences were evaluated by one–way ANOVA or Kruskal-Wallis test followed by Dunn test with Bonferroni correction using SPSS version 11. Haloperidol produced a time dependent increase in rigidity which exhibited as catatonia. The catatonia was progressively increased in intensity which reduced the locomotor activity (LMA) of the negative control group and attained complete recovery from rigidity at 22 hours on 8th day and 15th day (Table. 4). This was compared with the vehicle treated animals. Formulations II and III increased the LMA significantly which was comparable with the vehicle treated animals on the 15th day (Fig. 1).

Administration of haloperidol (1mg/kg) reduced LMA and increased the Morpurgo scoring at 2 hours in all the groups of animals (Fig. 2). The Morpurgo scoring showed reduction at 4 hours, 6hours with 0 scoring at 22 hours on 8th day and 15th day in all the treated groups of animals. However, the animals treated with formulations were comparable with the Morpurgo scoring with animals treated with haloperidol alone in negative control groups at 2 hours, 4 hours and 6 hours on 8th day and 15th day (Table.5). The catatonia scoring was recorded by Morpurgo method showed significant effect of reduction of rigidity in *Curcuma longa* pretreated animals ($F= 1.16$ at 4 hours and 0.66 at 6hours, $p< 0.05$). The effect of formulations on haloperidol induced catatonia tested by LMA and Morpurgo scoring showed the reduction in latency by increase in LMA after 4 hours on 15th day and reduction in rigidity by reduction in Morpurgo scoring after 4 hours on 15th day.

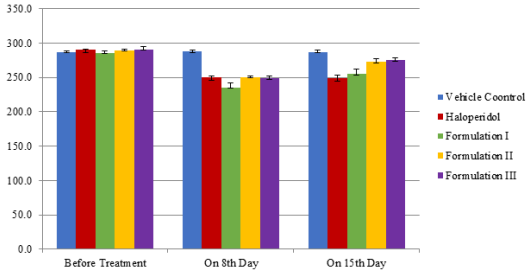
DISCUSSION:

There is no single laboratory model which can simulate parkinsonism with scientific significance to carry out a proper evaluation of antiparkinsonian activity. However, there is a positive correlation between catatonia in the laboratory animals and the extrapyramidal symptoms produced by haloperidol in humans as demonstrated by Morpurgo in the year 1962. Therefore, the haloperidol-induced catatonia, along with other tests adopted in this study may be considered a reasonable, though not total, approximation of the disease symptoms, providing at least one approach to evaluate the antiparkinsonian activity of aqueous extract of *Curcuma longa.*In this study, LMA and Morpurgo scoring indicated that administration of haloperidol significantly decreased the motor activity and increased the rigidity as exhibited by catatonia in mice. The findings were consistent with the previous study which has demonstrated that motor impairments following haloperidol administration.[26]In this study, aqueous extract of *Curcuma longa* at the dose of 100mg/kg and 200mg/kg in *Curcuma longa* pretreated mice produced significant augmentation in locomotor function which is in line with previous studies.[27]In CL + Haloperidol treated groups, when treated with CL of 100mg/kg and 200mg/kg produced significant improvement in muscular function which is in accordance with previous study which reported that CL extracts alleviated the dystrophic muscle pathology and enhanced muscle strength.[28]The present findings demonstrated that haloperidol induced locomotor dysfunction were reversed in aqueous extract of CL pretreated animals which further confirm the previous findings.[29]Therefore, the non-availability of Dopamine (DA) at the site of neuronal action responsible for the locomotor dysfunction and increase in rigidity of skeletal muscles. These alterations in DA and Dihydroxyphenylacetic acid (DOPAC) are associated with locomotor deficits and other motor disorders.[30]Studies have been reported that Curcumin improves DA levels.[31] In movement control DA acts as inhibitory neurotransmitter in basal ganglia and acetylcholine (Ach) acts as excitatory neurotransmitter. Due to decreased DA levels inhibitory influences are lost and excitatory mechanisms are overactivated. Increase in ACh levels due to lack of DA level in this study may be the cause of observed motor deficits in haloperidol treated mice. It may be suggested that in the present study treatment with aqueous extract of *Curcuma longa* activated the inhibitory mechanism and lowered the excitatory mechanisms as a result of which there was increase in DA levels which concomitantly normalized the levels of ACh and AChE activity. Therefore, administration of aqueous extract of *Curcuma longa* in this study by augmenting the cholinergic functions resulting in attenuation of typical catatonia which strengthens the protective role of curcumin present in the CL against cholinergic and dopaminergic imbalance which has not been studied earlier. These findings suggest the involvement of the central monoaminergic neurotransmitter systems for the locomotor effects of curcumin present in *Curcuma longa.* Kulkarni reported that curcumin water soluble extract is able to raise dopamine, norepinephrine and 5-HT levels in central nervous system.[32]It has also been reported that administration of curcumin (50, 100, 200 mg/kg) ameliorated cognitive deficits and mitochondrial dysfunctions symptoms in mice.[33]The neuro protective effects of CL in Parkinson's disease which is presenting with muscular rigidity are also related to its well-known anti-oxidant properties. Curcumin protects the neurons against reactive oxygen species (ROS) by restoring glutathione (GSH) and increasing superoxide dismutase (SOD). Some protective effects of the CL may be due to reduction of Ca^{++}, Na^{+} and enhancement of K^{+} level or 'anti-glutamatergic' effect. The neuroprotective effects of CL can occur via reduction of inflammatory cytokines as well as enhancement of anti-inflammatory cytokines, inhibition of the acetylcholinesterase activity and decreased DA levels in the neural system via modulating GABAergic and glutamatergic neurons, and also increasing amount of amino acids and serotonin (5-HT) in the neurotransmitters systems which may be investigated in continuing the studies in this line further.

CONCLUSION:

Animal models help us to clarify complex mechanisms and provide a reasonably reliable platform to test the potential of herbal extracts. They offer the opportunity to open a discussion between clinicians and biologists and shed new light through creative ideas that allow us to go beyond our usual way of thinking. The findings of the present study provide the evidence that daily administration of aqueous extract of *Curcuma longa* for period of fifteen days considerably alleviated the symptoms of parkinsonism like rigidity and bradykinesia when induced by haloperidol. It works by its unique mechanism of involvement in the monoaminergic neurotransmission in the central nervous system thereby promising newer avenues in the future management of drug induced Parkinsonism which has no specific remedial measures at present other than symptomatic long-term drug therapy. Studies of these animal models can thus help us to construct models that are specific to the psychopharmacology and neurobiology of human behavior, opening the path to innovative hypotheses and research.

FIG 1: Effect of formulation on locomotor activity using actophotometer:



Significant differences were obtained by one-way ANOVA followed by Dunnett post hoc test. $p<0.001$ as compared to control group ($n=6$). Values are mean ± SEM (n=6).

FIG 2: Effect of formulations on catatonia - assessed by morporgo scoring:

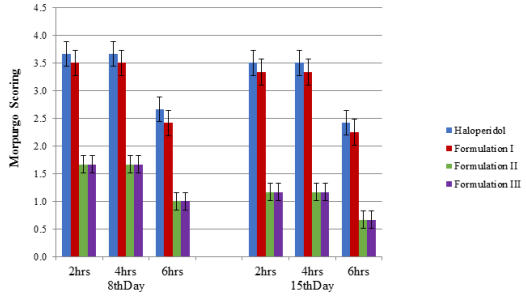


FIG 2: Effect of formulations on catatonia - assessed by morpurgo scoringValues are represented as mean ± SEM (n=6). Data was analyzed by Dunnett test following Kruskal Wallis. Mean values were significantly different than that for controls (p<0.05) and haloperidol (n=6) injected rats (p<0.05).

Table 1: Preparation Of Formulations

Formulation -1	*Curcuma longa* 50mg/kg + haloperidol 1mg/kg
Formulation-2	*Curcuma longa* 100 mg/kg + haloperidol 1mg/kg
Formulation-3	*Curcuma longa* 200 mg/kg + haloperidol 1mg/kg

TABLE 2: HALOPERIDOL INDUCED MODEL

GROUP	STUDY
1	Vehicle control
2	Negative control: treated with haloperidol(1mg/kg i.p)
3	Curcuma longa 50mg/kg + haloperidol 1mg/kg
4	Curcuma longa 100 mg/kg + haloperidol 1mg/kg
5	Curcuma longa 200 mg/kg + haloperidol 1mg/kg

TABLE 3: Morpurgo scoring assessment of severity of catatonia induced by haloperidol

STAGE	BEHAVIOUR	SCORE
STAGE 0	Mouse moves normally when placed on the table	0
STAGE 1	Mouse moves only when touched or pushed	0.5
STAGE 2	No movements seen in mouse when touched or pushed	0.5
STAGE 3	Mouse placed on the table with one of the front paws raised on a 3cm wooden block fails to correct the posture in 10 seconds	0.5 for each paw, therefore 0.5x2 = 1
STAGE 4	Mouse placed on the table with one of the front paws raised on a 9cm wooden block fails to correct the posture in 10 seconds	1 for each paw, therefore 1x2 = 2

TABLE 4: Effect of formulations on locomotor activity using actophotometer

Group	Drug Treatment	Lma Scorings			Percentage Change In Activity	
		Before drug administration	After drug administration			
			On 8th day	On 15th day	On 8th day	On 15th day
1	Vehicle control	286.41±1.99	287.41±2.67	287.00±2.44	0.34	0.20
2	Negative control Treated with Haloperidol 1mg/Kg (i.p)	290.33±1.00	250.08±1.33	249.33±3.95	-13.86	-14.12
3	CL 50mg/kg + Haloperidol 1mg/Kg(i.p)	285.83±2.59	235.50±6.73	254.91±7.60	-17.60	-10.81
4	CL 100mg/Kg + Haloperidol 1mg/Kg (i.p)	289.66±1.13	250.16±2.41	272.33±4.48	-13.63	-5.98
5	CL 200mg/Kg + Haloperidol 1mg/Kg (i.p)	290.58±4.11	248.50±3.00	275.00±3.53	-14.48	-5.36

CL-aqueous extract of *Curcuma longa*, LMA- Locomotor Activity Scoring

P<0.001, values are presented as mean ± SEM (n=6)

TABLE 5: Effect of formulations on catatonia - assessed by Morpurgo scoring

GROUP	DRUG TREATMENT	MORPURGO SCORING							
		ON 8th DAY				ON 15th DAY			
		2 Hours	4 Hours	6 Hours	22 Hours	2 Hours	4 Hours	6 Hours	22 Hours
1	Vehicle control	0.000.0	0.000.0	0.000.0	0.000.0	0.000.0	0.000.0	0.000.0	0.000.0
2	Negative control: treated with haloperidol (1mg/kg i.p)	3.660.2	3.660.21	2.660.21	0.000.00	3.500.22	3.500.22	2.410.27	0.000.00
3	CL 50mg/kg + haloperidol 1mg/kg	3.500.2	3.500.22	2.410.27	0.000.00	3.330.21	3.330.2	2.250.25	0.000.00
4	CL 100 mg/kg + haloperidol 1mg/kg	1.660.1	1.660.10	1.000.00	0.000.00	1.160.10	1.160.10	0.660.10	0.000.00
5	CL 200 mg/kg + haloperidol 1mg/kg	1.660.1	1.660.10	1.000.00	0.000.00	1.160.10	1.160.10	0.660.10	0.000.00

CL – Aqueous extract of Curcuma longa

P<0.001, values are presented as mean ± SEM (n=6)

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