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EVALUATING THE EFFECT OF EXTRACT OF HALELA SIYAH (*TERMINALIA CHEBULA* RETZ) ON CHEMICALLY INDUCED CATALEPSY IN MICE

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ABSTRACT

The objective of the present study was to evaluate the anticataleptic effect of *Halela siyah* (*Terminalia chebula* Retz) extract, on haloperidol induced catalepsy in swiss mice which were divided into four groups of six animals each. Animals in different groups were administered distilled water, scopolamine (1.0 mg/kg p.o) and hydroxy alcoholic (3:7) extract of *Halela siyah* (*Terminalia chebula* Retz), 1.5gm/kg and 3gm/kg p.o. respectively. Catalepsy was induced with haloperidol (1.0 mg/kg i.p.) administered 30 minutes prior to the drug administration. The duration of cataleptic time in the animals was assessed at 30 minute intervals up to 120 minutes and at the end of 240 minutes. Haloperidol induced catalepsy test was carried out for single dose study and after seven days of drug administration, to assess time and dose dependent effect of the test drug. The results showed that after the haloperidol administration, *Halela siyah* (*Terminalia chebula* Retz) extract in different doses was effective in reducing the cataleptic time significantly ($p<0.01$) in a time and dose dependent manner. The present study indicated that Bisfaij facilitates dopaminergic transmission and possibly acts as D2 receptor agonist and hence can be developed as an alternative/adjuvant drug in preventing and treating the extrapyramidal disorders.

INTRODUCTION: The fruit of *Terminalia chebula* Retz also called Halelah siyah in Unani system of medicine is being used for the treatment of different types of diseases and disorders since antiquity. *Terminalia chebula* Retz is a plant species belonging to the genus Terminalia, family combretaceae.

Terminalia chebula Retz occurs scattered in teak forests, mixed deciduous forests and is extending in to forests of comparatively dry types. It occurs at an altitude of up to 1500-2000m. The species is found on a variety of soils, clayey as well as shady [1, 2].

It is found in sub- Himalayan tracts from the river Ravi Eastwards to west Bengal and Assam and is also found in Central and South India [3]. *Terminalia chebula* Retz is called "the king of medicine" because of its extraordinary powers of healing with a wide spectrum of biological activity.

During the last five decades, apart from the chemistry of *Terminalia chebula* Retz constituents, considerable progress have been achieved regarding the biological activity and therapeutic use of *Terminalia chebula*.

It is now considered a valuable source of unique natural products for medicines against various diseases

and also for the development of industrial products. According to the Unani system of medicine *Halela siyah* is beneficial in *istirkha (*paralysis), *Izme Tehal* (splenomegaly), *Bawaseer* (piles), *Malikholia* (melancholia), *Juzam* (leprosy), coarsely powdered fruit with almond oil is *Mulayyin* (laxative) [3, 4, 5, 6]. Also the ripe fruit being purgative, tonic and carminative is used for diseases of spleen, blood nourishment, piles, brain tonic, cold in the head, opthalmia, and gum diseases and in paralysis [4, 6, 7].

The different compounds of *Terminalia chebula* Retz exhibited antioxidant activity at different magnitudes of potency.[8] The aqueous extract of the fruit possess protective effects on the tertbutyle hydroperoxide (t-BHP)-induced oxidative injury observed in cultured rat primary hepatocytes and rat liver [9]. It has strong antioxidant activity than alpha – tocopherol; HPLC analysis with diode array detection indicated the presence of hydroxybenzoic acid derivatives, hydroxycinnamic acid derivatives, flavonol aglycones and their glycosides, as main phenolic compounds [10].

Terminalia chebula Retz was found to possess antianaphylactic activities as it reduced the serum histamine levels in animals after induction of anaphylactic shock [11]. *Terminalia chebula* Retz resulted in the reduction of peroxidation of membrane lipids in the mice liver as well as decrease in radiation induced damage to DNA in mice who were given aqueous extract of the fruit prior to whole body irradiation [12].

A world wide problem observed in the treatment of psychiatric disorders is the neuroleptic induced movement disorders and also because of limited affordability of atypical antipsychotic drugs. Moreover, the atypical antipsychotics can cause extra pyramidal symptoms [13]. Catalepsy is observed in animals that have been given certain drugs, particularly dopaminergic blockers such as neuroleptics [14].

Strict correlation has been demonstrated between strength of cataleptogenic action of a neuroleptic and its efficacy. Thus, experimental catalepsy serves as a faithful index for the assessment of extra pyramidal syndromes in human beings and to study the behavioral mechanisms of neurochemical systems [15].

Haloperidol, a typical antipsychotic is known to induce catalepsy through the blockade of dopaminergic action in the nigro-striatal pathway producing extra pyramidal motor side effects such as dystonia, pseudo-parkinsonism etc [16]. Central cholinergic system has also been involved in haloperidol-induced catalepsy as its enhanced stimulation or antagonism results increased or decreased cataleptic state [1].

Thus, keeping in view the earlier studies carried out for screening the effect of *Terminalia chebula* Retz on CNS and the involvement of dopaminergic system in the behavioural changes, the present study was envisaged to screen its anticataleptic activity.

MATERIAL AND METHODS:

Physicochemical parameters: The physicochemical parameters of the powder of the seeds of *Terminalia chebula* Retz viz. Total ash, water soluble ash, acid insoluble ash, pH, volatile oil content, moisture content, presence of fixed oil and specific gravity were determined.

Animals: Adult Swiss Albino mice of either sex (weighing 25-30gm) and 1-2 months of age bred in the Central animal house facility, National Institute of Unani Medicine, Bangalore, were used for the study. They were acclimatized before the experiment to the laboratory conditions of the institute. They were housed in polypropylene cages at 25±2^{o}C, photoperiod: 12 hours natural light and 12 hrs dark, humidity 50%-55% and were provided with food and water *ad libitum*. Between 10:00 and 16:00 hrs all the experimental procedures were performed and each animal was used once. The experimental protocol was approved by Institutional Animal Ethics Committee for ethical clearance (protocol no. IAEC/IV/01/IA), study was carried according to CPCSEA guide lines.

Drugs and Dosage: The test drug samples i.e., dried fruits of Halela siyah (*Terminalia chebula* Retz) was procured from the market at Bangalore and was authenticated by a pharmacognocist at the Regional Research institute (Ayurveda), Ashoka pillar, Jayanagar, Bangalore with a voucher number RRI/BNG/SMP/Drug Authentication/2009-10/337. After that it was powdered and the powder obtained was extracted with 70% hydro alcohol by Soxhlet apparatus at a

temperature of 70°C – 80°C for 8 hours. The extract obtained was then concentrated using water bath, and yield percentage was calculated and was found to be 22.51% w/w. The doses of the drug for swiss mice were calculated as described by Frariech *et al*, interpolated from the clinical dose as stated in Unani texts [12].

The test drug Halela siyah (*Terminalia chebula* Retz) and scopolamine (Sigma- Aldrich Chemicals, USA) were dissolved in Tween-80 (1%) solution (vehicle). All the drug solutions were freshly prepared and were administered to the animals orally using gavage with a guide cannula (4cm×1mm OD), while haloperidol (RPG Life Sciences Ltd. Mumbai) was dissolved in distilled water and given intraperitoneally (i.p.). The number of animals and the treatment received by each group is shown in **table 1 and 2**.

Experimental design: For all the tests except otherwise, healthy Swiss mice of either sex were divided into four (4) groups, having equal number of animals, as under:

Group-I: Negative control group. It was administered Haloperidol 1mg/kg, i.p.

Group-II: Standard control group. It was administered scopolamine 1mg/kg, p.o

Group-III: Test group. It was treated with Halela siyah (*Terminalia chebula* Retz) extract 1.5gm/kg p.o.

Group-IV: Test group. It was treated with Halela siyah (*Terminalia chebula* Retz) extract 3gm/kg p.o.

Acute Study (Single dose study): The test was carried out by employing standard bar test [17]. Catalepsy was induced with haloperidol (1.0 mg/kg i.p.) and was assessed at 30 minutes intervals until 120 minutes and at the end of 240 minutes [18, 19]. Haloperidol (1mg/kg i.p.) was chosen so that it could elicit a moderate degree of catalepsy and thus enabled the detection of either attenuation or potentiation of the phenomenon.

Methodology: Animals in various groups as described were administered respective drugs 30 minutes prior to the administration of haloperidol 1mg/kg i.p. Catalepsy was assessed in terms of the time for which the mouse maintained an imposed posture with both front limbs extended and resting on a 4.5 cm high wooden bar (1.0 cm diameter). The end point for catalepsy was considered to occur when both front paws were removed from the bar or if the animal moved its head in an exploratory manner. Maximum cut-off time of 1100 seconds was applied. The animals were returned to their individual home cages after each assessment.

All observations were made between 10.00 and 16.00 hrs in a quiet room at 23-25°C. If an animal maintained the imposed posture for at least 20 seconds, it was considered to be cataleptic and was given one point. For every additional 20 seconds for which the cataleptic posture was maintained, one extra point was given. The animals were tested twice at 30 minutes time intervals and only the greater duration of immobility was considered [20].

Chronic study (Multiple dose study): In the chronic study, the animals in each group were administered their respective drugs in the same dosage as in acute study once daily, 30 min prior to the haloperidol administration for seven days. Catalepsy was assessed by the bar box 30 min after haloperidol administration on the first and on the seventh day of treatment.

Statistical Analysis: The data of different groups were statistically analyzed by using ANOVA One way followed by Tukey-Kramer multiple comparison test. The values were expressed as mean ± SEM, $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION:

Physicochemical studies: The successive extractive values, total ash, acid insoluble ash and water soluble ash are given in the Table 1. The results showed that the highest extractive value was in hydro-alcoholic solvent (27.44 ±0.61) followed by aqueous (21.32±0.33) and alcoholic solvents (5.72±0.53). The moisture content estimated by dry oven and Toluene distillation method showed 9.70% and 10%, respectively. The volatile content was found to be <1%, while the presence of fixed oil was observed. The pH was determined in 1% and 10% aqueous solution at 350C of temperature and found to be 6.6 and 6.3, respectively. The values are given in Table 1.

TABLE 1 : PHYSICOCHEMICAL OBSERVATION OF THE SEEDS OF *TERMINALIA CHEBULA* RETZ.

Ash values (%)	
Total ash :	8.23%
Water soluble ash :	1.48%
Acid insoluble ash :	3.85%
Moisture content :	9.7%
Volatile content :	<1%
Specific gravity :	1.023
Fixed oil : Present	
pH Values	
1% solution :	6.60
10% solution :	6.30
Loss on drying at 105^0 :	7.73%

Acute study (Single dose study): In the acute study, the results showed that at 30 minute all doses of the test drug gave cataleptic scores similar to that of the negative control. However, from 60minutes onwards after haloperidol administration, the standard drug (scopolamine) and all other groups showed significantly ($p<0.01$) lower cataleptic time than the negative control group.

When the mean cataleptic time of different groups at different time intervals were compared with respect to negative control at 30minutes, *Halelah siyah* (3gm/kg) at 120 minutes was found almost similar to negative control ($p>0.05$) at 30 minutes. Similarly, Halelah siyah in the doses of 1.5gm/kg and 3gm/kg at 240 minutes resulted significantly ($p<0.001$) lower score than the negative control at 30 minutes.

The mean cataleptic score of various groups when compared with respect to standard control (scopolamine, 1gm/kg) at 30 minutes it was observed that *Halelah siyah* (1.5gm/kg) at 120 minutes produced almost similar effect ($p>0.05$) on cataleptic time as that of standard drug. However, Halelah siyah (1.5gm/kg) at 240 minutes and *Halelah siyah* (3gm/kg) at 120 minutes and 240 minutes showed significant ($p<0.01$) reduction in cataleptic time.

The test drug was actually more protective against the haloperidol induced catalepsy than the standard drug (scopolamine). The mean cataleptic time of different groups at various time intervals when compared with respect to negative control at 240 minutes, showed statistically significant ($p<0.01$) reduction in the cataleptic score.

The mean cataleptic time of Halelah siyah (1.5gm/kg) at 30 minutes when compared with mean cataleptic time of other groups, also showed that Halelah siyah (1.5gm/kg and 3gm/kg) at 240 minutes reduced cataleptic time significantly($p<0.01$).The results are summarized in **table 2 and fig. 1 and 2**.

TABLE 2: EFFECT OF SINGLE DOSE ADMINISTRATION OF TEST DRUGS ON HALOPERIDOL –INDUCED CATALEPSY (Values aremean ± SEM)

Groups	Duration of catalepsy (in seconds)				
	30min	60min	90min	120min	240 min
Haloperidol 1mg/kg]	225.34±1.552 ^{c}	493.10±1.312 ^{a,b,c,,d}	675.36±2.503 ^{a,b,c,,d}	946.65±2.481 ^{a,b,c,,d}	1014.0±4.797 ^{a,b,,d,}
[Scopolamine (1mg/kg) +Haloperidol (1mg/kg)]	253.18±2.784 ^{c}	338.17±3.320 ^{a,b,c,,d}	441.16±2.408 ^{a,b,c,,d}	582.50±1.703 ^{a,b,c,,d}	344.32±2.301 ^{a,b,c,,d,}
[Halela (1.5 gm/kg) +Haloperidol (1mg/kg)	249.31±4.321 ^{c}	450.00±3.321 ^{a,b,c,,d}	339.16±5.523 ^{a,b,c,,d}	259.01±2.783 ^{a,c}	180.11±2.621 ^{a,b,c,,d,}
[Halela (3 gm/kg) +Haloperidol (1mg/kg)]	248.01±4.560 ^{c}	436.00±2.791 ^{a,b,c,,d}	313.51±2.599 ^{a,b,c,,d}	230.62±3.201 ^{b,c,,d}	157.50±3.129 ^{a,b,c,,d}

n=6 in each group, Test use: Intra Group Comparison: by Repeated ANOVA with Tukey-Kramer multiple comparison test as post test.Intergroup comparison: by Non- Repeated ANOVA with Tukey-Kramer multiple comparisons test as post test. A p< 0.001,a*-p<0.05w.r.t negative control group at 3o minutes. b-p<0.001, b*-p<0.05w.r.t standard control group at 30 minutes. c-p<0.001, c*-p<0.05w.r.t negative control at 240 minutes. d-p<0.001, d*-p<0.05w.r.t Halela (lower dose) at 30 minutes.

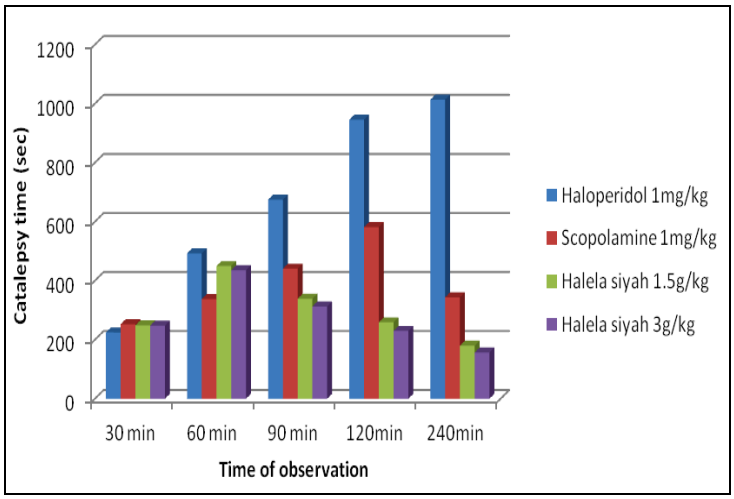

FIG. 1: EFFECT OF ACUTE ADMINISTRATION OF TEST DRUGS ON HALOPERIDOL INDUCED CATALEPSY

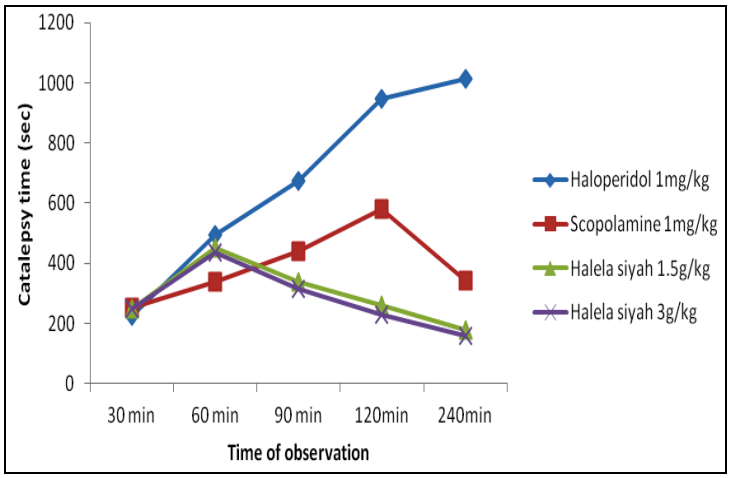

FIG. 2: EFFECT OF ACUTE ADMINISTRATION OF TEST DRUGS ON HALOPERIDOL INDUCED CATALEPSY

Chronic study (Multiple dose study): In the multiple dose study, cataleptic state of each group at 30 minutes when compared with respect to negative control was almost similar.

However, from 60 minutes onwards, after haloperidol administration, all the doses of the test drug and standard drug resulted in significantly lower cataleptic score than the negative control group.

Scopolamine (1gm/kg) at 240 minutes and Halelah siyah (1.5gm/kg) at 240 minutes showed statistically significant ($p<0.01$) reduction in the cataleptic time than the negative control at 30 minutes in a dose and time dependent manner. When the mean cataleptic time of different groups at different time intervals was statistically compared with respect to standard drug (scopolamine 1gm/kg) at 30 minutes, it was observed that Halelah siyah (3gm/kg) at 120 minutes and at 240 minutes showed statistically significant ($p<0.01$) reduction in the cataleptic time as compared to the standard drug. When the mean cataleptic time of different groups at various time intervals was compared with respect to negative control at 240 minutes, statistically significant ($p<0.01$) reduction in the cataleptic time was observed in almost all groups.

When the mean cataleptic time of different groups was compared with *Halelah siyah* (1.5gm/kg) at 30 minute, it was observed that, *Halelah siyah* (3gm/kg) at 120 minutes were almost equally effective ($p>0.05$). Halelah siyah (3gm/kg) at 240 minutes showed statistically significant ($p<0.01$) reduction in the cataleptic time than Halelah siyah (1.5gm/kg) at 30 minute. Thus the above observations indicate that, the Halelah siyah showed a dose and time dependent protective effect against haloperidol-induced catalepsy. The results are summarized in **table 3 and fig. 3 and 4.**

TABLE 3: EFFECT OF MULTIPLE DOSE ADMINISTRATION OF TEST DRUGS ON HALOPERIDOL –INDUCED CATALEPSY (Values aremean ± SEM)

Groups	Duration of catalepsy (in seconds)				
	30min	60min	90min	120min	240 min
[Haloperidol 1mg/kg]	254.82±2.591 [c]	361.65±3.879 [a,b,c,d]	498.01±4.812 [a,b,c,d]	682.79±4.037 [a,b,c,,d]	738.23±3.500 [a,b,c,d]
[Scopolamine (1mg/kg) +Haloperidol (1mg/kg)]	247.01±3.721 [c]	299.00±3.318 [a,b,c,d]	356.81±3.211 [a,b,c,,d]	321.32±2.599 [a,b,c,,d,]	272.17±2.471 [a,b,c,,d]
[Halela (1.5 gm/kg) +Haloperidol (1mg/kg)	239.00±2.879 [c]	301.81±4.391 [a,b,c,d]	379.49±2.410 [a,b,c,,d]	338.49±3.140 [a,c]	276.18±2.081 [a,b,c,,d]
[Halela (3 gm/kg) +Haloperidol (1mg/kg)]	241.80±4.560 [c]	421.00±2.291 [a,b,c,,d],	290.64±3.791 [a,b,c,d]	229.50±2.670 [b,c,d]	174.59±2.259 [a,b,c,d]

n=6 in each group, Test use: Intra Group Comparison: by Repeated ANOVA with Tukey-Kramer multiple comparison test as post test.Intergroup comparison: by Non- Repeated ANOVA with Tukey-Kramer multiple comparisons test as post test. A p< 0.001,a*-p<0.05w.r.t negative control group at 3o minutes. b-p<0.001, b*-p<0.05w.r.t standard control group at 30 minutes. c-p<0.001, c*-p<0.05w.r.t negative control at 240 minutes. d-p<0.001, d*-p<0.05w.r.t Halela (lower dose) at 30 minutes.

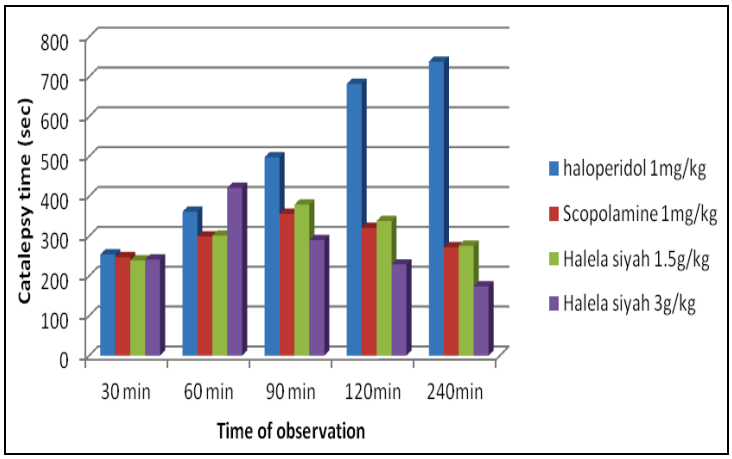

FIG. 3: EFFECT OF CHRONIC ADMINISTRATION OF HALELAH ON HALOPERIDOL INDUCED CATALEPSY

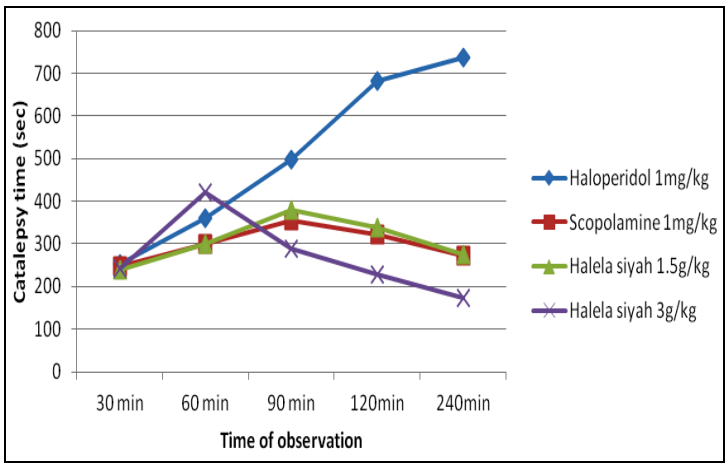

FIG. 4: EFFECT OF CHRONIC ADMINISTRATION OF HALELAH ON HALOPERIDOL INDUCED CATALEPSY

DISCUSSION AND CONCLUSION: The data obtained both in humans and laboratory animals, point to the blockade of a large number of the striatal dopamine D2 receptors by neuroleptics such as chlorpromazine, haloperidol and reserpine as a primary cause of neuroleptic induced extrapyramidal side effects. Thus catalepsy is used as a model to assess the extrapyramidal effects of antipsychotics. Besides dopamine receptor blockade and catecholamine depletion, other neurochemical hypothesis has been proposed for the development of catalepsy such as striatonigral, GABAergic, cholinergic, glutamate and serotonergic etc [21, 22].

In addition to various neurotransmitters, many preclinical and clinical studies have also proposed reactive oxygen species as causes of haloperidol induced toxicity. In an attempt to confirm that the observed catalepsy is not caused by peripheral mechanism, anticholinergic agent scopolamine, which is transported into the brain in vivo, was administered intraperitoneally. In presence of scopolamine, the catalepsy induced by the haloperidol was remarkably reduced, indicating that catalepsy reflects the effect in the central nervous system. In the present study Halela siyah (*Terminalia chebula* Retz) was protective against drug induced catalepsy as effectively as that of standard drug scopolamine.

Phytochemical studies have shown that the fruit of *Terminalia chebula* Retz. contains different pharmacologically active constituents, like gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulanic acid, ellegic acid, chebulagic acid, chebulinic acid, 1,2,3,4,6-penta- Ogalloyl- β-D-glucose, 1,6,-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-galloyl-Dglucose,terchebulinother constituents which have been shown to possess activity against many CNS disorders [23, 24, 25].

Thus, the results suggest that extracts of Halela siyah (*Terminalia chebula* Retz) contains constituents that facilitate dopaminergic transmission and possibly act as D2 receptor agonists.

CONCLUSION: The fruit of *Terminalia chebula* Retz has been used in a multitude of diseased conditions since from ages. The medicinal property of the *Terminalia chebula* Retz has been variedly described in different types of traditional medicines like Unani, Ayurveda, European and American. From the above study, it can be concluded that the drug possess protective effect in chemically induced catalepsy and can be used for various neurological and neurodegenerative disorders also**.** The presence of different pharmacologically active constituents may be responsible for the same. However, further study is needed to know the exact mechanism.

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