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Evaluation Of *Camellia sinensis*, *Withania somnifera* and their Combination for Antioxidant and Antiparkinsonian Effect

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Abstract:

Aims: *Camellia sinensis* and *Withania somnifera*, well known for antioxidant potentials, in present work hydroalcoholic extract of *Camellia sinsnsis* (HECS), *withania somnifera* (HEWS) and 1:1 combination mixture has been studied for protective effect against haloperidol, reserpine and tacrine induced neuronal damage.

Mehods: Albino Mice either sex were treated with haloperidol (0.5 mg/kg) and wistar rats either sex were treated with reserpine (1 mg/kg) and tacrine (5 mg/kg) intraperitoneally. HECS, HEWS and mixture was administered at different doses of 30 mg/kg and 100 mg/kg (p.o) indifferent groups 30 min prior to haloperidol, reserpine and tacrine. Behavioural changes due to neuronal damage and antioxidant status were analysed. Behavioural changes were observed by using bar test, Actophotometer and Plexiglas chamber.

Results: 1:1 mixture (HECS:HEWS) significantly (P<0.05) improved antioxidant status and behavioural activities altered by haloperidol induced catalepsy, reserpine induced hypolocomotion and tacrine induced vacuous chewing movement, orofacial brusts in a dose dependant manner.

Conclusion: 1:1 mixture possesses antioxidant activity and protects neuronal damage which is more noticeable at dose of 30 mg/kg against haloperidol induced catalepsy, reserpine induced hypolocomotion and tacrine induced vacuous chewing movements and orofacial brust.

Keywords: Antioxidant, Antiparkinson, *Camellia sinensis*, *Withania somnifers*, Haloperidol, Reserpine, Tacrine

INTRODUCTION:

Neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's and multiple sclerosis are associated with the process of memory loss and cognitive decline which results from selective degeneration of particular neuronal cells and the deposit of aggregated proteins. Parkinson's disease (PD) is mainly characterized as a movement disorder but non-motor symptoms are also involved. Since dopamine is associated with motor activity, the progressive loss of dopaminergic neurons in PD leads to muscle rigidity, tremors and bradykinesia as well as cognition, mental, sleeping, personality and behaviour disorders including depression and anxiety [1-2]. The mechanisms responsible for dopaminergic neuronal loss in PD are complex and yet unclear. Pathogenic factors such as oxidative and nitrosative stress, mitochondrial dysfunction, apoptosis, inflammatory responses and excitotoxicity have been proposed for the degeneration of dopaminergic neurons. Literature review suggests increased reactive oxygen species (ROS) and oxidative damage in the cascade of events leading to degeneration of dopaminergic neurons. This is mainly due to the observations that increased level of lipid peroxidation, modifications of proteins, and DNA and RNA oxidation products are seen in the brain of Parkinsonian patients [3-4]. Currently, there is no cure for PD and the drugs used for treatment are levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors, which provide only symptomatic relief. Levodopa has been considered the gold standard drug therapy for Parkinson's disease but it is limited only to relieving symptoms and its long term use may cause serious side effects that include involuntary movements (dyskinesia), the on-off effect may cause Parkinson's related movement problems to appear and disappear suddenly and unpredictably. The side effects of allopathic medicines for PD are highly alarming; hence, the current research is now focusing on herbs used in alternative systems of medicine as neuroprotective [5]. In this quest, some herbs have been found to be effective neuroprotectants. Phytoconstituents like polyphenols, flavonoids exhibit antiparkinsonian activity against experimentally induced PD. *Withania somnifera* and *Camellia sinensis* are an important plants used in Ayurveda for the treatment of various disorders of the CNS and are rich in polyphenols, flavonoids, alkaloids and lactones. *Camellia sinensis* is popularly known as Green Tea belonging to Theaceae family. The most important phytoconstituents of *Camellia sinensis* are polyphenolic compounds known as catechins including epigallocatechin gallate (EGCG), catechin (C), epicatechin (EC), gallocatechin (GC), gallocatechin gallate (GCG), epigallocatechin (EGC), and epicatechin gallate (ECG). Flavonols contribute to the antioxidant capabilities of tea leaves. The aglycones of the main flavonols in tea leaves are quercetin, kaempferol, and myricetin. Pharmacologically active constituents of *Camellia sinensis* have been shown to possess hepatoprotective, cardioprotective, neuroprotective, anticancer, antiobesity, antidiabetic, antibacterial, antiviral and antioxidant effects. Antioxidant property of catechin contributes to protection from neurodegeneration [6-7]. *Withania somnifera* commonly known as Ashwagandha, Asgand, Indian ginseng, and winter cherry belongs to the family Solanaceae is an important medicinal plant that has been used in Ayurvedic and indigenous medicine. The biologically active chemical constituents are alkaloids (isopelletierine, anaferine), steroidal lactones (withanolides, withaferins), saponins containing an

additional acyl group (sitoindoside VII and VIII), and withanolides with a glucose at carbon 27 (sitoindoside IX and X). *Withania somnifera* is used to calm the mind, relieve weakness and nervous exhaustion, build sexual energy and promote healthy sleep. The herb is termed a rasayana, means it acts as a tonic for vitality and longevity. Numerous studies indicated that *Withania somnifera* possesses antioxidant, antitumor, antistress, anti-inflammatory, immunomodulatory, hematopoietic, anti-ageing, anxiolytic, antidepressive, rejuvenating properties and also influences various neurotransmitter receptors in the central nervous system [8-9]. Dopamine transmission blockade results in catalepsy which has been used as an animal model for screening of antiparkinsonian drugs and haloperidol induces catalepsy via D2 receptor antagonism [11]. Dyskinesia a major symptom of Parkinson's disease and reserpine shows effect on monoamine-delpleting agent on motor activity hence reserpine induced hypolocomotion is suitable animal model for studying locomotor activity [15]. Vacuous jaw movements and purposeless chewing are different orofacial movements occurred in central muscarinic receptor stimulated rats, hence anticholinesterase inhibitor, tacrine, is used to induce orofacial dyskinesia [13-14, 27]. This experimental study was done to evaluate the neuroprotective activity of the Hydroalcoholic extracts of these two plants, *Withania somnifera* and *Camellia sinensis*, with different anti-parkinsonian animal models with a view that these plant extracts shall have no or at least reduced adverse effect so that it can be used for long duration.

MATERIALS AND METHODS:

Experimental Animals

Experiments were performed using Wistar rats either sex weighing 180-200g and Albino mice either sex 20-25g. Animals were maintained at 22°C ± 2°C on a standard pellet diet and tap water ad libitum. Institutional Animal Ethics Committee for Animal Experiments of Sanjivani College of Pharmaceutical Education and Research, Kopargaon, approved the study under the protocol SCPER/CPCSEA/IAEC/2019-20/01 and all experiments were conducted in accordance with guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Behavioural tests were performed during the light cycle between 10.00 a.m. and 4.00 p.m.

Drugs and Chemicals

Tacrine and Reserpine were purchased from Sigma, Aldrich, Mumbai. All other chemicals used were of analytical grade and purchased from standard manufacturer.

Plant material and extraction

Dry powder of *Withania somnifera* roots and *Camellia sinensis* leaves was purchased from local market and were authenticated from department of Pharmacognosy, Sanjivani College of Pharmaceutical Education and Research, Kopargaon.

Hydroalcoholic extracts were prepared using Soxhlet extractor. The extracts were filtered and dried. Extracts were subjected to phytochemical screening [10]. The extracts were administered in doses of 30 and 100 mg/kg (p.o.). Control group was given only vehicle in equivalent volume of plant extract.

Experimental design

Animals were randomly divided into seven groups of 5 animals each. Group I-Control: Haloperidol (0.5 mg/kg) or Reserpine (1 mg/kg) or Tacrine (5 mg/kg), Group II-HECS (30 mg/kg), Group III-HECS (100 mg/kg), Group IV-HEWS (30 mg/kg), Group V-HEWS (100 mg/kg), Group VI-1:1 Mixture (HECS:HEWS) (30 mg/kg) and Group VII-1:1 Mixture (HECS:HEWS) (100 mg/kg). These seven groups were used for treatment of Parkinson's symptoms.

Assessment of anti-parkinsonian activity

Haloperidol induced catalepsy

Albino mice either sex (weighing 20-25g) were divided into seven groups of five each. Animals were pre-treated with vehicle, HECS (30 and 100 mg/kg, p.o.), HEWS (30 and 100 mg/kg, p.o.), 1:1 HECS+HEWS (30 and 100 mg/kg, p.o.) and L-DOPA (30 mg/kg, p.o.) 30 min before haloperidol (0.5 mg/kg, intra-peritoneal). The duration of catalepsy was measured at 0, 30, 60, 90, 120, 150 and 180 min after haloperidol administration using bar test. Both the forepaws of the animals were placed on a wooden bar elevated 3 cm above the ground. The cut-off time (time for which animal was placed on elevated bar) was 300 seconds [11-12].

Tacrine induced jaw movements

The observation chamber consisted of a clear Plexiglas box measuring 28×28×28 cm, which had a wire mesh floor. The box was elevated 42 cm from the surface of the table, allowing behavioural observation from all angles. Rats were divided into groups and treated with vehicle, HECS (30 and 100 mg/kg, p.o.), HEWS (30 and 100 mg/kg, p.o.), and 1:1 HECS+HEWS (30 and 100 mg/kg, p.o.). After 30 min, tacrine (5 mg/kg i.p.) was administered and the number of chewing movements and orofacial bursts were measured every ten min for 60 min. Chewing movement was defined as a rapid repetitive movement largely of the jaw, which resembled to chewing but is not directed at any particular stimulus [13-14].

Reserpine-induced hypolocomotion

Reserpine was injected intraperitoneally at a dose of 1 mg/kg in a suspension with Tween-80, 30 min after the rats were treated with vehicle, HECS (30 and 100 mg/kg, p.o.), HEWS (30 and 100 mg/kg, p.o.), and 1:1 HECS+HEWS (30 and 100 mg/kg, p.o.). The effect of the study compounds on reserpine-induced hypolocomotion was assessed using Actophotometer (Dolphin, India). The locomotor activity of the animals was measured for 2 min, at 1 h, 2h and 3h after reserpine had been administered [15].

Antioxidant activity

DPPH scavenging assay

The free radical scavenging activity of the HECS and HEWS was measured in terms of hydrogen donating or radical scavenging ability using the stable free radical DPPH. 0.1 mM solution of DPPH in methanol was prepared and 1 ml of this solution was added to 3 ml of

HECS and HEWS solution in water at various concentrations (2-1000 µg/ml). The mixture was incubated for 45 min at room temperature and the absorbance was measured at 517 nm against the corresponding blank solution. Ascorbic acid was used as reference standard. Percentage inhibition of DPPH free radical was calculated using the following equation:

% inhibition= [(absorbance of control – absorbance of test)/absorbance of control] X 100

The antioxidant activity was expressed as IC_{50}. The IC_{50} value was defined as the concentration in µg/ml of the extract that inhibits the formation of DPPH radicals by 50% [16-18].

H_2O_2 scavenging activity

A solution of H_2O_2 (40 mM) was prepared in phosphate buffer (pH 7.4). 3.4 ml (16 – 1000 µg/ml) extract in phosphate buffer were added to H_2O_2 (0.6 ml, 40 mM). Absorbance was determined at 230 nm after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage of H_2O_2 scavenging of HECS and HEWS and ascorbic acid (reference standard) was calculated as:

% H_2O_2 Scavenging activity= [(absorbance of control – absorbance of test)/absorbance of control] x 100

The antioxidant activity was expressed as IC_{50} [16-18].

Statistical analysis

Results were expressed as mean ± SEM. Statistical analysis was done by using one way analysis of variance (ANOVA) followed by Dunnetts test. Statistical significant values were considered when $P<0.05$.

RESULTS:

Haloperidol Induced Catalepsy

At a dosage of 0.5 mg/kg i.p., haloperidol produced a significant cataleptic response. The duration of haloperidol-induced catalepsy was significantly ($P<0.05$) reduced by the administration of 30 and 100 mg/kg doses of HECS, HEWS and combination of thereof. Marked reduction ($P<0.001$) of catalepsy was observed in Mixture 1:1 of 30 mg/kg and 100 mg/kg as shown in Fig. no. 1.

Tacrine induced vacuous chewing movements and orofacial bursts

In tacrine induced vacuous chewing model, maximum number of vacuous chewing movements was observed during 30‑40 min interval. Pre-treatment with HECS (100 mg/kg) significantly ($P<0.001$) reduced the tacrine induced vacuous chewing movements. Mixture 1:1 (30mg/kg) pre-treatment also significantly ($P<0.001$) reduced the tacrine induced vacuous chewing movements as shown in Fig. no. 2. Tacrine induced orofacial bursts were significantly ($P<0.05$) reduced in all doses but1:1 mixture of 30 mg/kg and HECS 100 mg/kg showed significant ($P<0.001$) reduction in orofacial burst as shown in Fig. no. 3.

Reserpine induced hypolocomotion

Hypolocomotion is induced in animals by giving 1 mg/kg reserpine. Treatment with 30 mg/kg and 100 mg/kg HECS attenuated reserpine-induced hypolocomotion at 3h and at 1h respectively. As compared with control group, HEWS at 30 mg/kg attenuated reserpine-induced hypolocomotion from first to third hour shows significant ($P<0.01$) reduction in hypolocomotion as shown in Table No. 1.

Antioxidant activity

DPPH scavenging assay

Mixture of HECS & HEWS shown strong DPPH scavenging activity. The scavenging effect of mixture and HECS was comparable to ascorbic acid. The IC_{50} value of HECS, HEWS, Mixture (1:1), and ascorbic acid was 20.10, 19.16, 15.46 and 12.49 µg/ml respectively as shown in fig. no. 4.

H_2O_2 scavenging activity

Mixture of HECS & HEWS shown strong H2O2 scavenging activity. The scavenging effect of mixture and HECS was comparable to ascorbic acid. The IC_{50} values of HECS, HEWS, Mixture and ascorbic acid was 17.98, 18.85, 14.70 & 13.62 µg/ml respectively as shown in fig. no. 5.

Table no.1: Effect of HECS, HEWS and its mixture in reserpine induced hypolocomotion

Treatment	Locomotor count/5 min (mean ± SEM)		
	1h	2h	3h
Control	44.6±2.13	28.8±8.73	47.8±2.22
HECS (30mg/kg)	53±6.30	42.2±3.01	91.4±6.65**
HECS (100mg/kg)	133.4±3.22***	76.2±6.71	93.4±14.55
HEWS(30mg/kg)	139.6±11.96**	94.2±3.59**	54.6±1.54*
HEWS(100mg/kg)	41±2.55	41.2±2.69	60.2±1.77*
Mixture 1:1(30mg/kg)	36.6±2.56*	49.6±6.49	30.6±3.23*
Mixture 1:1(100mg/kg)	39±4.09	49.4±1.97	30.8±2.35**

All the values are expressed as mean ± SEM; n=5, *p<0.05, **p<0.01, ***p<0.001 significant compared to control (repeated measures ANOVA followed by Dunnett's test).

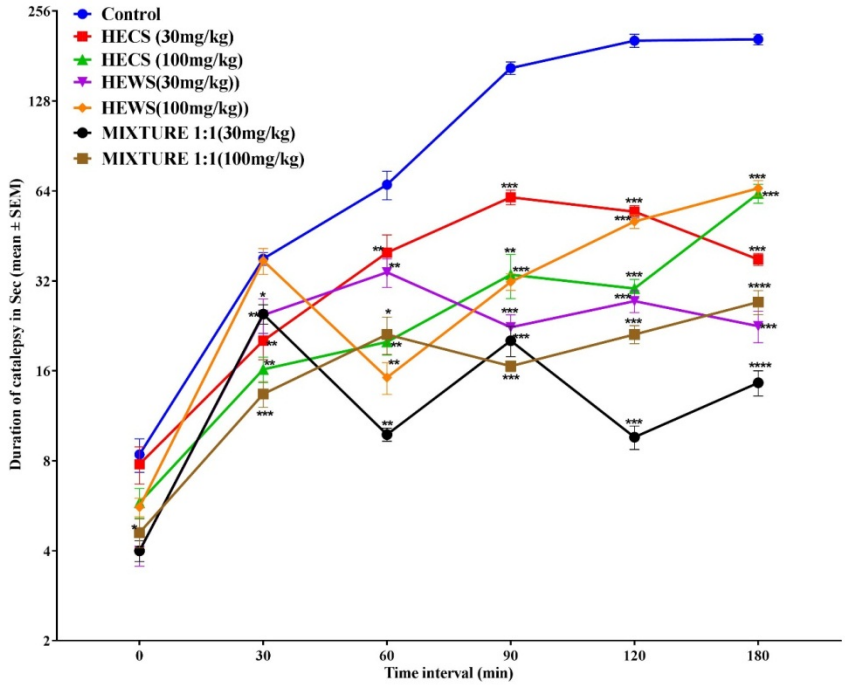

Figure no. 1: Haloperidol induced catalepsy

Effect of HECS, HEWS and its combination on Haloperidol induced catalepsy. All the values are expressed as mean ± SEM; n=5, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 significant compared to control (repeated measures ANOVA followed by Dunnett's test).

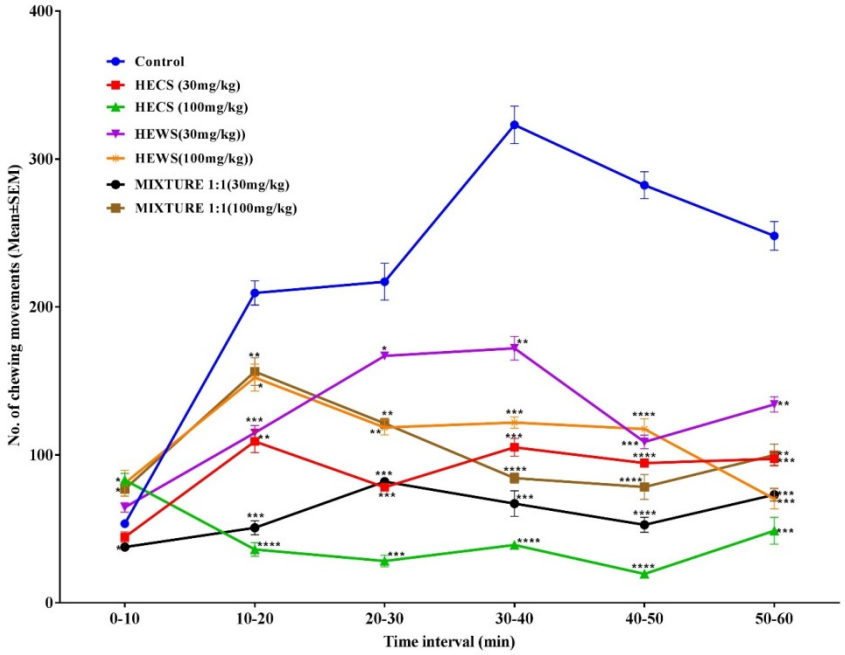

Figure no. 2: Tacrine induced vacuous chewing movements

Effect of HECS, HEWS and its combination on Tacrine induced vacuous chewing movements. All the values are expressed as mean ± SEM; n=5, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 significant compared to control (repeated measures ANOVA followed by Dunnett's test).

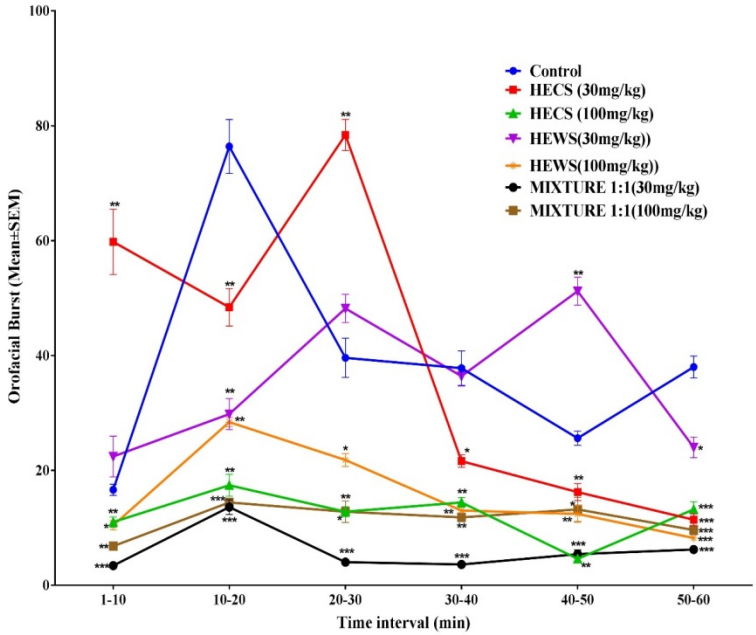

Figure no. 3: Tacrine induced orofacial brusts

Effect of HECS, HEWS and its combination on Tacrine induced orofacial brusts. All the values are expressed as mean ± SEM; n=5, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 significant compared to control (repeated measures ANOVA followed by Dunnett's test).

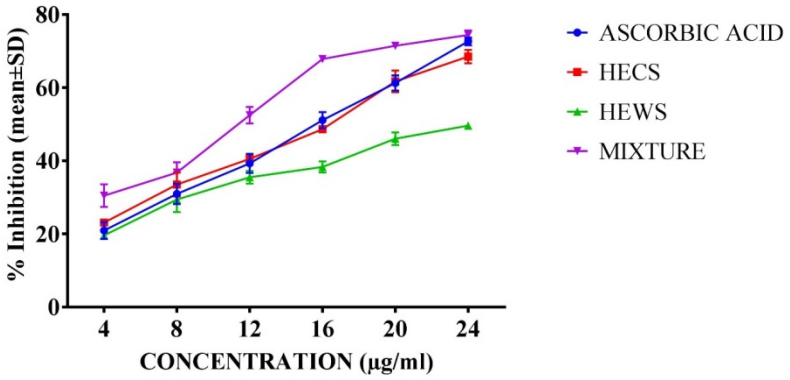

Figure no. 4: DPPH Scavenging assay

Percent inhibition shown by HENJ, HEMP and its mixture in DPPH scavenging assay. All the values are expressed as mean ± SD

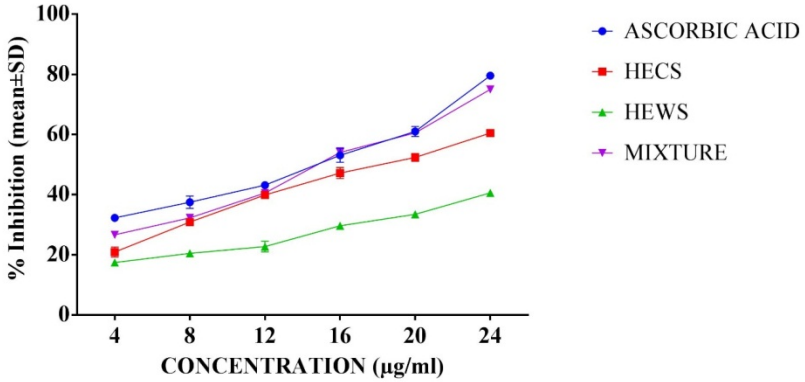

Figure no. 5: H_2O_2 scavenging activity

Percent inhibition shown by HENJ, HEMP and its mixture in H_2O_2 scavenging assay. All the values are expressed as mean ± SD.

DISCUSSION:

Antioxidant stress aggravates Parkinson's disease (PD). Antioxidants have therefore an important place in treatment of PD. Haloperidol induced catalepsy is associated with increased lipid peroxidation and several studies have shown inhibition of haloperidol induced catalepsy by antioxidants [19-20]. Haloperidol-induced catalepsy has been widely used to study the effect of drugs on dopaminergic system and intraperitoneal injection of GABA is reported to potentiate haloperidol-induced catalepsy [21]. It has been observed that in nigrostriatal region of Parkinson's patient, the dopamine and GABA concentrations are decreased [12]. Hence haloperidol an antipsychotic drug, which acts post-synaptically on dopamine receptors, is used to produce catalepsy [21].
Dopamine D_2 receptor antagonism by haloperidol results in extrapyramidal side effect such as akinesia and rigidity in animals (i.e. catalepsy) [14]. Catalepsy induced by haloperidol remain same in the control group and *Camellia sinensis* (CS), *Withania somnifera* (WS) and 1:1 mixture treated group showed significant (P<0.001) reduction in the duration of cataleptic.

CS is having potentials to regulate stress and act as stress mediator because of expression of different antioxidant enzymes by polyphenols present in CS prevents oxidative DNA damage and catechin suppress the neurotoxicity induced by various ways [16]. WS is having number of health benefits such as reduction in stress, enhancement of brain function, and improvement of memory due to chemical constituents present in WS such as sitoindosides VII-X, acylsterylglucosides and Withaferin-A etc. play important role in the effects of WS [17]. Orru et al., (2014) have reported that WS extract act on $GABA_A$ and $GABA_B$ receptors and this effect might be responsible for the reduced haloperidol-induced catalepsy, as described earlier by Balsara et al., (1980) [22]. Similarly, Liao et al., (2017) have shown involvement of GABA in the effects of CS. These observations of Orru et al., (2014) and Liao et al., (2017) supports the anticataleptic activity of WS and CS extracts respectively [23].

Vesicular monoamine transporter 2 (VMAT-2) inhibitor reserpine blocks dopamine vesicular uptake which results in dopamine oxidation by-products accumulation i.e. dopamine-quinones and depletion of glutathione as antioxidant and thus increases reactive oxygen species and causes oxidative damage which leads to hypolocomotion [15]. Kasture et al., (2015) have shown that epigallocatechin gallate present in CS potentiates anticataleptic and locomotor sensitizing effects in mice and is also responsible for antioxidant activity [16, 24]. Major constituents in WS is sitoindosides VII-X and withaferin-A are having potent antioxidant effect [18]. Due to the antioxidant potentials of CS and WS they have their effect on CNS i.e. on rat brain frontal cortex and striatum and thus resist the reserpine induced hypolocomotion. Further, Manjunath and Muralidhara (2015) have shown that WS extract offset rotenone-induced locomotor deficit [25]. It has been shown that the antioxidant, quercetin which as neuroprotective effect also improve locomotor activity (Beckmann et al., 2014), thus WS and CS having strong antioxidant activity improved locomotion in reserpine treated animals in our experiments [26]. In the present study it has been observed that HECS and HEWS in combination more significantly (P<0.01) reduces hypolocomotion induced by reserpine, the effect was observed due to the presence of various CNS stimulant chemicals in extract and protection of neuronal damage.

Acetylcholinesterase inhibitor tacrine has central side effects like cogwheel rigidity, tremor and bradykinesia [24]. Tacrine induces vacuous jaw movement and orofacial bursts by inhibiting cholinesterase and enhancing cholinergic activity in ventrolateral striatum and increased muscarinic receptor stimulation [27]. CS contains L-theanine a neuroprotective and cognitive enhancing agent which cross the blood brain barrier and produce effect within 30 min directly on brain and reduces cortisol levels and reduces psychological and physiological stress for relax feelings [28]. WS reduces lipid peroxidation level and increases number of tyrosine hydroxylase in substantia nigra and show effect on parkinsonian tremor [19]. Present study reveals that HECS and HEWS has significantly (P<0.001) reduces vacuous chewing movements and orofacial brusts due to neuroprotection by abating cholinergic activity.

DPPH assay is regarded as a reliable parameter for measurement of antioxidant activity. Both HECS and HEWS showed antioxidant activity, and antioxidant activity of HECS was equivalent to that of ascorbic acid and the mixture of HECS and HEWS was more effective than ascorbic acid in scavenging the free radicals. Nadia et al., (2011) have reported high catechin contents in *Withania somnifera*, being responsible for free radical scavenging activity in the DPPH assay. Camellia sinensis is also a rich source of catechins [29].

In presence of bacteria and fungi phagocytes get activated and generate hydrogen peroxide. By oxidation of essential thiol (-SH) group hydrogen peroxide inactivates few enzymes also cross cell membrane rapidly and interact with Fe^{2+} and Cu^{2+} ions to form toxic hydroxyl radicals. Scavenging of H_2O_2 by phenolic compounds present in HECS, HEWS and in mixture are neutralizing H_2O_2 in to water by donating electrons. Both the extracts exhibited antioxidant potential in the Hydrogen Peroxide assay [16-18].

CONCLUSION

Thus, in conclusion, HECS was found to be more effective than HEWS in reducing the duration of haloperidol-induced catalepsy, and Tacrine-induced vacuous chewing movements. The HECS was also having better antioxidant activity than HEWS. More important, in the lower dose, combination of both the extracts was more effective in antioxidant activity, haloperidol induced catalepsy, reserpine induced hypolocomotion and tacrine induced VCM and OB.

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