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# Effects of Nigella Sativa Aqueous Extract on Serotonin (5-HT) *Neurotransmitter:* A Therapeutic Marker for Neurological Diseases and Related Disorder

**Farhat Bano[1*], Naheed Akhter[2]**
[1]Associat Professor, Department of Biochemistry, University of Health Sciences Lahore, Pakistan
[2]Professor, Department of Biochemistry University of Karachi, Pakistan

**Original Research Article**

***Corresponding author**
*Farhat Bano*

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**Abstract:** Anxiety is a neuropathlogical condition which disturbs the normal routine life and CNS function. Serotonin is well known *neurotransmitter responsible* for pathogenesis of neurological diseases such as *epilepsy*, *migraine*, *multiple sclerosis* and *Parkinson's* disease &neuropsychiatric diseases like depression, anxiety and stress. Malfunctioning of 5-HT receptor, 5-HT transporter and mutation in gene code for its synthesis may contribute to abnormal function of serotonin. Nigella sativa is most common herb use as medicinal plant .In present investigation aqueous extract of Nigella sativa given to rats exerts anxiolytic and hyperserotonergic effect by increasing serotonin level in rat brain. Significant anixolytic effects were observed in open filed box and elevated plus maze. All these findings proved that Nigella sativa can be beneficial to treat neurological behavior defect which is due to hypoactivity of serotonergic neuron in brain.

**Keywords:** Serotonin(5-HT),Tryptophan (Trp), Parkinson's disease (PD), 5-hydroxyindoleacetic acid (5-HIAA), *Selective serotonin reuptake inhibitors* (*SSRIs*), Nigella sativa aqueous extract (NSAE). Open field box (OFB), elevated plus maze (EPM).

## INTRODUCTION

Serotonergic neurotransmission is a crucial target for numerous pharmacological agent uses in psychiatry treatment. Serotonin cell bodies located in dorsal and median raphe [1]. Covering lateral cortical regions, amygdala and the hypothalamus effect on emotions and stress behavior [2]. The synthesis of 5-HT exhausted by decreasing the availability of precursor molecule Trp [3].

Increase Trp which inturn increase brain serotonin level because brain cannot synthesize serotonin and totally depended on Trp availability in plasma. Trp can cross the blood brain barrier and reach in to brain where it convert into serotonin [4]. Administration of L-tryptophan increases serotonin synthesis in rats and humans [5, 6].Acute tryptophan depletion produces an average decrease of 81% in plasma TRP concentration [7, 8-9].Researcher believed that disturbance in serotonin metabolism link with neuropathological disorder such as migraine [10], epilepsy [11], Parkinson's disease and neuropsychiatric disorders like depression, stress and anxiety [12].Anxiety is a major psychic symptom of epilepsy, depression in Parkinson and stress is developed in migraine. These all behavior can be monitor by using different behavioral animal module for example elevated plus maze use to measure anxiety in laboratory animals. Anxiogenic animal spend more time in closed arm [13].Open filed box used to monitor general locomotors activity in animals increase in locomotors activity monitor in anxiolytic drug [14]. The utilization of herbal remedies, extract and combination of herbs successfully use throughout the world population .Nigella sativa commonly known as "black cumin played an important role over the years in ancient Islamic system of herbal medicine, several therapeutic effects observed including antihypertensive effect [15], analgesic [16], antidiabetic[17], antiobesity and hyperlipidemic [18]. Present study designed to evaluate the effect of Nigella sativa in neurochemical alteration of 5-HT and their association with neurological disorder and behavioral affect.

## MATERIALS AND METHODS

24 Albino Wistar male rats weight between 280-320 grams were used. All animals were placed in separate cages under 12 h light-dark cycle and control room temperature [23±2$^{o}$C] with free access to specially prepared diet and water for one week, prior to starting the experiment so that rats could adopt themselves to new conditions.

### Preparation of Extract

The 50 gram seeds were crushed in blender. The powder seeds was soaked in 200 ml of water and left for 24 hour at 4C$^{o}$ .The mixture was filtered and the filtrate was stored until ready to use.

**Experimental Protocol**

The animals were divided into two experimental groups. The test group received 2ml NSAE. The control group received water, amount equivalent to that of aqueous Nigella sativa. Behavioral activities were monitored in elevated plus maze and open field box apparatus. After significant difference in behavioral activity rats were decapitated using guillotine. Brain samples were collected and stored at -70°C for the estimation of brain 5-HT, 5-HIAA and brain and plasma Trp. Estimation of neurotransmitters and their metabolites in the whole brain samples of rats was made by HPLC-EC method as reported by [2].

**RESULTS**

Data of present study shows significant increase in 5HT (figure.1), 5-HIAA (figure.2), brain and plasma Trp level respectively (figure. 3 & figure 4). Increase exploratory activity were monitored in open field box in turn increase number of boxes cross in five minute (figure.5A) and significant decreased in corner sitting in open field box (OFB) (figure.5B) and significant time spend in open arm of EPM (figure.6).

Values are shown as mean ± SD (n=12).Significant differences following student t-test **p<0.01, as compare to control (Fig-4).

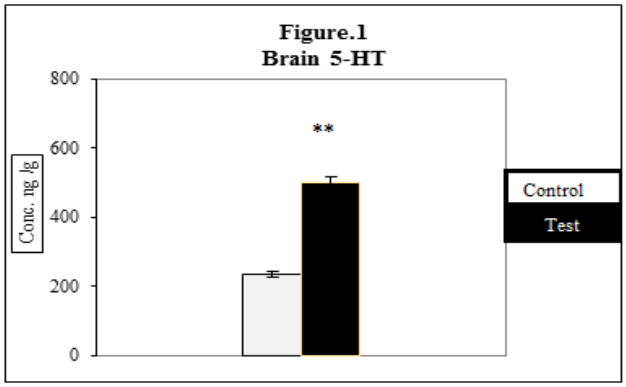


**Fig-1: Effect of NSAE on whole brain 5-HT level in rats. Values are shown as mean ± SD (n=12).Significant differences following student *t-test* **p<0.01, as compare to control**

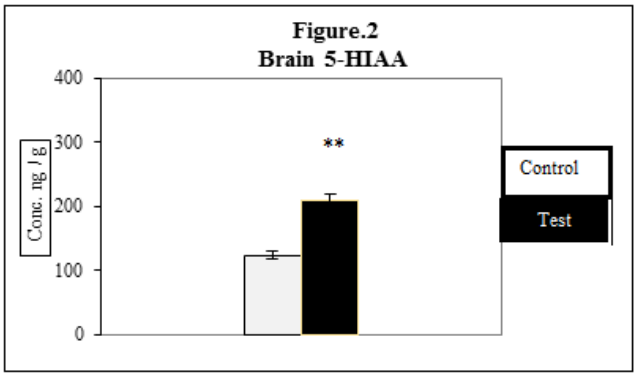


**Fig-2: Effect of NSAE on whole brain 5-HIAA level in rats. Values are shown as mean ± SD (n=12).Significant differences following student t-*test* **p<0.01, as compare to control**

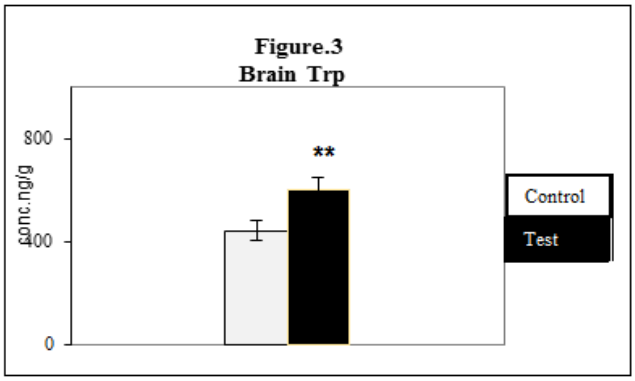


**Fig-3: Effect of NSAE on whole brain Trp in rats. Values are shown as mean ± SD (n=12).Significant differences following student t-test **p<0.01, as compare to control**

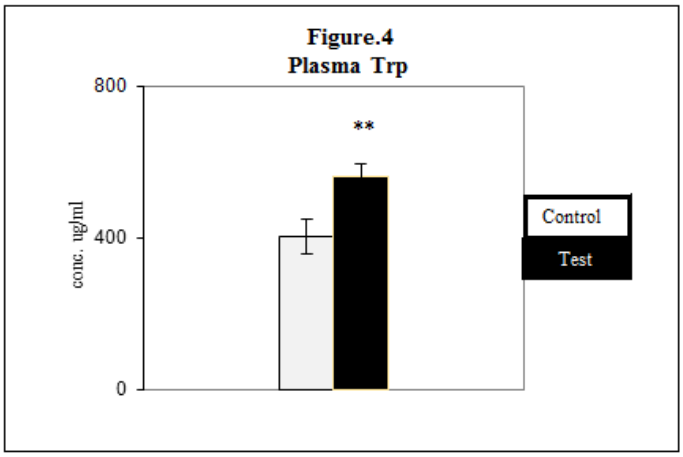


**Fig-4: Effect of NSAE on plasma Trp in rats**

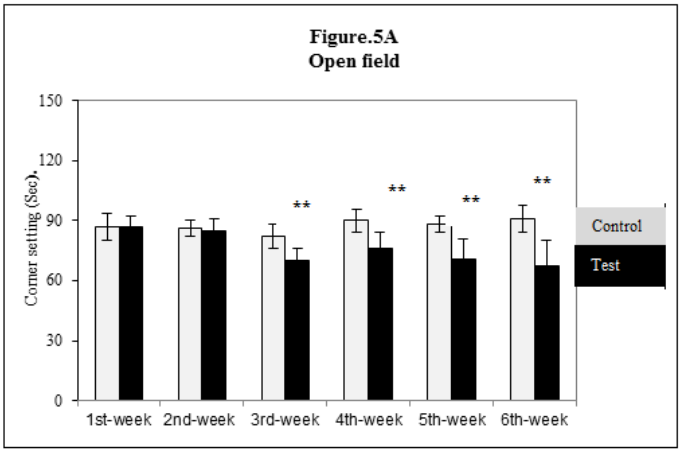


**Fig-5A: Effect of NSAE on number of square crossing in open field box of rats. Values are shown as mean ± SD (n=12).Significant differences following student *t-test* **p<0.01 as compare to control**

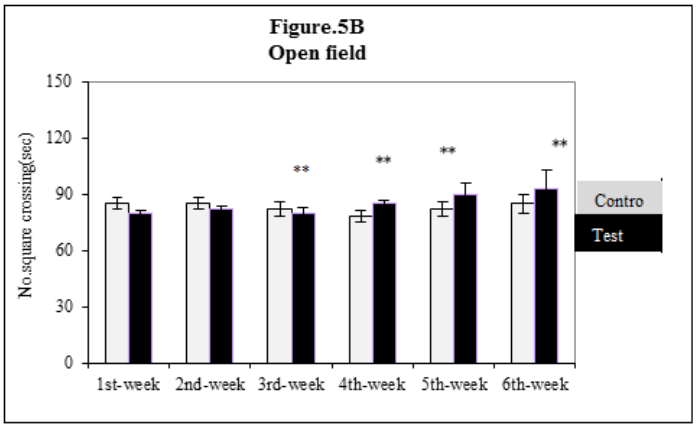


**Fig-5B: Effect of NSAE corner sitting time in open field box of rats. Values are shown as mean ± SD (n=12).Significant differences following student t-test **p<0.01 as compare to control**

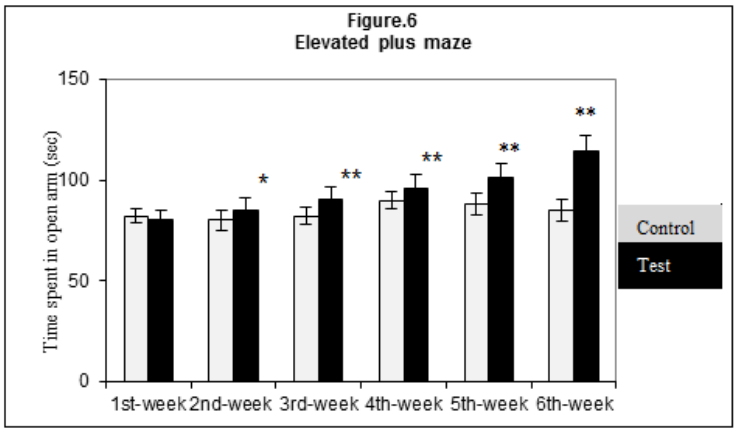


**Fig-6: Effect of NSAE on elevated plus maze activity of rats. Values are shown as mean ± SD (n=12).Significant differences following student t-test *p, 0.01, **p<0.01, as compare to control**

## DISCUSSION

Anxiety is most common psychiatric disorder. Up to 15% population faces anxiety in their life [19] and its treatment is expensive and link with critical social problems [20]. Malmetabolism of serotonin are hallmark of several neurological diseases. Here we discuss the concentration of serotonin and their metabolites and its link in developing neurological diseases and use of Nigella sativa as therapeutics agent. Worldwide 11 % adult suffer in migraine. Incessant low serotonin due to defect in synthesis lead to migraine and related symptoms [21].Decrease 5-HT and increased 5-HIAA also level observed in CSF of migraine patient [22], 5-HT receptor agonist triptans [5-HT1B/1D] and SSRIs (selective serotonin reuptake inhibitors) are successfully used in migraine headache [23].

Epilepsy is malfunction of brain activity due to disturbance in serotonin neurotransmitter. It is well establish since 1957 that 5-HT can inhibit epileptic attacks. Carbamazepine and valprote drug use to treat epilepsy by releasing 5-HT while lamotrigine drug inhibited 5-HT uptake [24] SSRI drugs used to prevent and relive the psychic symptom of epilepsy such as fear and anxiety [25, 26].

Postmortem, animal and functional imaging studies demonstrate the malfunction of serotonergic system [27].Parkinson's disease is incurable progressive disorder of the nervous system that affects motor and nonmotor function including autonomic function degradation of serotonergic system and develops anxiety and depression [28].

Data of present research show increase in whole brain5HT and 5-HIAA its mean NSEA increase serotonin level by increasing Trp in brain and plasma. All above discussion of neurological disease and treatment by β-blocker and SSIRs. SSIRs inhibit the reuptake of 5-HT and permit the serotonin remain in serotonergic area for their function but cannot regulate its synthesis. Herb is natural way to increasing synthesis of serotonin. The results of NSAE extract shows same mode of action as SSIRs and increases the 5-HT concentration in whole brain by increasing the synthesis of 5-HT. All above study shows that all diseases due to defect in serotonin system can be cure and treated if serotonin level become normal.

Next important portion of our research is to study the effect of NSAE in different behavior module. Behavioral activities of all animals were weekly monitor observed.

Significant effects were monitored in square crossing in OFB from fourth week of treatment (Figure. 5A), while decrease corner sitting period were monitor in open field box (Figure. 5B) as compare to control, Tahira and coworker demonstrated that administration of NSO show an increment in open field activity[29]. Anxiolytic drug produce hyperlocomotion in OFB [30], treated animal also show improvement in elevated plus maze from 2$^{nd}$ week of treatment and show more exploration in open arm (figure.6).Oral administration of NSAE increase brain 5-HT, Trp level in plasma and whole brain of rats. It is in agreement with previous researcher who reported, repeated administration of NSO increase 5-HT in brain and increase Trp in plasma and brain [31]. Increase in Trp level is strong base for increase in %-HT level and responsible for their pharmacological affect.

## CONCLUSION

NSAE induce hyperserotonergic and hyerlocomotive affect. The present study highlighted the concentration of 5-HT and 5-HIAA in whole rat's brain and their possible relation in developing neurologic diseases and behavioral disorder. The results of present research demonstrate that NSAE might be useful for the treatment of neurologic disorder due to low level of serotonin (5-HT) in brain and also can be used to improve behavioral deficit like anxiety and depression.

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