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"Evaluation of anti-psychotic activity of Nigella sativa (Black cumin)".

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ABSTRACT: - Medicinal plants have attracted great attention in the recent years and is increasingly applied instead of the chemical drugs .In the recent year's different medicinal plants and their main components have been shown in psychotic therapy. The present study was carried out to evaluate the role of *Nigella sativa* (Black cumin) in animal model of antipsychotic activity. Thymoquinone is the main chemical constituents present in *Nigella sativa* and has various pharmacological activity. Dopamine is an inhibitory neurotransmitter involved in the pathology of antipsychotic. Thymoquinone (TQ) (20mg/kg, intraperitoneally) was administered daily for 28 days in mice. Different models of antipsychotic such as haloperidol - induced catalepsy ,forced swim test and elevated plus- maze test were used after the last dose of thymoquinone on the 28th day ,behavioral tests were performed followed by biochemical estimations. The present study observed antipsychotic actions in different animals models of antipsychotic and also improved memory. Our results are preliminary, further research is warranted toestablish role of black cumin as a new candidate in antipsychotic.

Key words: - antipsychotic, black cumin, *Nigella sativa* ,Thymoquinone ,dopamine,neurotransmitter.

1. INTRODUCTION: -

Black seed (also called black cumin; Nigella sativa) could be an annual seed plant belonging to the family Ranunculaceae and is a native of Southern Europe, geographic region, and Southwest Asia. Black cumin is cultivated within the geographical regionMediterranean region, Southern Europe, Northern India, Pakistan, Syria, Turkey, Iran,and Kingdom of Saudi Arabia. Nigella seeds and their oil have a protracted history offolklore usage in Indian and Arabian civilization as food and medicine (yarnell and abascal, 2011). Nutmeg flower might be raised to 20-90 cm, with divided leaves. Theflowers are fine and in white, yellow, pink pale blue or pale purple colour (Ahmed etal., 2013). The plant fruit may be a large capsule filed by 3-7 united follicles, with numerous

seeds (Forouzanfar et al., 2014).

Figure-1: black seed

Nigella sativa and TQ have numerous advantageous properties with relevance to varied neurological illness. As an example, they need anticonvulsant, anxiolytic, antidepressant, and antipsychotic potential. They also counter memory impairments and enhance cognitive functioning yet as attenuate drug tolerance and dependence. The roasted dry seeds are accustomed flavor curries, vegetables, and pulses in Indiandishes, one among the ingredients in spice mixture (Panchu phoron) and lots of recipesof Bengali cuisine. Black seed also used as a flavouring additive in bread, pickle, sauces, and salads of Persian foods (P sudhakar et al., 2020).

Chemical constituents:-

Chemical composition of N. sativa seeds includes oil, protein, carbohydrate, fibre, and saponin. The oil chemical compositions of N. sativa are polyunsaturated fatty acid, oleic acid, hexadecanoic acid, arachidic acid, eicosadienoic acid, octadecanoic acid, polyunsaturated fatty acid, and saturated fatty acid (Mohammad Reza Khazdair,2015). NS is beneficial to treat a range of diseases of the systema nervosum, the consequences of this plant on these diseases are going to be described.

The black cumin oil consists of main medicinal components like ocopherols, phytosterols, polyunsaturated fatty acids, thymoquinone, ρ-cymene, carvacrol, t- anethole and 4-terpineol.Thymoquinone (2-isopropyl-5-methylbenzo-1, 4- quinone)(TQ), the most ingredients of the N. sativa seeds, has been found in many medicinal plants like several genera of the Lamiaceae family (Monarda), and also theCupressaceae family (Juniperus). TQ is that the main bioactive component of N. sativawith molar mass 164.20 g mol−1 and chemical formula C10H12O2 (Samarghandianet al).

The bioactive constituents of N. sativa include terpenes such as thymoquinone (TQ),dithymoquinone (DTQ), carvone, limonine, trans-anethol, and p-cymene, indazole alkaloids like nigellidine and nigellicine, and isoquinoline alkaloids including nigellicimine, nigellicimine-N-oxide and α-hederin (khan MA,Afzal M.,2016).

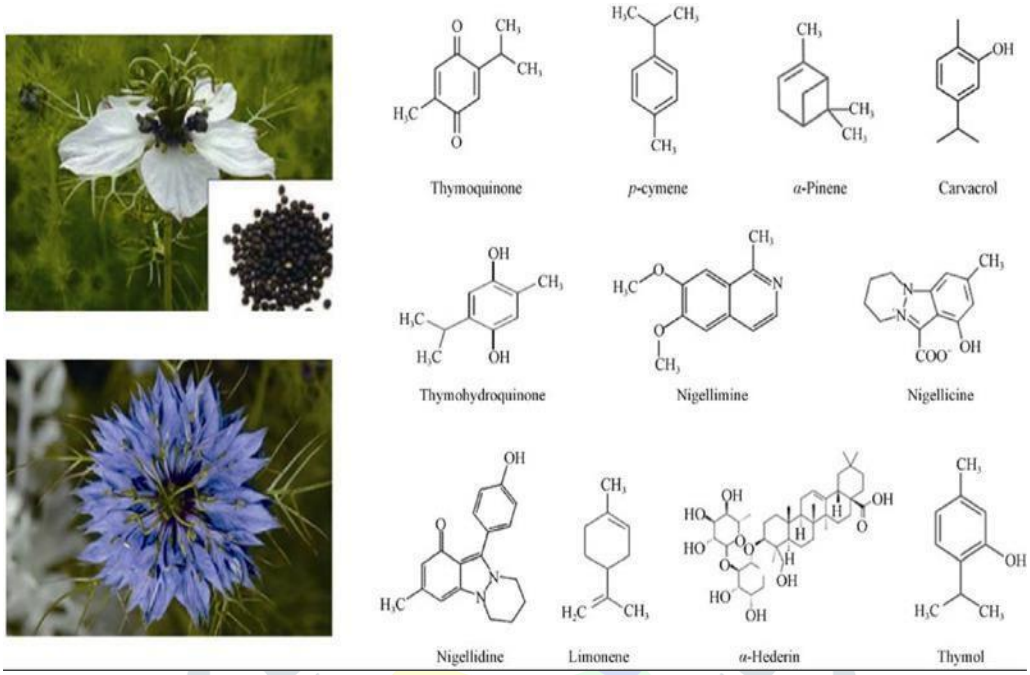


Figure-2: chemical composition of nigella sativa

Health benefits of nigella sativa: -

Nigella sativa has been widely used as a spice and favouring agent in type of food preparations like in bread, yogurt, pickles, sauces, and salads. Black seed or black cumin (English), Habbatul Barakah (Arabic), Tikur azmud (Amharic), has longbeen employed in traditional remedy within the Arabian countries, Far East Asia, Europe, and Africa .Nigella sativa has also been described because the miraculous plant and regarded by earliest herbal specialists as "Te herb from heaven" . Te ProphetMohammed (PBUH) had described the curative powers of the black seed as "Hold onto use this black seed, because it contains a remedy for each illness except death. Avicenna, a widely known physician of 10th century famous for his book "Te Canon of drugs," has recommended use of Nigella seeds for enhancement of body's energy and also support during recovery from fatigue and dispiritedness. Nigella sativa is additionally mentioned for its curative property within the Holy Bible and isadditionally labelled as Melanthion by Hippocrates and Dioscorides (Ebrahim M. Yimer et al., 2019).

Figure-3: benefits of black cumin seeds.

Thymoquinone may be a monoterpene diketone and a very important bioactive compound that forms 18.4%–24% of those essential oils with a boiling point and freezing point of 230–232°C and 44-45°C, respectively. Its mass is 164.204 g/mol, and value of Log P is 2.20 denoting lipophilicity of TQ. Moreover, it's the flexibilityto penetrate the barrier (BBB) as a result of its mass (less than 500 g/mol) and Log P(less than five) value. Thus, it'd be suitable for clinical trials. Structurally, it'shomologous with ubiquinone, a vital antioxidant of the electron transport chain (Md.Jakaria et al., 2018).

Synonym of black seeds in various languages:-

English: Black cumin, Love-in-a-mist.
Arabic: Habatut Barakah; Sonez; Habatut – sauda; Kamune-asvad.
Hindi: Kalonji.
Sanskrit: Krishana – Jiraka.
Persian: Siyadanah (Tembhurne et al., 2011)

Various Pharmacological activities:-

Antioxidant capacity of Nigella sativa:-

A number of in vitro and in vivo antioxidant studies are conducted with N. sativa extracts, seed oil and TQ. The finding is suggesting having potential radical scavenging and inhibitory effects of oxidative stress. TQ effectively changed the parameters including enzyme (ADA), catalase (CAT), myeloperoxidase (MPO), lipid peroxidase (LPO), reduced glutathione (GSH), glutathione-S-transferase (GSH-ST), peroxidase (GPx), enzyme (SOD) and gas (NO). It also reduced the malonilealdehyde(MDA), conjugated diene (CGD) levels and pro-inflammatory mediators interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and prostaglandin (PGE2) instead of interleukin-10 (IL-10) (Islam etal., 2017).

Neuroprotective Effects.

Neurological disorder like depression is amongst the foremost prevailing illnesses globally. It's principally laid low with the hypo activity of neurotransmitters, particularly thanks to inadequate activity of Serotonin. Stress is that the chief triggering aspect within the initiation of depression and this premise is steadily supported by various clinical observations. Studies in experimental animals displayed that overwhelming stress conditions produce neurochemical modifications and behavioural deficits. An outsized number of medicinal herbs and their isolated compounds are revealed to possess medicinal benefits and therapeutic potential. Among the promising medicinal plants, black cumin may be a worthwhile herb with an expensive historical and non-secular basis to manage depression and plenty of other neurological disorders (Ebrahim M. Yimer et al., 2019).

Effects on withdrawal syndromes

Studies demonstrated N. sativa oil can attenuate the event of tramadol tolerance and dependency in mice through blockade of NO overproduction and oxidative stress. Additionally, the hydro alcoholic extract of N. sativa inhibited tolerance and reduce withdrawal symptoms in morphine through its antioxidant properties. Also, it can inhibit NO overproduction and oxidative stress induced by morphine. Clinical studies showed N. sativa was effective in opioid dependence in long-term administration. Thanks to different activities like antiallergic, antibacterial, antinociceptive, and beingstuffed with amino acids, it doesn't only cure the opioid dependence but also cures theinfections, weakness, and opioid withdrawal syndrome .Another study suggested usage of N. sativa as a supplement in patients in Methadone Maintenance Treatment centers, caused better tolerance of withdrawal syndrome (S. JAVIDI ET AL., 2016).

Nigella sativa use in covid-19

The potential of Nigella sativa (black cumin seeds) to treat the patients with COVID-19 analysed, as Prophet Muhammad (PBUH) stated that "In the black cumin, there's a cure for each disease except death". additionally, the black cumin is additionally mentioned in Holy Bible as "Curative black seed" and is described as 'Melanthion of Hippocrates and Dioscorides' and as 'Glitch of Pliny'(khan MA,2019).Moreover, the active constituents of N.sativa including nigellidine and α-hederin are identified as potential inhibitors of SARS CoV-2(Naina Mohamed Pakkir Maideen.,2020).

Antidiabetic activity

Streptozotocin (STZ) treated animals answer NS extracts with normalizing blood sugar through extra pancreatic actions instead of by stimulated insulin release and ascertain to be protective against type-2 diabetes .The significant increase in lipid peroxidation by STZ is additionally controlled by NS and has protective effect in diabetes by decreasing oxidative stress and regeneration/proliferation of the beta-cells within the islets of Langerhans. A petroleum ether extract of NS exhibits insulin- sensitizing activity and therefore the mechanism of NS extract within the control of diabetes has been shown to be through controlled insulin release .At the identical time,amendment within the blood lipids profile has been suggested by the employment ofNS extracts. Arachidonic acid induced protoplasm aggregation and coagulation are inhibited by NS indicating its potential use in thrombosis.TQ is involved within the inhibition of arachidonic acid generated eicosanoids and lipid peroxidation (M.Akram Khan.,2016).

Effects of Nigella sativa on Learning and Memory

Learning and memory are the foremost important executive functions performed by the human brain, the loss of which could be a prominent feature in dementia. Dementiawill be caused by aging, physical and/or chemical injuries, or neurodegenerative diseases, which in most cases would affect the standard of learning and memory of the concerned individuals. The latter include health problems like Alzheimer's disease(AD) or Parkinson's disease (PD), which are characterized by the build-up of protein aggregates on the surface or inside the neurons. Disturbances, which cause oxidativestress and elevated cortisol levels, can result in neurodegeneration that will subsequently induce a fall in cognitive ability. Any chemical, natural, or synthetic substances that enhances executive functions of the brain is of immense clinical significance (Mohammad Khairul Azali Sahak., 2016).

Effects on epilepsy

Epilepsy, a neuro-related disease characterized by seizures, may also cause poor cognitive functions. Within the pentylenetetrazole- (PTZ-) induced epileptic model, the NS hydroalcoholi extract was reported to be beneficial by preventing the educational and memory decline (Z. Hassanzadeh et al., 2015).

ANTIPYSCHOTIC ACTIVITY OF BLACK CUMIN (NIGELLA SATIVA)-

Definition of Psychosis: - Psychosis is also a severe mental condition within which asufferer experiences a distortion or loss of contact with reality and clouding of consciousness. Patients diagnosed with psychosis may present with one or more of the following symptoms: hallucinations, delusions, catatonia, disordered thoughts, orimpaired social cognition. Psychosis is commonly seen in patients suffering from schizophrenia, bipolar disorder and Parkinson's disease. Furthermore, some surgery patients have brief episodes of post-

operative psychosis. A study by van der Mast et al. reported that post-operative psychosis occurred in 13.5% of cardiac surgerypatients (castagne et al.). It's characterized by depression, hallucination, anxiety, sleepdisturbance, thought disorder, Social withdrawal and impaired role functioning (abdulwakeel Ayokun– nun ajao et al., 2017).

The TQ was found to possess a neuroprotective effect on primary dopaminergic neuronal cells against 1-methyl-4-phenylpyridinium (MPP+) and rotenone toxicities by preserving the tyrosine hydroxylase (TH) immunoreactive cells, presumably via its antioxidant properties (Md Fauzi et al).

Furthermore, TQ was found to affect neurotransmitters in counteracting the effect ofarsenic (AS) induce toxicity. The TQ reduced the implications of AS by increasing the quantity of DA, norepinephrine (NE), acetylcholine esterase (AChE), and decreased the degree of nitrite/nitrate (NO), serotonin (5-HT), lipid peroxidation (MDA), and tumour necrosis factor (TNF-α). The TQ acted as an antioxidant during this event (Kassab RB, El-Hennamy RE., 2017).

An amazing data about TQ showed significant antipsychotic effects and memory improvement. This result could even be related to the brain dopamine level reductionby TQ. Other mechanism including decrease in AChE enzymatic activity and increasein GSH content are also involved (Khan et al., 2014).
Antipsychotic drugs (APDs) are generally classified as either typical or atypical. Thisclassification relies on the increased liability of typical APDs to produce extrapyramidal side effects (EPS), including dyskinesia (TD), at clinically relevant doses. Typical APDs are relatively selective dopamine (DA) D2/D3 receptor antagonists. Antagonism of these DA receptors is that the premise of both their efficacy and side effects. The importance of serotonergic mechanisms for the antipsychotic and pro-cognitive effects of atypical APDs is supported by many lines of evidence, particularly those which are based upon the hypo glutamate hypothesis of schizophrenia, now widely thought to higher reflect the pathophysiology ofschizophrenia than hyper dopaminergic models.

Within the sphere of schizophrenia, such translational approaches have largely targeting the cognitive aspects of schizophrenia because these is investigated in constant fashion both in humans and in animals. More florid psychotic manifestations,like hallucinations, delusions or paranoia, being essentially human, are less readily amenable to such an approach (Castagne et al., 2009).

The major tranquillizer are used for the treatment of psychosis .The neuroleptic bind mainly to dopamine receptor 2 (D2) as antipsychotic drugs can mediate through the potential site. The dopamine hypothesis is led by the association between neurolepticdrugs and D2, DA receptors for upset. Therefore, the event of medication is targetedto act at central DA receptors (maurya et al., 2017).

2. Materials and methods:-

Animals:-

Albino rat 25 to 35g are taken. The mice were maintained on a 12h light/ 12 h darkcycle across with free access to food.

The mice were maintained on a pellet feed and water impromptu during the fullduration of study (28days for every group).

Chemicals and reagents:-

Thymoquinone, haloperidol, diazepam and imipramine. Thymoquinone wasdissolved in vegetable oil, whereas other drugs were dissolved in normal saline.

All the chemicals and reagents used were of analytical grade.

Sample collection and characterization:-

The fresh seeds of black seeds (Nigella sativa) were obtained. The seeds were sorted resolute remove all the possible stones and dirty materials and grounded into powderto boost the efficiency of extraction of the active component(s). Quantification of phenolic compounds by HPLC-DAD reverse-phase chromatographic analyses was allotted under gradient conditions (Akintunde et al., 2018).

Extraction of the oil:-

Pulverized ten（10g) grams of the black seed was extracted by steeping in 100 mL ofmethanol overnight, for 24hrs at 25℃. Thereafter, the mixture was filtered through Whatman No. 1 paper. The filtrate, subsequently referred to as oil was concentrated and stored at －4℃ for further analysis. About 5 mL of the oil was obtained after methanol removal (Akintunde et al., 2018). The particle size of solid materials, liquidvolume for extraction, and extraction temperature and time are all the key factors of oil extract technology. So, these factors were adopted to optimize extract technology of N. sativa seed oil in this research. The oil yield can be calculated by using the following formula:

Extraction rate ＝weight of extracted oil / weight of the seed × 100% (Changyang Maet al., 2019)

Methods of oil extraction:-

1. Cold pressing. Black cumin seeds were pressed at room temperature (25 ◦C) without any thermal treatment. Mesilla was stored for one night at room temperature to separate oil phase from Mesilla then oil was filtered over anhydroussodium thiosulphate and cotton filter using glass funnel.
2. Conventional Soxhlet extraction. Seeds were extracted using n-hexane in a Soxhletapparatus for 4 h (M.

Kiralan et al., 2014).

Methods:-

Drug induced psychosis:-

Drugs and treatment: - Ketamine hydrochloride (50 mg/mL, ampoules), haloperidol(5 mg/mL, ampoules). All drugs were dissolved in distilled water and administered intraperitoneally (i.p) in volumes of 10 mL/Kg body weight. Haloperidol (0.1 mg/Kgor 0.2 mg/Kg) were administered alone or thirty minutes before ketamine (10 mg/Kg).Control animals received distilled water in the same period.

Rota rod (RR) - The method of Dunham and Miya was used on rota rod test. Animalswere placed with the paws on a 2, 5 cm diameter bar, 25 cm above the floor, which rotates 12 times per minute. The number of falls (up to three falls) and the time ofpermanence on the bar for one minute were registered.

Measures to check drug induced psychosis:-

Behavioral Measures: - Behavioural measures are methods that attempt to quantify and interpret the actions of an animal. The underlying hypotheses are that 1) the actionbeing evaluated informs the biology related to psychosis, and/or 2) the animal's behaviour is informative about some mental construct or process, and/or 3) altering the animal behaviour using a treatment is predictive of effects of that treatment in humans. The validity of these assumptions will be addressed individually within eachsection.

a. Passive avoidance:-The one-trial passive avoidance task is one of the oldest procedures for evaluating drug effects on learning and memory. A rat or a mousereceives an aversive stimulation in a recognizable environment and on a later occasion shows that it has remembered by avoiding the environment. Although simple and rapid, the procedure is notoriously variable from one laboratory to another and is now rarely used except for screening memory impairing effects. Indeed, most typical and atypical antipsychotics administered alone impair passive avoidance performance .In contrast, in the same study, the atypical antipsychoticsclozapine, quetiapine, and risperidone but not olanzapine or aripiprazole reversedthe deficits induced by MK-801. Haloperidol was also without effect against MK-801-induced deficits.

b. Hyperactivity: - Hyperactivity in animal models is a behavioral measurement thathas been associated with the agitation and disorganized behavior of psychosis. Many early antipsychotics functioned as dopamine agonists; therefore hyperactivity has been hypothesized to originate from a hyperdopaminergic state. Hyperactivity, however, remains a consistent measurement even in models wheredopamine release is not directly induced. It is suggested that the hyperactivity observed in such models is due to secondary effects on dopamine transmission. The maintenance of hyperactivity in models that do not directly influence dopamine supports the idea of elevated

dopamine neurotransmission beingcharacteristic of psychosis, but not necessarily the source of psychosis.

Haloperidol induced catalepsy in mice:-

Haloperidol induced catalepsy was wont to observe the negative symptoms in animals.It's the widely employed method for screening of neuroleptic drugs in rodents. Catalepsy was induced with haloperidol (2 mg/kg p.o) and was resolute every hour upto 4 h by means of a customary bar test. The phenomenon was measured because the time when the mouse maintained an imposed position with both front limbs extendedand resting on a 4 cm horizontal bar (0.4 cm diameter). The overall time during whichanimal stayed on the bar (even if it climbed back up) was recorded for a maximum period of 300 s.

Methodology:-

All the animals were divided into five groups of six animals each. Group I animals were corn oil treated; group II, normal control saline treated; group III, pathogenic control (haloperidol,); group IV, TQ per se; group V, co-administration of TQ with haloperidol. TQ (20 mg/kg) was administered daily intraperitoneally (i.p) for 28 days, but one single dose. Haloperidol was administered per orally (2 mg/kg, p.o) single dose on the 28th day. Behavioural tests were performed on the 28th day, 1 h after thelast dosing regimen. Animals were sacrificed after behavioural tests and therefore thebrains were removed for biochemical estimations (Khan et al., 2014).

Elevated plus-maze test in mice:-

The plus-maze test was accustomed study the drugs affecting learning and memory. The plus maze was constructed from synthetic resin, and consisted of two open arms(5 × 30 cm) and two enclosed arms (5 × 30 × 15 cm) facing one another. The completeapparatus was elevated to a height of 40 cm above the ground. The open arms and central platform were colored white and covered with cellophane, and therefore the enclosed arms were colored black. On day 1, a purchase trial was performed as follows: the mice were placed individually at the tip of 1 open arm facing far away from the central platform, and also the time each mouse took to move from the open arm to either of the enclosed arms (transfer latency, TL) was recorded. The mice were allowed to explore the plus-maze for 150 s. On day 1, if the mice didn't enter the enclosed arm within 90 s, they were pushed gently (on the back) into the enclosed armand were permitted to explore the plus-maze for a further 60 s. In such cases, TL wasrecorded as 90 s. unit of time later, a retention test was performed within the same manner as on day 1, and TL was recorded. If the mice didn't enter the enclosed arm within 90 s on day 2, the test was stopped and TL was recorded as 90 (Khan et al., 2014).

Forced swim test:-

Rats were moved from the animal house to the laboratory in their own cages and allowed to adapt to the laboratory conditions for 1–2 h. Rats were forced to swim in an open cylindrical container (diameter 20 cm, height 45 cm), containing 38 cm of water at 25°C ± 1°C. All rats were divided into six different groups (Group I–VI). Therats were tested in two sessions: An initial 15 min training session latter after 24 h bya 6 min test session. Following the training session rats were far from the cylinder, towel dried so returned to the house cage for testing them again after 24 h latter.

Group I and II received H2O (1 ml/kg of body weight) for 7 days as control group, onday 7 Group II received imipramine (15 mg/kg) as standard before 1h of test. Group (III–VI) received N. sativa extracts from different germination phases (1 g/kg of bodyweight) orally for 7 days. On day 7, after 1 h of treatment, each rat was forced to swimfor a period of 6 min test. After an initial period of two min which may be a period ofvigorous activity, each animal assumed a typical immobile posture. A rat was considered to be immobile when it remained floating within the water withoutstruggling, making only minimum movements of its limbs necessary to stay its head above the water. The entire duration of immobility was recorded during the following4 min of the entire test duration of 6 min by a blind observer (Islam, et al., 2015).

Tail suspension test:-

Tail suspension test (TST) used the uncontrollable, inescapable stressor of tail suspension to elicit immobility. The rats were treated within the same manner as in FST for 7 days. Each rat was individually suspended to the sting of a table, 50 cm above the ground, by tape placed approximately 1 cm from the tip of the tail. The whole period of immobility was recorded manually for six min.

Animals were considered to be immobile when it didn't show anybody movement, hung passively and completely motionless.

RESULT AND DISCUSSION:-

Effect of drug induced psychosis: - The Rota rod test, ketamine (Ket: 14.06 ± 4.1) significantly decreased the time of animals permanence on the bar compared to control(57.01 ± 0.6). The pretreatment with neuroleptics alone induced no changes. However,animals that received Ketamine after have being treated with haloperidol at 0.2 mg (Hal 0.2 mg/Kg + Ket: 39± 5.5). Ketamine (Ket: 2.7 ± 0.1) increased the number of falls (Table 2) compared to

control (control: 0.12 ± 0.01), and this effect was not changed by the neuroleptic pretreatment [F (9,120) = 11.15; p < 0001].

Table-1. Effects of antipsychotic drug haloperidol and ketamine on the Rota rodtest in mice.

Group	Time of performance (s)	Nº falls
Control	57.01 ± 0.6	0.12 ± 0.01
Ketamine	14.06 ± 4.1a	2.7 ± 0.1a
Hal (0.1mg/kg)	54.06 ± 1.3b	53.06±1.3b
Hal 0.1 + Ketamine	27.03 ± 5.2a,c	2.56±0.2a,c 1.5
Hal (0.2mg/kg)	44 ± 3.7 b	± 0,3 a
Hal 0.2 + Ketamine	39 ± 5.5b	2.2 ± 0.3 a

Values are reported as means ± e.p.m. for the number of mice shown in parentheses. a,b and c ($p<0.05$) as compared to control, Ketamine (Ket 10), and Hal 0.1, respectively. Analysis of variance and Tukey as the post-hoc test.

Effects of thymoquinone on haloperidol induced catalepsy in mice:- Administration of haloperidol (2mg/kg p.o), TQ (20 mg / kg i.p) alone and together produced catalepsy. A highly produced combination of catalepsy times were observed together group post two hours drug administration ($p<0.001$) (table-1).

Effect of thymoquinone on elevated plus maze test: - Transfer latency was recorded on day 1 and a couple of. Administration of TQ decreased transfer latency (TL) on day 2 compared with day 1. Scopolamine (0.5 mg/kg, i.p) exhibit prolongation of TL. Concurrent administration of scopolamine and TQ (20mg/kg, i.p) reduced it ($p<0.001$)

There was no change within the percentage alternation of animals in TQ treatedgroup as compared to their vegetable oil treated control group .However, a majorreduction within the percentage alteration in scopolamine treated group was observed ($p<0.001$). A big possible alternation was observed in scopolamine and TQ in and of itself and TQ + scopolamine treated group as compared to theirrespective controls ($p<0.001$) (table-3).

Effects of thymoquinone on dopamine levels: - In haloperidol induced catalepsy, haloperidol (2 mg /kg p.o) treated group showed reduction in dopamine levels ($p<0.001$). Administration of TQ (20 mg / kg i.p) alone and together with haloperidol showed further reduction in dopamine levels ascompared to their respective controls ($p<0.001$)(table-2).

Administration of scopolamine (0.5mg/kg, i.p) in elevated plus maze test,showed significant increase in dopamine levels as compared to controls ($p<0.001$).However , when thymoquinone and scopolamine got together , a discount in dopamine levels as compared to regulate was observed ($p<0.001$)(table-4).

Effect of nigella extracts of various germination phases on maximal electroshock induced seizures in rats: - black caraway extracts from differentgermination phases exhibited a discount within the immobility of rats during FST and TST, as compared with the reference standard Imipramine 15 mg/kg of weight. Furthermore, extracts of 5th and 7th day germination phases showeda big reduction in immobility in rats (table-5).

Table-2 effects of thymoquinone on haloperidol induced catalepsy in mice.

Group (n=6) drug treatment	Catalepsy behaviour (s)			
	After1h	**after2h**	**after3h**	**after4h**
I corn oil (1ml /kg ip)	32.32±4.5	42.46±3.7	38.66±9.8	28.75±5.5
II Normal saline (1ml /kg ip	11.45±0.18	12.78±5.8	10.54±3.6	7.59±5.9
III HAL (2mg /kg p.o)	159.13±7.42^{ab}	244.33±7.07^{ab}	256±7.16^{ab}	272±3.78^{ab}
IV TQ (20 mg / kg i.p)	134.27±2.92^{ab}	234±6.17^{ab}	257±7.09^{ab}	263±5.68^{ab}
V TQ (20 mg / kg i.p)+ HAL (2mg /kg p.o)	280±5.68^{abc}	291±1.57^{abc}	292±3.62^{ab}	295 ±1.94^{ab}

All values were expressed as a mean ± standard error of mean (SEM), analyzedby ANOVA followed by dunett

multiple comparison test .p value<0.05 was considered significant and p value<0.001 was considered highly significant .n=6no of animals in each group [a]p <0.001vs. Corn oil [b]p<0.001vs normal saline [c]p<0.001vs group III.

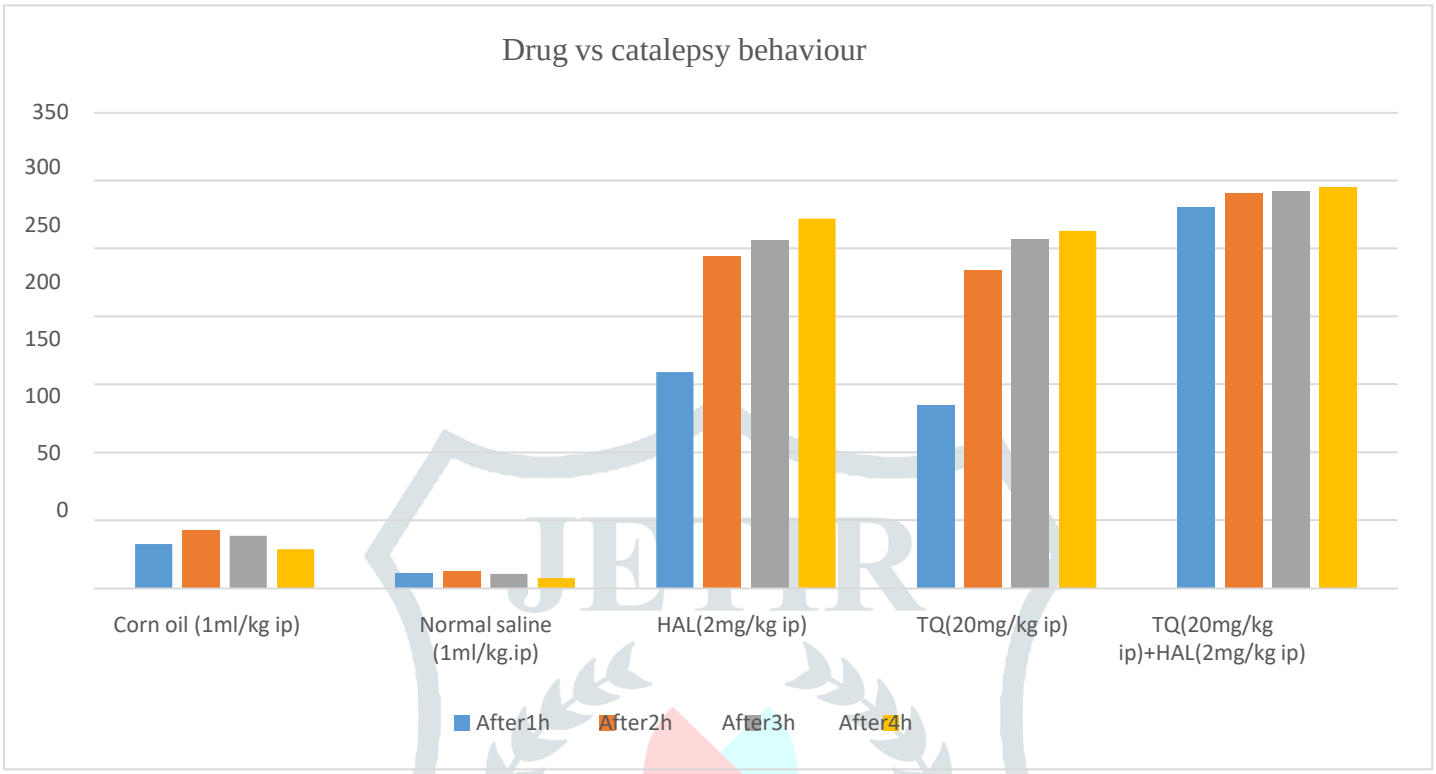


Table -3 Effects of thymoquinone on dopamine levels in haloperidol inducedcatalepsy in mice.

Group(n=6)	drug treatment	Dopamine (ng/g wt. of tissue)
I	corn oil (1ml /kg ip)	13.11±1.1
II	normal saline (1ml /kg ip)	13.52±0.96
III	HAL (2mg /kg p.o)	5.67±0.57$^{***###}$
IV	TQ (20 mg / kg i.p)	9.31±0.33**
V	TQ (20 mg / kg i.p)+ HAL (2mg /kg p.o)	4.23±0.23$^{***###}$

All values were expressed as a mean ± standard error of mean (SEM), analyzedby ANOVA followed by dunett multiple comparison test .p value<0.05 was considered significant and p value<0.001 was considered highly significant .n=6no of animals in each group *p<0.01vs. Corn oil, **p<0.001vs Corn oil, $^{\#\#}$p<0.001vs. normal saline.

Table -4 Effects of thymoquinone on Elevated plus-maze test in mice.

Group (n=6)	drug treatment	Transfer latency (s)		Alteration (%)	Possible alteration(s)
		On day1	on day 2		
I	corn oil (1ml /kg ip) Normal	24.33±2.3	11.13±1.2	51.61±5.32	28.5±1.1
II	saline (1ml /kg ipSCOP (0.5	21.32±1.56	9.04±0.39	47.77±3.7	30.46±2.3
III	mg/kg i.p)	54.37±5.23[ab]	45.71±3.7[ab]	25.37±1.87[ab]	11.32±0.08[ab]
IV	TQ (20 mg / kg i.p)	23.38±1.97	15.88±2.13	61.49±7.24[b]	23.53±2.1
V	TQ (20 mg / kg i.p)+SCOP (0.5 mg/kg i.p)	42.23±5.78[ab]	30.66±4.1[ab]	38.76±5.76[ab]	16.66±1.9[ab]

All values were expressed as a mean ± standard error of mean (SEM), analyzedby ANOVA followed by dunett multiple comparison test .p value<0.05 was considered significant and p value<0.001 was considered highly significant .n=6no of animals in each group [a]p <0.001vs. Corn oil [b]p<0.001vs normal saline [c]p<0.001vs group III.

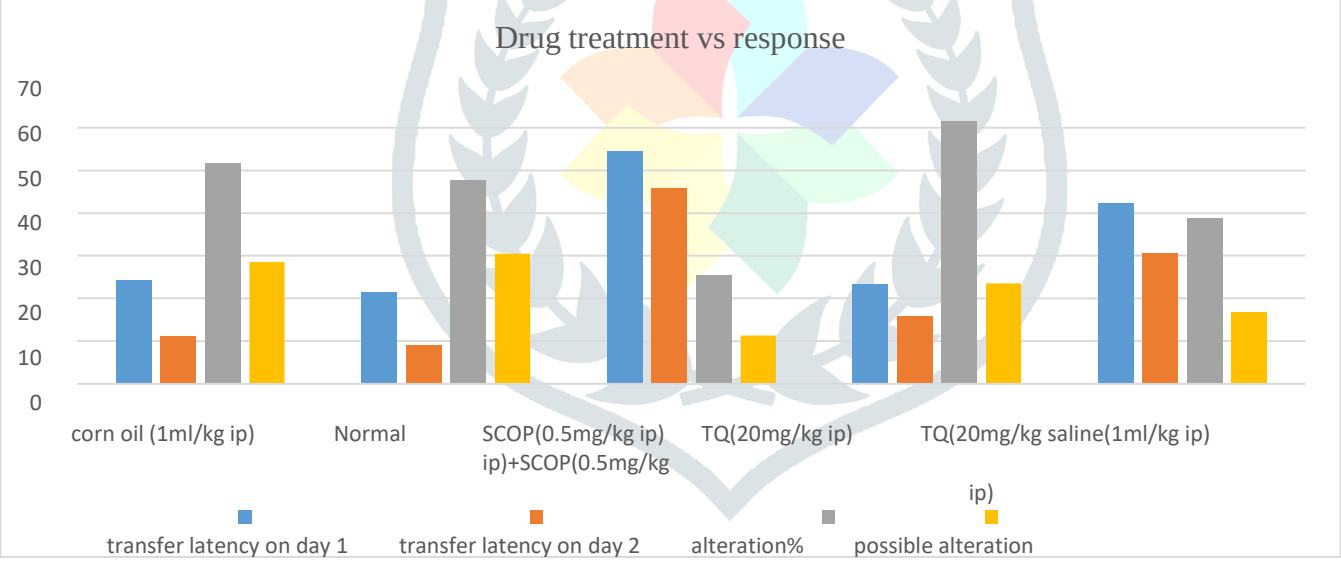


Table -5 Effects of thymoquinone on dopamine levels in Elevated plus-maze test inmice.

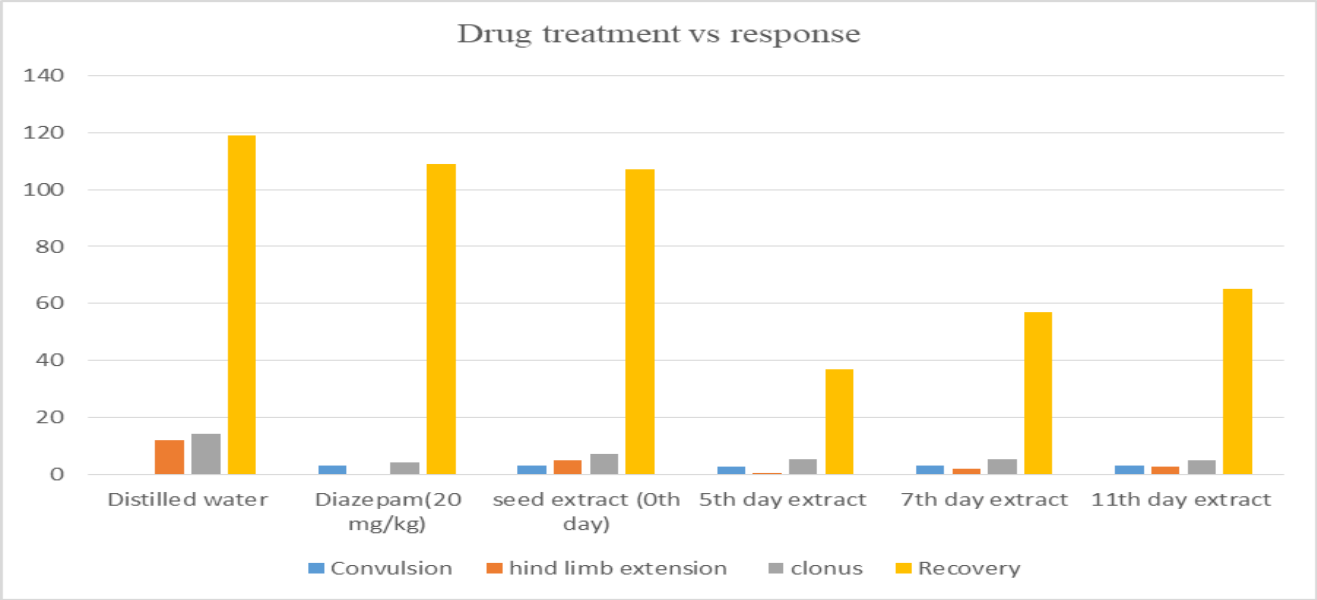
Group (n=6)	drug treatment	Dopamine (ng/g wt. of tissue)
I	corn oil (1ml /kg ip)	13.12±1.1
II	Normal saline (1ml /kg ip)	13.52±0.96
III	SCOP (0.5 mg/kg i.p)	15.66±1.96
IV	TQ (20 mg / kg i.p)	9.41±0.42*#
V	TQ (20 mg / kg i.p) + SCOP (0.5 mg/kg i.p).	11.30±0.49

All values were expressed as a mean ± standard error of mean (SEM), analyzedby ANOVA followed by dunett multiple comparison test .p value<0.05 was considered significant and p value<0.001 was considered highly significant .n=6no of animals in each group *p<0.05 vs. Corn oil p<0.05 001vs normal saline group.

Table 6: Effect of Nigella sativa extracts of different germination phases onmaximal electroshock induced seizures in rats.

Group	Treatment	Convulsion(s)	Hind limb extension (s)	Clonus (s)	Recovery (s)
I	Distilled water	9.21±0.13	12.2±0.15	14.2±0.14	119±2.7
II	Diazepam (20 mg/kg)	2.999±0.13a	0±0.00	4.32±0.20a	109±3.1a
III	Seed extract (0th day)	3.2±0.30a	4.9±0.33a	7.13±0.31a	107±2.2a
IV	5th day extract	2.7±0.09a	0.3±0.01a	5.17±0.13a	37±2.4a
V	7th day extract	3.2±0.20a	2.11±0.12a	5.25±0.22a	57±1.6a
VI	11th day extract	3.12±0.21a	2.6±0.10a	5.12±0.12a	65±2.1a

[a]P<0.001, compared with group I (control).



CONCLUSION:-

The aim of the study was to develop antipsychotic activity of nigella sativa which is commonly known as black cumin. N. sativa has been considered worldwide as an important medicinal herb and is widely used in pharmaceuticals. The investigation represents use of the essential oil for various disease. The present study observed the role of nigella sativa in different antipsychotic model, which is used for memory impairment and learning problem. TQ exhibited antipsychotic likeactivity in various model. The role of dopamine in human evolution has received little theoretical attention. TQ decreased the DA levels which suggests its antipsychotic like action.

Bibliography:-

1. Hanna, M.A.; Rahman, M.A.; Sohag, A.A.M.; Uddin, M.J.; Dash, R.; Sikder,M.H.; Rahman, M.S.; Timalsina, B.; Munni, Y.A.; Sarkar, P.P.; et al. Black Cumin (Nigella sativaL.): A Comprehensive Review on Phytochemistry , Health Benefits, Molecular Pharmacology, and Safety. Nutrients 2021, 13, 1784. https://doi.org/10.3390/nu13061784.

2. Ebrahim M. Yimer et al. Nigella sativa L. (Black Cumin): A Promising Natural Remedy for Wide Range of Illnesses. Evidence-Based Complementary and Alternative Medicine Volume 2019, https://doi.org/10.1155/2019/1528635.

3. Khan et al., ameliorating effect of thymoquinone in rodent models of schizophrenia. African journal of pharmacy and pharmacology, vol.8 (15), pp. 413-421, 22 April 2014, DOI: 10.5897/AJPP2014, 3968

4. Soheila Javidi et al., A review of Neuropharmacology Effects of Nigella sativa and Its Main Component, Thymoquinone, Phytother. Res. (2016) Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ptr.5634

5. Saeed Samarghandian et al., A Review on Possible Therapeutic Effect of Nigella sativa and Thymoquinone in Neurodegenerative Diseases. CNS & Neurological Disorders - Drug Targets, 2018, 17, 412-420. DOI: 10.2174/1871527317666180702101455.

6. Krishnapura Srinivasan, Department of Biochemistry, CSIR – Central Food Technological Research Institute, Mysore 570 020, Food Quality and Safety, 2018, 2, 1–16. DOI:10.1093/fqsafe/fyx031.

7. Hosseinzadeh L, Monaghash H, Ahmadi F, Ghiasvand N, Shokoohinia Y. Bioassay-guided isolation of neuroprotective fatty acids from Nigella sativa against 1-methyl-4-phenylpyridinium-induced neurotoxicity. Phcog Mag 2017;13:627-33.

8. Elkhayat ES, Alorainy MS, El-Ashmawy IM, Fat'hi S. Potential antidepressant constituents of Nigella sativa seeds. Phcog Mag 2016;12:S27S31. DOI: 10.4103/0973-1296.176118.

9. Akintunde Jacob Kehinde et al., Functional Oil from Black Seed Differentially Inhibits Aldose-reductase and Ectonucleotidase Activities byUpregulating Cellular Energy in Haloperidol-induced Hepatic Toxicity in RatLiver. DOI: 10.5650/jos.ess17036 J. Oleo Sci. 66, (9) 1051-1060 (2017).

10. Md. Jakaria et al. Oxidative Medicine and Cellular Longevity, Review Article Neuropharmacological Potential and Delivery Prospects of Thymoquinone for Neurological Disorders .Volume 2018, Article ID 1209801, 17 pages. https://doi.org/10.1155/2018/1209801.

11. Alireza Tavakkolia et al., Oxidative stress and dietary antioxidants inneurological diseases- 2020, 326-340. https://doi.org/10.1016/B978- 012817780-8.00021-9.

12. Akintunde JK, Jimoh YO, Boligon AA (2018) Essential Oil from Nigella Sativa Seed Differentially Ameliorates Steroid Genesis, Cellular ATP and Prostate Functions in Anti-Psychotic Drug-Induced Testicular Damage of Rats.J Clin Toxicol 8: 371. DOI:10.4172/2161-0495.1000371.

13. Md Fauzi NFA, Abu Bakar NH, Mohamad N, Mohd Adnan LH, Mustafa NS, Ahmad NZ. Regulatory Effects of Thymoquinone on Dopamine Level in Neuronal Cells Exposed to Amphetamine: An in Vitro Study. J Cell Mol Anesth.2020; 5(4):216-23. https://doi.org/10.22037/jcma.v5i4.32096.

14. Abdulwakeel Ayokun-nun Ajao, Afolakemi Abibat Alimi, Olusanya Abiodun Olatunji, Fatai Oladunni Balogun & Sefiu Adekilekun Saheed (2017):A synopsis of anti-psychotic medicinal plants in Nigeria, Transactions of the Royal Society of South Africa, DOI:10.1080/0035919X.2017.1386138.

15. H.J. Rogier Hoenders, Agna A. Bartels-Velthuis, Nina K. Vollbehr, Richard Bruggeman, Henderikus Knegtering, Joop T.V.M. de Jong J Nerv Ment Dis. 2018 Feb; 206(2):81–101.Published online 2018 Jan 30 .PMCID: PMC5794244.

16. Harleen Kaur et al., advances in neuropharmacology: drugs and therapies.Antipsychotic drugs .294-312, jan 2020. DOI: 10.1201/9780429242717-15.

17. Forouzanfar F, Bazzaz BSF, Hosseinzadeh H. 2014. Black cumin (Nigella sativa) and its constituent (thymoquinone): a review on antimicrobial effects. Iran J Basic Med Sci 17:929–938.

18. Ahmad A et al. 2013. A review on therapeutic potential of Nigella sativa: Amiracle herb. Asian Pac J Trop Biomed 3: 337–352.

19. Yarnell, E., Abascal, K. (2011). Nigella sativa: holy herb of the Middle East.Alternative and Complementary Therapy, 17: 99–105.

20. Maurya, P. K.; Rizzo, L. B.; Xavier, G.; Tempaku, P. F.; Zeni-Graiff, M.; Santoro, M. L.; Mazzotti, D. R; Zugman, A.; Pan, P.; Noto, C. Shorter Leukocyte Telomere Length in Patients at Ultra High Risk for Psychosis. Eur. Neuropsychopharmacol. 2017, 27,538-542.

21. Wesam Kooti, Zahra Hasanzadeh-Noohi, Naim Sharafi-Ahvazi, Majid Asadi-Samani, Damoon Ashtary-Larky. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa) [J]. Chin J Nat Med, 2016, 14(10):732-745.P Sudhakar et al., Role of Indian spices in CNS disorders: A review. Journal of Medicinal Plants Studies 2020; 8(4): 171175.

22. Beheshti F, Khazaei M, Hosseini M. Neuropharmacological effects ofNigella sativa. Avicenna J Phytomed, 2016; 6 (1): 124-141.

23. Purva Bhishnurkar et al ., Simultaneous determination of β-sitosterol and gallic acid in Nigella Sativa seeds using reverse phase high performance liquid chromatography .SN Applied Sciences (2020) 2:1873 | https://doi.org/10.1007/s42452-020-03709-8.

24. Ralf Brisch et al., The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue-Review article. 19 may, 2014. DOI: 10.3389/fpsyt.2014.00037.

25. Bahmani M, Taherikalani M, Khaksarian M, Soroush S, Ashraf B, HeydariR (2019) Phytochemical profiles and antibacterial activities of hydroalcoholic extracts of origanum vulgare and hypericum perforatum and carvacrol and hypericin as a promising anti-staphylococcus aureus. Mini-Rev Med Chem 19(11):923–932.

26. M. Hosseini, T. Mohammadpour, R. Karami, Z. Rajaei, H.R. Sadeghnia, and M. Soukhtanloo, "Effects of the hydroalcoholic extract of Nigella Sativa on scopolamine-induced spatial memory impairment in rats and its possible mechanism,"Chinese Journal of Integrative Medicine, vol. 21, no. 6, pp. 438–444, 2015.

27. Susheela UR (2000) Handbook of spices, seasoning, and favorings. Technomic Publishing Co., Inc, Lancaster, p 329.

28. Islam et al., Neuroprotective effects of Nigella sativa extracts during germination on central nervous system Pharmacognosy Magazine, AprilJune 2015, Vol 11, Issue 42 (Supplement 1). DOI: 10.4103/0973-1296.157729.

29. AS, Kamel R, Sherief MAE. Effect of thymoquinone on hepatorenal dysfunction and alteration of CYP3A1 and spermidine/spermine N-1-acetyltransferase gene expression induced by renal ischaemia-reperfusion in rats. J Pharm Pharmacol 2011; 63(8): 1037-42.

30. Kassab RB, El-Hennamy RE. The role of thymoquinone as a potent antioxidant in ameliorating the neurotoxic effect of sodium arsenate in female rat. Egyptian Journal of Basic and Applied Sciences. 2017; 4(3):160-7.

31. HY Meltzer and BW Massey., The role of serotonin receptors in the action of atypical antipsychotic drugs ,Current Opinion in Pharmacology 2011, 11:59–67 .Edited by Nicholas Barnes1471-4892/$ – see front matter# 2011 Elsevier Ltd. All rights reserved. DOI 10.1016/j.coph.2011.02.007.

32. Islam MT, Guha B, Hosen S, Riaz TA, Shahadat S et al. (2017) Nigellalogy:A Review on Nigella Sativa. MOJ Bioequiv Availab 3(6): 00056. DOI: 10.15406/mojbb.2017.03.00056.

33. Khan MA. Thymoquinone, a constituent of prophetic medicine-black seed,is a miracle therapeutic molecule against multiple diseases. Int J Health Sci. 2019; 13(1):1-2.

34. M. Akram Khan, M. Afzal; Chemical composition of Nigella sativa Linn: part2 recent advances, Inflammopharmacol (2016) 24:67–79.DOI 10.1007/s10787-016-0262-7.

35. F. Vafaee, M. Hosseini, Z. Hassanzadeh et al., "The effects of Nigella sativahydro-alcoholic extract on memory and brain tissues oxidative damage after repeated seizures in rats," Iranian Journal of Pharmaceutical Research, vol. 14,no. 2, pp. 547–557, 2015.

36. Mohamad Khairul Azali Sahak,et al ., Review Article-The Role of Nigella sativa and Its Active Constituents in Learning and Memory; Hindawi Publishing Corporation ,Evidence-Based Complementary and Alternative Medicine
;Volume 2016, Article ID 6075679, 6 pages http://dx.doi.org/10.1155/2016/6075679.

37. S. V. Tembhurne*, S. Feroz, B. H. More and D. M.Sakarkar ; A review on therapeutic potential of Nigella sativa (kalonji) seeds., Vol. 8(3), pp. 167-177, 17 January, 2014, DOI: 10.5897/JMPR10.737ISSN 1996-0875 ©2014 Academic Journals http://www.academicjournals.org/JMPR.

38. M. Kiralan et al. / Physicochemical properties and stability of black cumin (Nigella sativa) seed oil as affected by different extraction methodsIndustrial Crops and Products 57 (2014) 52–58. http://dx.doi.org/10.1016/j.indcrop.2014.03.026

39. Changyang Ma et al. Research Article -Optimum Extraction Technology forthe Seed Oil of Nigella sativa L. Hindawi ,Journal of Food Quality Volume 2019, Article ID 2592731, 6 pages. https://doi.org/10.1155/2019/2592731.

40. SUBRATTI et al.,ORIGINAL ARTICLE on Efficient extraction of black cumin (Nigella sativa L.) seed oil containing thymol, using liquefied dimethyl ether (DME) J Food Process Preserv.2019;e13913. https://doi.org/10.1111/jfpp.13913.

41. Van der Mast RC, et al. Incidence of and preoperative predictors for delirium after cardiac surgery. J Psychosom Res. 1999; 46(5):479–83. [PubMed: 10404482].

42. M. Arruda et al.; Research article Open Access Activities of the Antipsychotic Drugs Haloperidol and Risperidone on Behavioural Effects Induced by Ketamine in Mice., Sci Pharm. 2008; 76; 673–687.

43. Forrest et al., Animal Models of Psychosis: Current State and Future Directions. Curr Behav Neurosci Rep. 2014 June 1; 1(2): 100–116. Doi: 10.1007/s40473-014-0013-2.