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A REVIEW ON THE CURATIVE AND PROTECTIVE EFFECT OF TRADITIONAL KALONJI SEED AGAINST ANTIEPILEPTIC DRUGS CAUSING TOXICITY ON THE LIVER AND KIDNEY

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ABSTRACT

Epilepsy is one of the most prevalent and frequently occurring neurological disorders. It is a pervasive brain condition, that puts a significant burden on individuals, families, and healthcare systems. Approximately 50 million people worldwide currently suffer from epilepsy. According to estimates, India is home to more than 12 million epileptics. Long-term use of antiepileptic medication develops hepatotoxicity because the liver is the major organ for drug processing and disposal. The hepatotoxic effects of antiepileptic medications including phenytoin and valproic acid are widely established. Antiepileptics result in numerous morphological and metabolic abnormalities in the liver. The development of reactive metabolites and reduction of beta-oxidation may contribute to their hepatotoxic effects. Due to the medications' poor efficacy and significant side effects, traditional medicine is being used more frequently. *Nigella sativa* seed popularly known as black cumin is a plant that is indigenous to northeastern India called Kalo jeera, a member of the Ranunculaceae family. It has been used for centuries to treat various illnesses. It is found that thymoquinone, a key component of *Nigella sativa*, is effective against epilepsy by enhancing the inhibitory activity of the GABAergic system. The plant is also found to be beneficial against agents causing hepatotoxicity like valproic acid by inhibiting lipid peroxidation and also by repressing the activities of liver toxicity markers. The review work includes information on native plants of Assam, *Nigella sativa*. Their involvement in protecting against several prevalent neurological disorders like epilepsy, as well as details on their possible mechanisms and boosting hepatoprotective benefits.

KEYWORDS: "Black seed", "hepatoprotective", "nephroprotective", "anti-epileptic", *"Nigella sativa".*

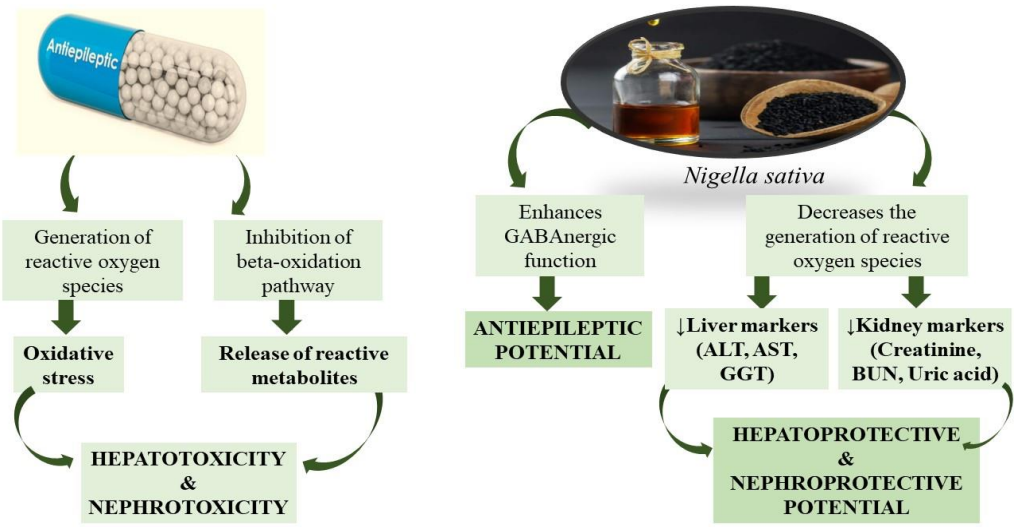

Fig: Graphical Abstract.

I. INTRODUCTION

The use of herbal medicine has increased dramatically during the past few years in the global medical community. One of the most significant traditional medicines used throughout the world is herbal medicine. Owing to their accessibility and low cost, medicinal plants have been employed as the primary form of healthcare in developing nations. The annual plant *Nigella sativa* (NS), a member of the Ranunculaceae family, is widely spread, especially in North Africa, the Middle East, Europe, and Asia. It is also known as "black cumin" or "black seeds." Black cumin is an effective natural treatment for a wide range of diseases, particularly for the management of eczema, asthma, inflammation, cough, and other flu-like illnesses. The seeds also possess diuretic, carminative, and deworming abilities. Numerous extracts and additional bioactive substances derived from the seeds, in particular the essential oil and thymoquinone (TQ), its main compound, are responsible for a variety of biological activities, including antioxidant, anti-inflammatory, antihepatotoxic, analgesic, antineoplastic, antimutagenic, anti-nephrotoxic immunostimulant, hypoglycemic, antiulcer, antimicrobial, and antiparasitic activities.[1,4,23,89]

Many important bodily processes are carried out by the liver and kidney. In fact, the harm to the body's metabolic system that results from liver disease or damage can be fatal. Numerous studies have previously shown that antioxidants protect against hepatotoxicity and nephrotoxicity by reducing ROS production, lipid peroxidation, and the activity of liver and kidney indicators. Black seeds are a well-known seed that contains antioxidants.[30,69] Thymoquinone, a vital component of *Nigella sativa*, has been found to be useful against epilepsy by raising the GABAergic system's inhibitory activity.[46]

The goal of the current review was to draw attention to the potential benefits of *N. sativa* and its constituents for treating epilepsy as well as their protective role against hepatotoxicity and nephrotoxicity.

II. Methodology for conducting literature survey

This review was compiled based on the comprehensive information obtained from research and review articles, and textbooks published on the plant Nigella sativa according to the preferred reporting for Systemic Review and Meta-Analysis (PRISMA). For developing strategic search, various electronic database systems were used, which include scientific data from Scifinder, PubMed, science direct, ACS publications, Wiley online library, and Google Scholar. The advanced literature search was accomplished up to 28th June 2023, including various operator keywords, viz. "black seed", "hepatoprotective", "nephroprotective", "anti epileptic", *"Nigella sativa".*

III. Epilepsy

A neurological condition called epilepsy is characterized by recurrent periods of unconsciousness, sometimes accompanied by seizures and aberrant electrical activity in the brain. Epilepsy is a seizure disorder that manifests clinically as an aberrant and excessive firing of a group of neurons in the brain.[80]

An aberrant, excessive excitation and synchronization of a cortical neuron group results in a clinical condition known as a seizure. It is brought on by abrupt, excessive nerve-cell discharges in the brain, which result in unusual body function, including loss of consciousness and odd sensations or overactive muscles. Seizures can be both epileptic and non-epileptic.[25]

Etiology: The etiology includes genetic factors, brain infections, strokes, brain tumors, high fever (particularly in babies), previous head injuries, and other neurological diseases.[81]

a. Pathophysiology

Seizures are caused by an imbalance of excitatory and inhibitory neurotransmitters in the cortical neuron network. An unstable cell membrane, or the cells surrounding it, is the fundamental physiology of a seizure episode. It comes from any cortical or subcortical region's grey matter. At first, only a few neurons fire improperly. Normal membrane conductance, the breakdown of the inhibitory synaptic current, and enhanced excitability can occur simultaneously and result in either a focal or generalized seizure. By way of physiological networks, this onset spreads to nearby regions. Depending on the location of the seizure's genesis and its connections, this disruption may cause a variety of symptoms and indicators. Seizures within the epileptic focus are caused by greater excitation or decreased inhibition, according to a model that involves communication between two neurons, with the activity of the second neuron having a measurable effect. The need for blood flow to the brain increases during a seizure in order to transport CO2 out of the body and bring the substrate for the neurons' metabolic activity. As the convulsions continue, the brain's ischemia worsens, causing neuronal death and permanent brain damage.[51,61,45,87]

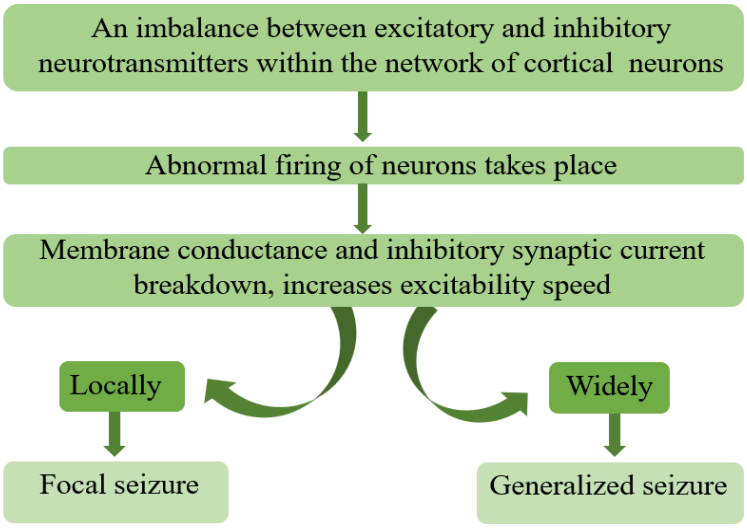

Figure 1: Pathophysiology of Seizure.

b. Classification of seizures

Seizures can be broadly classified into 2 types: Partial seizures and generalized seizures.[17,31,32,61]

Table 1: Classification of Seizure.

Types of seizures	Clinical Features	Area Affected	Function Affected
1. PARTIAL SEIZURE	Discharge starts at "localized" area of the brain		
i) Simple partial seizure	Seizure activity occurs while the person is alert	Frontal	Motor
ii) Complex partial seizure	Seizure activity occurs with a change in awareness of the surroundings	Temporal	Sensory
iii) With the secondary generalization	Seizure activity occurs in one area and then spread	Parietal	Sensory
2. GENERALIZED SEIZURE	Involves initial activation of both hemispheres of the brain.	All parts of the brain are affected	
i) Tonic-clonic seizure	Stiffening, falling and jerking of the body,Tonic and clonic convulsions, loss of consciousness	All parts of the brain are affected	Motor, consciousness
ii) Myoclonic seizure	Jerking limbs	All parts of the brain are affected	Motor
iii) Absence seizure	Staring and blinking without falling, brief period of reduced awareness	All parts of the brain are affected	Attention, consciousness

c. Treatment approaches

The following are few targets for anti-Epileptic drugs.

- ✓ Diminishment of the excitatory neurotransmitter glutamate.
- ✓ Increased levels of the inhibitory neurotransmitter Gamma Amino Butyric Acid (GABA).
- ✓ Voltage-gated positive current (Na+ and Ca+2) regulation
- ✓ Enhance the positive outward current.[56,57,74]

Table 2: Antiepileptic drugs- its mechanism of action and adverse effects.

Drugs	Mechanism of action	Adverse Effects	References
Phenytoin	It is a voltage-gated, sodium channel blocker, it also enhances the release of the inhibitory neurotransmitter, GABA	Megaloblastic anemia, hyperglycaemia, hirsutism gingival hyperplasia	[73]
Lamotrigine	It blocks the voltage-gated sodium channel, it diminishes the excitability of neurons	Headache, insomnia, ataxia, drowsiness	[74]
Carbamazepine	It blocks the voltage gated sodium channel	Dizziness, diplopia, headache, hyponatraemia, nausea, drowsiness,	[36]

		neutropenia	
Oxcarbazepine	Inhibits voltage-dependent fast sodium channels.	Hyponatremia, sedation, dizziness.	[61]
Zonisamide	Blockade of sodium channels, reduction of voltage dependent calcium currents and glutamate induced synaptic excitation.	Sedation, dizziness, cognitive impairment.	[26]
phenobarbital	Binds and activates GABAA receptor which increase the frequency of Cl^{2+} channel opening.	Tiredness, Depression Insomnia, Hyperkinesia, Irritability Aggression, Poor memory, Folate deficiency	[93]
Ethosuximide	Inhibition of T-type calcium channels..	Nausea, Anorexia, Vomiting.	[39]
Diazepam	Binds and activates GABAA receptor, which increase the frequency of Cl^{2+} channel opening. Drowsiness, fatigue, muscle weakness.	Drowsiness, fatigue, muscle weakness.	[61]
Clobazam	Clobazam Binds and activates GABAA receptor, increasing the frequency of Cl^{2+} channel opening.	Fatigue, Drowsiness, Dizziness, Ataxia Irritability, Weight gain.	[28]
Sodium valproate	Prolongation of Na+ channel inactivation and augments release of GABA.	Hepatotoxicity, nephrotoxicity, Weight gain, alopecia, Anorexia Dyspepsia, Alopecia, Drowsiness, Hyperammonaemia, Amenorrhoea,	[37, 21]
Vigabatrin	It Inhibits GABA-transaminase and increases synaptic GABA concentration.	Drowsiness, Fatigue, Headache, Ataxia Nystagmus, Diplopia, Irritability Aggression, Weight gain, Tremor Impaired concentration.	[72]
Tiagabine	Tiagabine Inhibits GABA uptake.	Dizziness, Headache, Difficulty concentrating, Light-headedness.	[74]
Felbamate	Felbamate Increases intracellular Ca2+and blocks excitatory postsynaptic potentials.	Anorexia, nausea, vomiting, headache, insomnia.	[18]
Levetiracetam	Levetiracetam Enhances the release of inhibitory neurotransmitters. Sedation, behavioral disturbance.	Sedation, behavioral disturbance.	[18]
Topiramate	Topiramate Potentiation of GABAA receptor-mediated currents.	Anorexia, Weight loss, Impaired concentration, impaired memory.	[18]

d. Effect of antiepileptic drugs on liver

Many antiepileptic medications are metabolized and eliminated primarily by the liver, which makes it vulnerable to drug-induced toxicity. Hepatotoxic responses can range widely, from minor, temporary increases of liver enzymes to catastrophic hepatic failure (Arroyo et al., 2001). Drug-induced liver toxicity is defined as an increase in ALT levels that are three times above normal and in total bilirubin levels that are two times above normal. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) are examples of liver enzymes that might act as markers for hepatocellular damage or cholestasis, an obstruction of the bile flow. In cases of liver disease, these enzymes are increased.[5] Antiepileptic medications can cause a variety of severe side effects, as is the case with carbamazepine (CBZ), valproic acid (VPA), and phenytoin (PHT). Antiepileptic drug-induced hepatotoxicity is rather uncommon compared to other consistently known hepatotoxic medicines, yet it might result in severe liver failure or death, either of which would necessitate a liver transplant.[33] Antiepileptic drugs can cause liver damage by either producing reactive toxic metabolites or by depleting the beta-oxidation pathway.[2,55,85]

e. Effects of antiepileptic drugs on kidney

Some antiepileptic medicines have been known to cause kidney malfunction or damage. AEDs generally pose a minimal risk of evident renal harm. Rarely reported side effects of several AEDs include acute kidney damage (AKI), interstitial nephritis, and abrupt renal failure; these events typically occur in conjunction with multi-organ hypersensitivity syndrome.[40]

Children with epilepsy receiving valproic acid therapy have been observed to develop Fanconi's syndrome, an acute kidney disease in which the renal tubules become incapable of reabsorbing electrolytes, phosphate, urea, glucose, amino acids, and protein. Children receiving Valproic acid and Carbamazepine mono- or polytherapy have been documented to have renal glomerular or/and tubular impairment.[44]

The three primary functions of the renal system are glomerular filtration, tubular secretion, and tubular reabsorption. These three functions are markers of kidney damage. Evidence of glomerular and/or tubular dysfunction points to renal impairment. Measures or markers of kidney function include serum creatinine and creatinine clearance (CrCl), blood urea nitrogen (BUN), serum electrolytes, and urine examination for specific

gravity, hematuria, and urinary 24-hour protein excretion.[40]

Although the exact mechanism of kidney damage caused by antiepileptic medicines is unknown, it has been linked to the production of harmful drug metabolites, reactive oxygen species, and free radicals.[71]

f. Reactive oxidant species and hepatotoxicity

The liver is the body's main metabolic organ and is in charge of a number of vital processes. In fact, the harm to the body's metabolic system that results from liver disease or damage can be fatal. Antioxidants have been shown to delay the toxicity of the liver by inhibiting lipid peroxidation, the production of ROS, and the activities of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP).[30] The antioxidant properties of the N. sativa seed's bioactive components have received much research. Reactive oxygen species are primarily to blame for the majority of liver injuries because they deplete anti-oxidant enzyme supplies and reduce cells' capacity to fend off damage.[66] The three main enzymes that produce ROS in the body are nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, nitric oxide synthases (NOS), and myeloperoxidases. Reactive oxygen species are by-products of regular cellular metabolic activities. They include super-oxide anion radical (O2), hydrogen peroxide (H2O2), peroxynitrite (ONOO-), hydroxyl radical (OH-), and hypochlorous acid (HOCl-). When the ratio of ROS to antioxidants is out of balance, the favourable effects of ROS are disrupted. This imbalance is referred to as oxidative stress. The primary cellular components, polyunsaturated lipids and protein sulfhydryl groups, play crucial roles in cellular function and disturbance of their structural characteristics by free radicals may result in the termination of cellular functions.[12] The liver has a high metabolic rate, making it extremely vulnerable to oxidative stress and the harm that free radicals can do. By creating free radicals, scavenging them, or strengthening the anti-oxidant defence, reactive oxygen species' harmful effects can be avoided.[94] Hepatocellular carcinoma, alcoholic liver disease, hepatic stellate cells, fibrosis/cirrhosis, ischemic/reperfusion liver injury, fatty liver, viral hepatitis, paracetamol-induced liver damage, and chemical pollutant-induced liver damage are some of the liver disorders caused by oxidative stress.[12]

IV. Nigella Sativa

Natural traditional therapies for the prevention and treatment of liver conditions have gained popularity in the last decade around the world; nevertheless, there is inadequate information on the biological activities and processes of these treatments. Despite being thought to be indigenous to the Mediterranean region, "black cumin seed," also known as "black seed," or Nigella sativa L. in botanical terms, has been planted all over the world. Its seeds, known as cyahdane in Persian, have been crucial over time in traditional Islamic practice.[33]

Its many therapeutic properties, including anticancer, diuretic and hypotensive, antihistaminic, antihypertensive, hypoglycemia, anti-inflammatory and analgesic, as well as antifungal and antibacterial actions, have been the subject of several investigations. The oil is beneficial for illnesses where free radicals exist, such as cancer, arteriosclerosis, rheumatoid arthritis, anoxia, and ischemia of the brain and heart.[24]

The plant is grown throughout Asia, the Mediterranean, the Middle East, and Africa. Due to its claimed antiviral, anti-inflammatory, anti-diabetic, immune-modulatory, anti-cancer, and hepatoprotective effects, NS is traditionally used to treat a variety of disorders. Additionally, kalonji lessens the harmful side effects of a number of chemotherapy drugs.[33]

a. Plant description

Kingdom- Plantae
Subkingdom- Tracheobionta
Phylum- Magnoliophyta
Class- Magnoliopsida
Subclass- Magnoliidae
Order- Ranunculales
Family- Ranunculaceae
Genus- Nigella
Species- N.sativa

b. Characteristics and morphology

N. sativa is a 20–90 cm long plant with finely divided leaves and leaf segments that range from narrowly linear to threadlike. Pale blue flowers are borne on a solitary, lengthy peduncle. The fruit capsule of the bisexual plant contains numerous white trigonal seeds.[4]

The fruit is fashioned like a large, inflated capsule and is composed of 3–7 connected follicles. The seeds inside mature fruit capsules turn black (black seeds) as they open to the air. There are the trigonous, dark-colored seeds.[4,33,89]

c. Phytoconstituents present

A number of bioactive substances derived from black seeds have been identified in the literature; thymoquinone being the most significant of these. Sterols and saponins, phenolic compounds, alkaloids, new lipid components, fatty acids, and volatile oils of various compositions are some of the other major phytochemicals found in many types.[82]

About forty different compounds were included in the essential oil composition (0.4-0.45%) reported in various studies, with trans-anethole, p-cymene limonene, carvone, -thujene, dithymoquinone, carvacrol, and pinene with varying concentrations being the most abundant constituents.[15]

Table 2: Composition of black seed.[15,82,89]

Constituents	% Range
Oil	31-35.5
Protein	16-19.9
Carbohydrate	33-34
Fiber	4.5-6.5
Saponin	0.013
Moisture	5-7

d. Constituents on *N Sativa* seed oil

The general constituents are Linoleic acid (44.7-56), Oleic acid (20.7-24.6), Linolenic acid (0.6-1.8), Arachidic acid (2-3), Palmitoleic acid (3), Eicosadienoic acid (2-2.5), Palmitic acid (12-14.3), Stearic acid (2.7-3), Myristic acid (0.16), Stroles (0.5).[15,89]

e. Traditional use

Traditional Uses of kalonji in Folk Remedies as a spice and flavoring agent in a variety of food preparations such as in bread, yogurt, pickles, sauces, and salads. Black seed or black cumin (English), has long been used in traditional remedies in the Arabian countries, Far East Asia, Europe, and Africa. *Nigella sativa* has also been described as a miraculous plant and considered by earliest herbal specialists as "Te herb from heaven". The Prophet Mohammed (PBUH) had described the curative powers of the black seed as "Hold on to use this black seed, as it has a remedy for every illness except death". The medicinal use of black cumin seeds in various traditional herbal systems is known for a wide range of ailments which include different airway disorders, pain such as chronic headache and back pain, diabetes, paralysis, infection, inflammation, hypertension, and digestive tract-related problems administered in different kind of preparations. It has also been used topically where it is applied directly to blisters, nasal abscesses, orchitis, eczema, and swollen joints.[60, 82, 89]

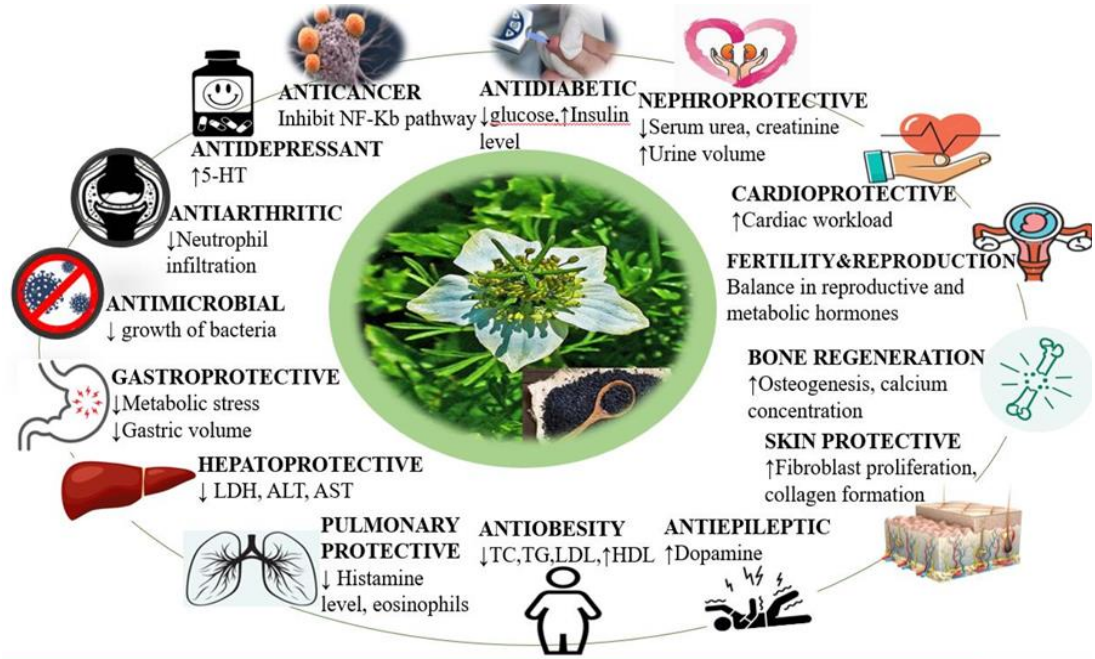

Figure 2: Pharmacological activity of *Nigella sativa*.

V. Mechanism of hepatoprotection of *N. Sativa* and its main constituents

A number of studies have shown the antioxidant properties of black cumin seeds. TQ impairs Fe-dependent LPO in a dose-dependent manner. There has been strong O-2 scavenging activity reported. Because of this property, TQ can lessen oxidative stress and strengthen the body's antioxidant defense. Thiol content and glutathione GSH levels increase after TQ therapy, but malondialdehyde (MDA) and other oxidative stress indicators decrease.[2]

GSH is a chemical that is particularly plentiful in the liver and is believed to play a vital role in cellular defence mechanisms. As a result of oxidative stress, which also results in protein inactivation, lipid peroxidation, protein oxidation, disruption of calcium homeostasis, and protein oxidation, cells lose their overall viability. TQ may deplete free radicals, which reduces their capacity to harm DNA and increase the risk of cancer.[10]

TQ inhibits the biotransformation of numerous xenobiotics into reactive radical derivatives that are genotoxic by the hepatic CYP1A1/A2 isozymes.[64] TQ's capacity to fight cancer is what causes its anti-schistosomal activity, which reduces the liver damage caused by parasites.[63] The harmful consequences of ROS generated in the I/R state can be minimised and lessened by TQ's antioxidant qualities. TQ increases catalase (CAT) activity, which is essential for the liver's ability to protect itself from I/R damage.[42] It also

protects against kidney damage brought on by I/R by acting as an antioxidant and decreasing the expression of the genes for spermidine/spermine N-1-acetyltransferase (SSAT) and CYP3A1.

I/R significantly increased the expression of CYP3A1 mRNA in the tissues of the kidney and liver. I/R cause the kidney and liver tissues to express more spermidine/spermine N-1-acetyltransferase SSAT, a catabolic enzyme involved in polyamine modification.[77] In the liver and kidney, SSAT mRNA expression declines considerably. By increasing the activities of GST and quinone reductase, TQ was a promising preventative agent against synthetic carcinogenesis and bad quality in liver tissues when taken orally. The oxidation of pyridine nucleotides, which has been linked to the impairment of calcium sequestration by endoplasmic reticulum and mitochondria, followed by the leakage of cytosolic enzymes, was the long-term effect of the treatment of oxidative stress.[55] The treatment of oxidative stress was initiated by tert-butyl hydro peroxide, as an oxidative agent on isolated rat hepatocytes. TQ has the ability to guarantee the perception of the hepatocyte's tissue membrane while also suppressing blebs' course of action. TQ can suppress the expression of iNOS, which contributes to the condition of oxidative stress, which in turn boosts the expression of cellular antioxidant proteins such GSHPx and SOD. TQ may lower NADH, which would lessen the NADH/NAD+ fluctuations and inhibit the hepatocytes' ability to produce lipogenesis. In vitro experiments using TIB-73 cells revealed that the N. sativa seed extract treatment dramatically increased cell viability and reduced the production of reactive oxygen species. In vivo trials on rats have it has also restored the alterations in blood lactate levels, pH, anionic gap, and ion levels brought on by toxicant exposure. It has been shown to have lower levels of hepatic lipid peroxidation, increased SOD levels, decreased glutathione concentrations, and decreased glutathione concentrations, as well as decreased levels of ALT, aspartate aminotransferase, lactate dehydrogenase, and ALP. The effect of N. sativa oil (NSO) at cytotoxic concentrations on the expression of apoptotic marker genes (p53, caspase-3, caspase-9, bax, and bcl-2) and oxidative stress markers (GSH/lipid peroxidation(LPO)), ROS production, and mitochondrial membrane potential was investigated. The results demonstrated a significant, concentration-dependent decline in the rate of cell suitable for HepG2, MCF-7, and A-549 cells. The amount of mRNA expression of the apoptotic marker antibodies (p53, caspase-3, caspase-9, and bax) was up-regulated following the treatment of HepG2 cells with NSO, whereas the antagonistic anti-apoptotic gene bcl-2 was down-regulated, according to real-time PCR data. The findings showed that NSO caused HepG2 cells to become toxic and to die via the production of ROS, which is probably mediated by the p53 pathway.[75, 83, 69]

a. Anti-inflammatory Mechanism

TQ use has also been demonstrated to have anti-inflammatory benefits in a variety of inflammatory illnesses. *N. Sativa's* hepatoprotective effects in hepatocytes encouraged signalling pathways that cause cell damage.[20] TQ has been demonstrated to be a powerful inhibitor of thromboxane B2 and leukotriene B4 eicosanoid production. This may be accomplished by blocking the COX and LOX enzymes. These regulators play two key functions in hepatocyte cell membrane bleb formation and free radical generation.[59] Numerous research have examined TQ's previously reported antioxidant abilities.[52] TQ is also rddddddddd for its ability to reduce inflammation in a number of inflammatory illnesses. By exposing cells to the TQ compound, the ratio of helper to suppressor T cells increased, natural killer cell activity increased, IL-3 production increased, and macrophages were stimulated.[11] MPO activity was elevated in the liver tissue as a result of inflammatory reactions and activated neutrophils. MPO increases the generation of free radicals and lipid peroxidation, which worsens liver damage.[48,67] TQ decreased inflammation by reducing MDA and LPO products, the number of cytokines by preventing NF-B from functioning, and the generation of cytochrome c from mitochondria by preventing ROS in the liver.[13,16,29,35,70]

Table 3: Protective effect of *N. Sativa* against various hepatotoxicants.

Hepatotoxicants	Results	Mechanism of Action	References
Higher cytotoxic response in HepG2 cells	↑ROS ↑LPO ↓GSH ↓MMP	Antioxidant mechanism ⊤ p53 pathway	[9]
Carbon tetrachloride (CCl4)-treated rats	↓LPO ↓Liver enzymes ↑Antioxidant activity	Antioxidant mechanism	[10]
Hepatic ischemia–reperfusion injury	↓ Liver enzymes ↓Antioxidant activity ⊥ NF-κB ⊥COX ⊥ LOX	Antioxidant mechanism ↓NF-κB ↑COX ↑LOX	[84]
Paracetamol-induced hepatotoxicity	⊤Centrilobular necrosis ⊤Pyknosis of hepatocytes ⊤Neutrophils infiltration.	Antioxidant mechanism	[27]
Liver injury caused by thioacetamide	⊤ CAT ⊤SOD ⊤GPx ⊤TBA]	Antioxidant mechanism	[3]
Bee honey (BH) and Nigella sativa (NS) on HepG2 cell. mechanism [206]	↓Nitric oxide ↑Total antioxidant ↑caspase-3 activity	Antioxidant mechanism Apoptosis mechanism	[62]

Ischemia reperfusion injury	↑TAC ↓MPO ↓Total oxidative status ↓ OSI	Antioxidant mechanism	[43]
CCl4 -induced hepatotoxicity	┬ ALT ┬AST	Antioxidant mechanism	[41]
Toluene-induced hepatotoxicity	↓ GSH]	Antioxidant mechanism	[50]
Diethylnitrosamine-induced hepatotoxicity	↑CAT ↑GSHPx ↑GST ↑ GST ↑GSHPx ↑CAT	Antioxidant mechanism	[58]
Lead acetate-induced liver toxicity	↑ CAT	↑ cytokines ↓Antioxidant ↑Immune system	[14]
Cholestatic liver injury	↓GGT ↓ALP ↓AST ↓ALT ↓ LDH ↓TOS ↓OSI ↓MPO ↑ TAC ↑CAT	↓ IL-1 α ↓ TNF-α ↓ IL-6	[54]
HCV infection	↓Viral load ↓α-fetoprotein ↓ liver function parameters	Insulin-mediated mechanism of action	[1]
TNBS-induced colitis	↓ LOP ↓ Liver enzymes ↑Antioxidant defense system activity	↓IFN-α	[82]
Carbon tetrachloride-induced hepatotoxicity in rats.	↑ Lysosomal enzyme activity	Antioxidant mechanism	[85]

VI. Protective effect of *N. sativa* and thymoquinone on epilepsy

The effect of *N. sativa* oil (NSO) on alterations in amino acid neurotransmitters (epilepsy) produced by pilocarpine (380 mg/kg, i.p.) was studied. Following pilocarpine injection, the levels of aspartate, glutamate, GABA, glycine, and taurine increased dramatically in the cortex and glycine and taurine decreased and aspartate increased significantly in the hippocampus. The irregularities brought on by pilocarpine could not be appreciably improved by N. sativa oil (4 mL/kg).[65]

On a rat model of pentylenetetrazole (PTZ, 40 mg/kg b.w.)-induced seizures, the effects of the aqueous seed extract of black seed were investigated. N. sativa extract decreased locomotion, prolonged sleep, and worsened motor coordination. The pretreatment animals with plant extract had higher convulsion resistance than the control animals. In the group treated with *N. sativa*, the severity score reduced while the length of the seizure's onset rose. Additionally, picrotoxin, a GABAA antagonist, and the lengthening of seizure latency were prevented by *N. sativa*.[19]

On PTZ (35 mg/kg, i.p.)-induced kindling seizures in mice, the anticonvulsant and antioxidant effects of NSO were examined. When compared to valproate + PTZ mice, NSO (12 mL/kg, p.o.) significantly reduced the seizure score and protected against the convulsive behaviours and mortality brought on by PTZ. Additionally, when compared to the PTZ group, NSO significantly boosted GSH levels and lowered MDA levels.[6]

In a clinical investigation, the effectiveness of aqueous *N. sativa* extract (40 mg/kg) in lowering the number of seizures in children with epilepsy (aged 13) was assessed. For a period of four weeks, each patient (a total of 20 kids) either got an extract (40 mg/kg) or a placebo three times each day. Using the plant extract as a therapy resulted in a considerable reduction in the mean frequency of seizures.[49]

a. Thymoquinone on epilepsy

TQ's neuroprotective properties have drawn the attention of various researchers by improving learning and memory functions and preventing diabetes-related cognitive impairment, potentially by lowering oxidative stress.[76] As it showed a 10-fold greater ability to block nonenzymatic peroxidation than *N. sativa* oil, it appears that TQ is the most potent neuroprotective component in the plant.[53]

When administered intraperitoneally (IP) at doses of 40 and 80 mg/kg for epilepsy, TQ was helpful in minimising seizures brought on by either maximum electroshock (MES) or pentylenetetrazole (PTZ), as well as lowering fatality rates to 71.4% and 100% for both doses, respectively.[35] In this epileptic model that closely resembles the petit mal, the myoclonic seizures have been dramatically lengthened and their durations have been greatly reduced, demonstrating this neuroprotective effect. It is conceivable that TQ contributed to an increase in GABAergic tone given that PTZ produces a reduction in GABAergic tone.[79] One hypothesis that needs to be considered is that TQ indirectly activates -opioid receptors.[49] In fact, this activation has been associated with anticonvulsant properties because Ca2+ channel blockage.[86] When TQ (oral, 40 mg/kg) and vitamin C (IP, 250 mg/kg) were administered to rats with PTZ-induced generalised epilepsy, Ullah et al. (2015) postulated a somewhat similar mechanism. Pre-treated rats with either treatments or a combination of treatments displayed a significant reduction in seizure activity as well as a reduction in neurodegeneration and mortality. Additionally, high-grade seizures were less common, and the onset of seizures was delayed. Both treatments—or any one of them—reversed a number of pathogenic factors that were previously amplified during seizures, such as decreased GABAB receptor expression, decreased phosphorylation of cAMP response element-binding protein (CREB), and decreased calcium/calmodulin dependent protein kinase II (CaMKII) pathway.[91]

Shao and coworkers looked into how TQ could lessen SE-induced brain damage in another epileptic rat model. An electroencephalogram and the Racine scale were used to determine the severity of the seizures after lithium and pilocarpine injections to produce them. TQ was given IP (10 mg/kg) to one group of rats, while another 31 got normal saline as a control. The authors discovered that the TQ group had significantly decreased seizure frequency and power overall. TQ provides protection due to its strong antioxidant effects, which is consistent with the fact that SE would eventually cause neuronal injury and death through neurotoxicity, inflammation, and the induction of oxidative stress. This was demonstrated by the higher expression of various antioxidants in the TQ-injected rats compared to the control group, including Nrf2, heme oxygenase-1 (HO-1), and SOD. Another protective mechanism suggested by earlier research on TQ's effects on SE using the same seizure-induced model suggests that TQ uses an anti-inflammatory pathway to reduce seizure activity by inhibiting cytokine expression (TNF- and COX-2) and the inflammation-mediating NF-B signalling. Another form of intractable epilepsy, known as temporal lobe epilepsy (TLE), which is characterised by increased oxidative stress, neuronal loss, and increased astrogliosis, was also significantly impacted by TQ. Malondialdehyde (MDA, an important indicator of oxidative stress) in the hippocampus, astrogliosis, hippocampal neuronal loss, and the intensity of mossy fibre sprouting were all reduced as a result of TQ injection (10 mg/kg) in an intrahippocampal kainate rat model, according to research by Dariani and team.[6,47,49]

Table 4: Potential mechanism of action of TQ on epileptic models.

Epileptic model	Potential mechanism of action of TQ
Petit mal	κ-opioid receptor-mediated augmentation of GABAergic tone
Status epilepticus	Activation of an antioxidant mechanism via increasing the expression of Nrf2 and HO-1 proteins and SOD
Status epilepticus	Inhibition of NF-κB signaling which mediates inflammation
Temporal lobe epilepsy	Attenuation of malondialdehyde in the hippocampus, astrogliosis, hippocampal neuronal loss and mossy fiber sprouting intensity
PTZ-induced generalized epilepsy	Enhancing the expression of GABA B1 receptors and activation of CREB and CaMKII pathways

The anticonvulsant effect of TQ in produced seizures induced by PTZ intracerebroventricular (i.c.v.) injection was studied. The duration and onset of tonic-clonic seizures were shortened by the TQ injections shortened by the injection of TQ (200 and 400 µmol, i.c.v.). Thymoquinone had a 50% and a 45% lethality-protective effect in doses of 200 and 400 µmol, respectively. The effects of TQ on models of induced seizures including maximum electroshock (MES) and PTZ were also examined. Through an elevation in GABAergic tone mediated by the opioid receptor, TQ (40 and 80 mg/kg) reduced locomotor activity and had anticonvulsant effects.[6,49]

TQ (1 mg/kg) was tested in a pilot, crossover clinical investigation on children with refractory epilepsy. For a period of four weeks, the patients (a total of 22 kids) were divided into two groups and given either TQ or a placebo. When compared to the placebo group, the TQ group's seizure frequency was significantly lower.[6]

Table 5: Protective effect of *N. sativa* and thymoquinone on epilepsy.

DRUG	DOSE	RESULTS	REFERENCES
N. sativa oil	4 mL/kg	Did not improve significantly the pilocarpine-induced abnormalities	[68]
N. sativa oil	12 mL/kg	Decreased the seizure score, protected against the convulsive behaviors and mortality, increased the GSH levels, and decreased the MDA level compared to the PTZ group	[49]
N. sativa	40 mg/kg	Mean frequency of seizures was decreased	[6]
TQ	200 and 400 μmol	Reduced the duration of tonic-clonic seizures	[46]
TQ	40 and 80 mg/kg	Reduced the locomotor activity	[46]
TQ	1 mg/kg	Reduced the frequency of seizures	[6]

VII. Nephroprotective effect of *Nigella sativa*

Vitamin C and *N. sativa* oil have been found to protect rabbit kidneys against the nephrotoxicity caused by gentamicin (GM). For all of the rabbit groups, serum creatinine, blood urea nitrogen, and antioxidant activity were assessed as markers of nephrotoxicity. Both vitamin C and black seed oil were found to have nephroprotective effects since they reduced serum creatinine, blood urea nitrogen, and antioxidant activity as compared to data in the GM control group. These two antioxidants had a synergistic nephroprotective effect when administered together.[78]

In recent times, it was discovered that cisplatin-induced nephrotoxicity is characterized by an inherent deficiency in the control of renal organic anion and cation transporters. In rats given cisplatin treatment, the impact of TQ on changes in the renal expression of organic cation and anion transporters as well as multidrug resistance-associated proteins was revealed. In rats given TQ, the cisplatin-induced rise in MDA and 8-isoprostane was shown to be significantly diminished. The expression of the efflux transporters MRP2 and MRP4 rose as a result of the induced kidney damage in cisplatin-only treated rats, but OAT1, OAT3, OCT1, and OCT2 expression decreased. Expression of MRP2 and MRP4 proteins was downregulated in the kidneys of rats given a combination of TQ and cisplatin treatment. On the other hand, in cisplatin-treated rats, TQ administration boosted levels of OCT1, OCT2, OAT1 and OAT3 and decreased levels of 8-isoprostane and MDA. This means that TQ works in concert with its nephroprotective action to protect rats' kidneys against acute renal injury brought on by the drug cisplatin.[7]

In addition, the protective effects of black cumin seed oil on methotrexate-induced nephrotoxicity were examined in albino rats. This study indicated the preventive role of Black cumin in methotrexate-induced nephrotoxicity.[5]

The protection provided by *N. sativa* against ischemia-perfusion injury to kidney tissue was investigated. In both kidney tissue and blood, TAC, CAT, TOS, OSI, and MPO were assessed. The amounts of serum urea and creatinine were also measured. The histology of kidney tissue was also assessed. Black seeds was successful in lowering serum levels of urea and creatinine as well as the tubular necrosis score. Treatment with N. sativa markedly decreased OSI and TOS levels and elevated TAC levels in blood and renal tissue. Results showed that *N. sativa* has a protective effect against renal I/R injury in rat kidneys.[90]

NSO was studied for its ability to prevent chronic cyclosporine A (CsA)-induced nephrotoxicity in rats. NSO considerably enhanced the histological and functional metrics while reducing the oxidative stress brought on by CsA. In order to avoid renal dysfunction and morphological abnormalities brought on by chronic CsA treatment, NSO shields kidney tissue from oxygen-free radicals. When compared to the GM group, the intra-peritoneal injection of N. sativa with GM led to significantly lower levels of creatinine, urea, MDA, and NO production and higher levels of SOD and GSH-Px activities, indicating nephroprotective efficacy. To counteract the harmful effects of GM in the biochemical and histopathological parameters, N. sativa functions in the kidney as a powerful free radical scavenger.[88]

VIII. Toxicity profile

Nigella sativa: Black seeds typically have a low level of toxicity. Following an intraperitoneal (IP) injection of black seed extract at high doses (50 mg/d) for 5 days, the liver and renal functions in rats were unaffected. Similarly, mice given fixed oils orally at a dose of 10 mL/kg for three months had normal histopathological results and no harmful consequences were described. Pure N. sativa oil used topically to humans in two cases resulted in allergic contact dermatitis.[38,8]

Thymoquinone: The monoterpene compound TQ has the chemical structure 2-methyl-5-isopropyl-1, 4-benzoquinone. The volatile oil of *N. sativa* is thought to contain the most bioactive component, known as TQ. El-Dakhakhny made the first attempt to extract it from the essential oil in 1963. Several plants from the Lamiaceae genera (including Coridothymus, Agastache, Monarda, and Origanum), Tetraclinis, Cupressaceae, and to a lesser level in the seeds of Nigella arvensis are also sources of TQ in addition to the plant. Supercritical fluid extraction could be used to extract TQ from essential oils. Food-grade liquid carbon dioxide in high-pressure cylinders can be used for this. A Clevenger-style device might likewise be used for hydro-distillation.[92]

IX. Pharmacokinetic profile

TQ's pharmacokinetic properties have been studied in animals after being given via IV, oral, intragastric, or IP routes, and the results reveal promising clinical and pharmaceutical relevance.[96]

TQ dosages of 5 mg/kg for intravenous injections and 20 mg/kg for oral administration were most frequently reported. The retail sale of pharmaceuticals to the general public includes a pharmaceutical consultation inextricably. The mean computed clearance was 7.19 0.83 ml/kg/min, and the volume of distribution at steady state was estimated to be 700.9055.01 ml/kg after IV injection. Furthermore, the estimated oral administration half-life (t1/2) was 274.61 min, whereas the estimated IV injection half-life (t1/2) was 63.43 min and the estimated IV injection half-life (t1/2) was roughly 217 min. Up to 99% of TQ has been observed to bind to proteins. Overall, these findings show that TQ is quickly eliminated after oral treatment while being absorbed slowly.[92,95,96]

X. Conclusion and future prospectives

The review work focused on natural neuroprotective medications which includes information on *Nigella sativa*, an Assam native plant. Their involvement in neurological disorders, such as epilepsy, also their potential mechanisms and boosting hepatoprotective benefits due to the rise in neurodegenerative diseases and their low side effects.

The current review highlights the importance of Kalonji, and special attention is given to its protective effect against various hepatoprotective, nephroprotective, and antiepileptic potentials. In this review, several animal studies are summarized to list out the shielding effect of *N. sativa* and thymoquinone against various intoxications induced by various drugs.

Numerous in-vitro and in-vivo studies indicated that black seed has outstanding antiepileptic, hepatoprotective, and neuroprotective properties. However, a dearth of human research. To further understand the neuroprotective mechanism and lower the risk of chronic disease, better-designed clinical trials in humans are required.

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Conflict of interest

The authors report no conflict of interest.

Author contributions

Debika Sarmah (Corresponding Author): Wrote the article, designed the pictures, and wrote the references as per the journal's requirements. **Professor Dr. Rupa Sengupta** Comprehended the idea, provided guidance, and resources, and reviewed the article as per the journal's requirement.

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