

A study on the Therapeutic Effects of Nigella Seeds (Kalonji)

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Abstract –

Nigella seeds, also known as Kalonji & Black cumin seed, Scientific name is Nigella Sativa, is a plant full of medicinal properties that are used all over the world and commonly found especially in most Asian countries. Nigella seeds are very famous and popular due to their medicinal properties and it have been used since ancient times in India. They are extensively used to make Ayurvedic, Tibetan, and Unani medicines to treat many different diseases and ailments. Based on the pieces of evidence of many previous researches, it can be said that it has been used since ancient times in the treating of skin conditions as well as making liver tonics, diuretics, digestive, anti-diarrheal, appetite restorative, and palliative. Till now, there are many such types of research done on nigella seeds among the previous researches in which a lot of money was spent to test or observe its medicinal and pharmacological properties, including anti-diabetic, anti-cancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepato-protective, renal protective, gastro-protective, antioxidant properties, etc., and after all the investigation it is proved that N. Sativa is the best herbal medicine with amazing healing abilities. In addition, this also divulges that the leading bioactive component of the essential oil, thymoquinone, is the helm for the preponderance of the plant's medicinal dexterities. This present review aims to deliver an in-depth analysis of the literature on scientific investigations exploring the therapeutic benefits and medicinal advantages of the seeds of N. Sativa.

Keywords- Nigella Seeds, Kalonji, nigella sativa, pharmacological effects, antioxidants, anti-diabetic, anti-cancer, therapeutic properties, and medicinal advantages.

Introduction –

For an epoch, both traditional medicines and various indigenous medical systems are using all beneficial plants which are furnished with valuable medicinal properties, to treat various diseases and it is also believed that treatment with medicinal plants is more useful and safer than any allopathic treatment. Medicinal plants are also used in the manufacturing of herbal medicines. Till now very few such plants have been found that have medicinal properties, hence the focus of the researchers is to investigate only such plants that have medicinal properties, therapeutic features and potential, mode of action, safety assessment, and toxicological investigations.

There is a huge amount of study data available about Nigella Sativa and the conclusion of all of them explains that NS is full of medicinal and pharmacological properties in abundance and all of this call it a miraculous medicinal plant herb with a rich ancient and religious background. It is also known as black seed. The name N. sativa is derived from the Latin word nigellus, which means "black." It refers to "Blessing Seeds." Black cumin has even been considered a "miracle herb." In English, the seed is known as black cumin or black seed, although in old Latin, it was known as Panacea, which means "cure-all." South Europe, North Africa, and Southwest Asia are the domain territory of N. sativa. Also, it is agriculture in many other countries or areas throughout the world, including the Middle East Mediterranean region, South Europe, India, Pakistan, Syria, Turkey, and Saudi Arabia (Ahmad et al., 2013). Nigella seeds are the ultimate solution that has been advocated in folk medicine for a variety of illnesses and conditions, including eczema, anorexia, amenorrhea, arthritis, rheumatism, headache, back pain, and hypertension, to name a few. Nigella seeds are also available as an essential oil, paste, powder, and extract (Balyan et al., 2022). The wide range of medicinal features of N. seeds, which include antioxidants, anti-inflammatory, immunomodulatory, anti-cancer, neuroprotective, antimicrobial, antihypertensive, cardioprotective, anti-diabetic, gastroprotective, nephroprotective and hepatoprotective properties, are hugely amenable for these seed's history of traditional uses.(Majeed et al., 2021). Thymoquinone (TQ), thymohydroquinone, thymol, carvacrol, nigellidine, nigellicine, and -hederin are primarily in charge of the pharmacological actions and therapeutic advantages of nigella seed, especially its essential oil (Ahmad et al., 2021). Despite receiving less attention in scientific literature, nigella seeds have a high nutritional value due to its acceptable protein and lipid content as well as their significant amounts of important fatty acids, amino acids, vitamins, and minerals. Due to its essential minerals and active phytochemicals, which strengthen the immune system and the overall health of the human body, black cumin is a culinary plant that is a valuable source of nutraceuticals (Kabir, Shirakawa, and Komai, 2019). N. sativa is a herbaceous perennial that flourishes exceptionally well in tropical and subtropical regions with sandy soil. It is classified as part of the Ranunculaceae family. The plant characteristics are tiny, multi-seeded flowers and thin, thread-like leaves. It may attain a height of 20 to 60 cm. The plant is an upright, branching herb with divided leaves and colorful, yellow-to-white blooms. It also has a tap root system. Except for the stamens, which are many, the plant is pentamerous in general. Large fruits yield seeds (Ashiq Rabbani, Ghafoor, and Shahid Masood, 2011). Oleic acid, palmitic acid, linoleic acid, and trans-anethole were isolated from nigella seeds and identified as their main constituents in earlier research (Nickavar et al., 2003). According to a study by (Venkatachallam et al., 2010) the plant included phenolics and Quinones (thymoquinone, thymol, dithymoquinone, and thymohydroquinone). The oils of nigella seed, which primarily

included thymoquinone, were used by (Vickers, 2017) to identify 48 distinct chemicals. According to (Chalannavar et al., 2014) *N. sativa* seeds produced a variety of chemicals that were predominately monoterpene hydrocarbons. According to (Piras et al., 2013), *N. sativa* seeds include proteins, oils, phenols, and alkaloids. More recently, (Srinivasan, 2018) and (Papoutsis et al., 2018) claimed that the plant contained a variety of biochemicals, with phenols, terpenes, and flavonoids making up the majority of these compounds. Hippocrates, Dioscorides, and Pliny the Elder were all said to have appreciated the preventative and therapeutic capabilities of nigella seed (Black Seed, the Magical Herb). Hippocrates (5th century B.C.) considered *Nigella sativa* to be a helpful cure for hepatic and intestinal diseases. It has been proven to be a very beneficial treatment for snakebites and scorpion stings, along with this, it uproots even the oldest tumors, abscesses, and skin rashes (Hussain and Hussain, 2016). The Greek physician Dioscorides, practiced on nigella seed as a remedy for managing intestinal spongers, migraines, sinus congestion, and toothaches. He went on to explain that they were prescribed as a diuretic to promote milk production and menstruation. In his five-volume pharmacology "De Materia Medica," which served as a guide for herbal therapy during the Middle Ages, he acknowledged the plant as melanthion (Bhikha, 2021).

Table 1: Chemical composition, including active principles, of *N. Sativa* seed

Group	Sub-group	Components
Fixed oil (32-40 %)*	Unsaturated fatty acids	Arachidonic, eicosadienoic, linoleic, linolenic, oleic and almitoleic acid, ¹²⁻¹³
	Saturated fatty acids	Palmitic, stearic and myristic acid, ¹²⁻¹³
Volatile oil (0.4-0.45 %)*		Beta-sitosterol, cycloeucalenol, cycloartenol, sterol esters and sterol glucosides
		Nigellone, thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, α & β -pinene, d-limonene, d-citronellol, p-cymene and 2-(2-methoxypropyl)-5-methyl-1,4-benzenediol ^{6,16-18}
Proteins (16-19.9 %)*	Amino acids	Arginine, glutamic acid, leucine, lysine, methionine, tyrosine, proline and threonine, etc. ¹³
Alkaloids		Nigellicine, nigellidine, nigellimine-N-oxide
Coumarins		6-methoxy-coumarin 7-hydroxy-coumarin 7-oxy-coumarin ¹⁹⁻²³
Saponins:	Triterpenes	Alpha-hedrin ²⁴
	Steroidal	Steryl-glucosides, ²⁵ acetyl-steryl-glucoside
Minerals (1.79-3.74 %)*		Calcium, phosphorous, potassium, sodium and iron ^{13,26}
Carbohydrates (33.9%)*		
Fiber (5.5 %)*		
water (6 %)*		

In the book named "The Canon of Medicine," it is clearly stated that black seed "evokes the body's energy and promotes recovery from fatigue or dispiritedness." His viewpoints are still relevant for Tibb (Islamic Medicine) practitioners today. The nigella seed is a variety of grain known as "alwanak" in the Sigzi dialect, according to Muslim historian al-Biruni, who published a book on the early roots of Indian and Chinese medications. SuharBakht later corroborated this, explaining that it was habb-iSajzi (Sigzi grains). This reference to black seed as "grains" suggests that the seed may have been used nutritionally in the tenth and eleventh centuries (Ahmad et al., 2013).

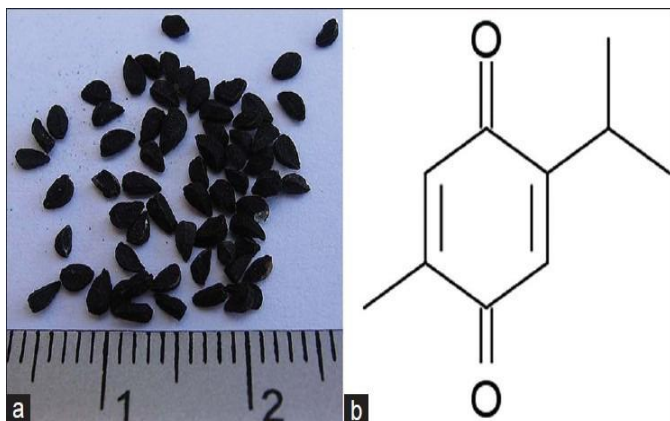


Figure 1.



Figure 2.
Nigella Sativa plant flower

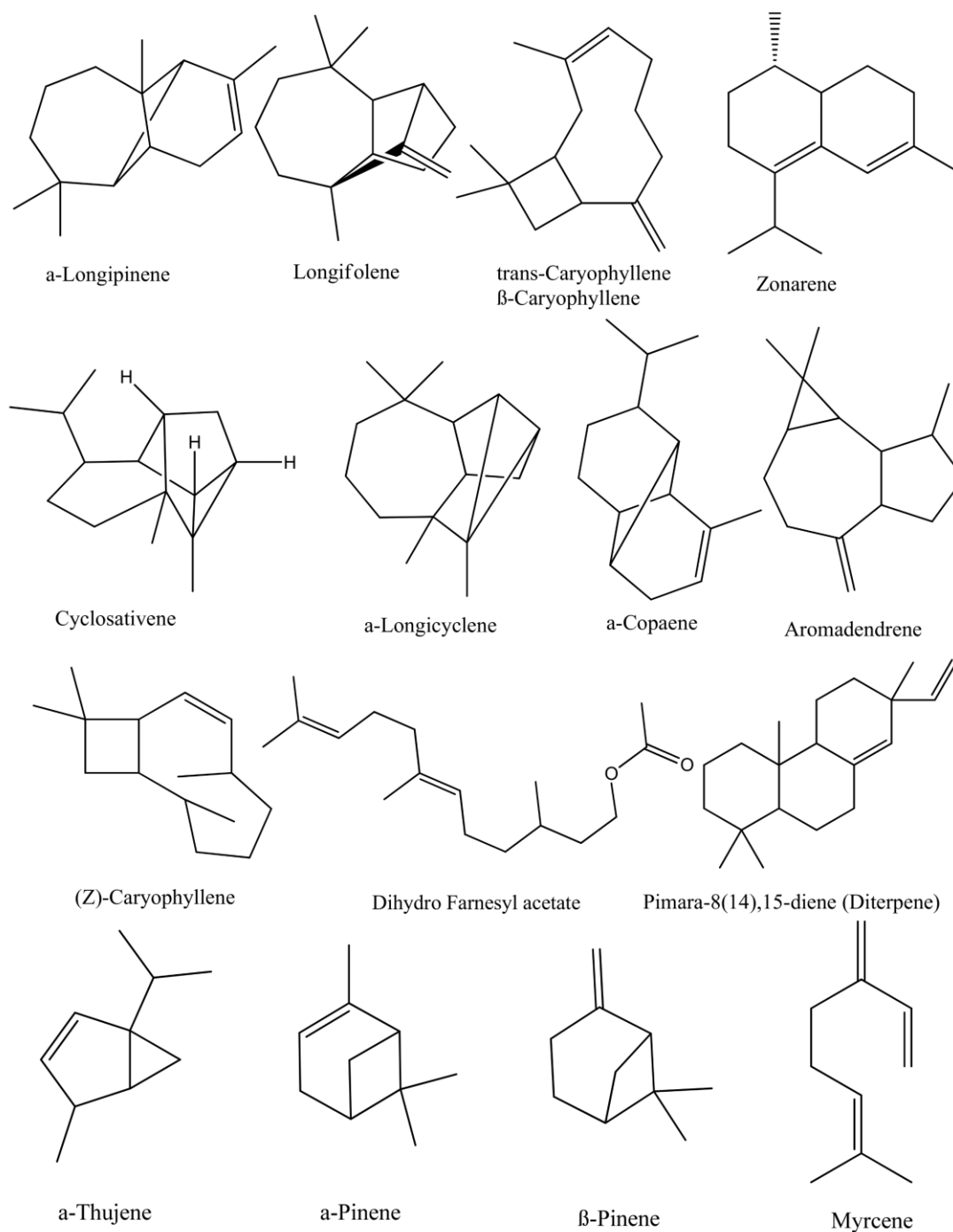
Profiles of Phytochemical Compounds present in nigella seeds –

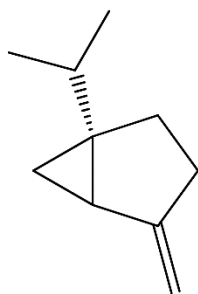
Depending on the growing region, maturation stage, processing processes, and isolation procedures, the phytochemical profile of the nigella seed fluctuates. The bioactive phytochemicals of nigella seeds, which include major and minor metabolites that are secondary, have been classified into various chemical classes.

1) Terpenes and Terpenoids

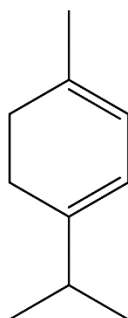
Thymoquinone (TQ) and its related substances, including carvacrol, 4-terpineol, -pinene, thymol, t-anethol, thymohydroquinone (THQ), dithymoquinone, p-cymene, sesquiterpene longifolene, and several other compounds, comprise the terpenes and terpenoids family (Figure 3A). The existence of quinine components, the most common of which is TQ, contributes to the flexibility of black cumin's pharmacological properties (Kabir *et al.*, 2020).

Figure 3. Chemical structure of (A) terpenes and terpenoids, (B) phytosterols, (C) alkaloids, (D) tocals, and (E) polyphenols.

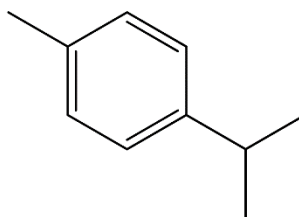




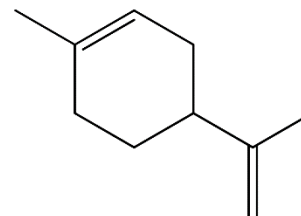
Sabinene



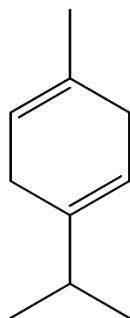
α -Terpinene



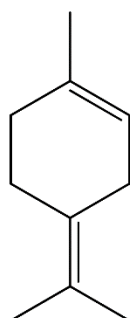
p-Cymene



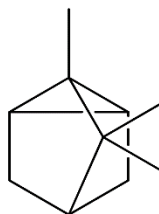
Limonene



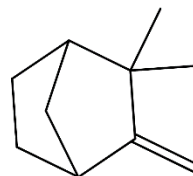
γ -Terpinene



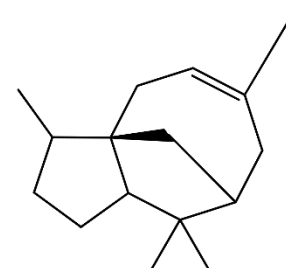
Terpinolene



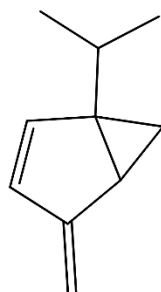
Tricyclene



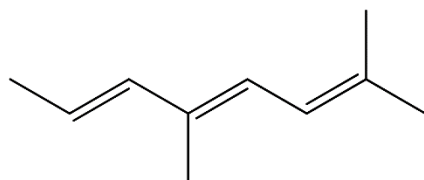
Camphene



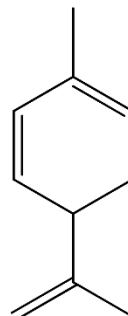
α -Longipinene



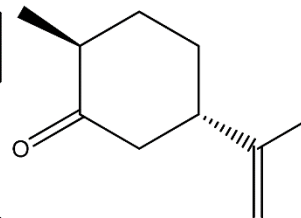
2,4,(10)-Thujadiene



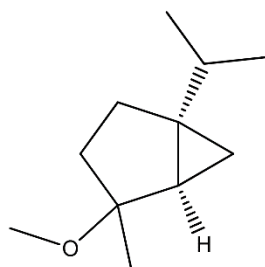
alloocimene



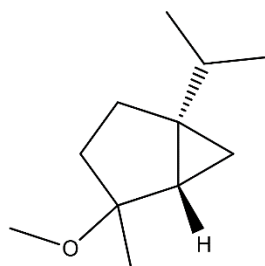
p-Mentha-1,5,8-triene



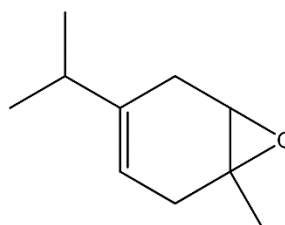
trans-Dihydrocarvone



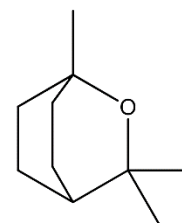
cis-4-Methoxythujane



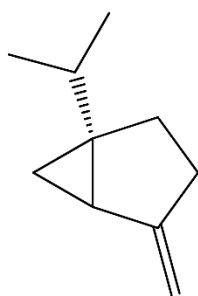
trans-4-Methoxythujane



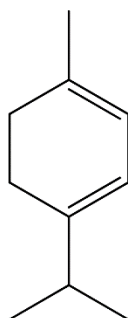
4,5-Epoxy-1-isopropyl-4-methyl-1-cyclohexene



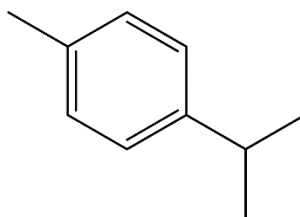
1,8-Cineole/Eucalyptol



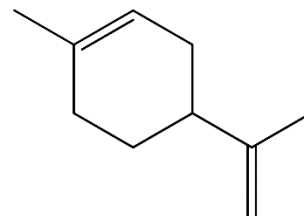
Sabinene



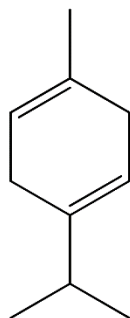
α-Terpinene



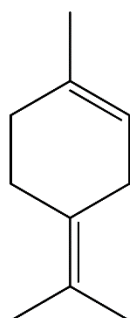
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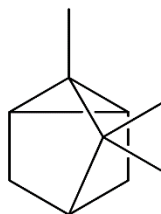
Limonene



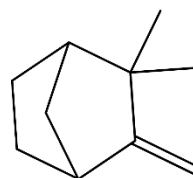
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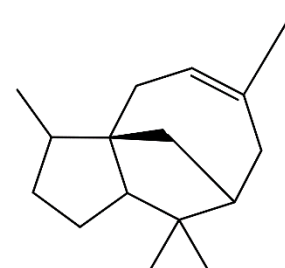
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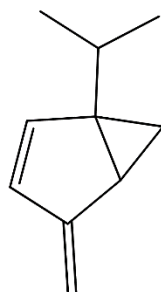
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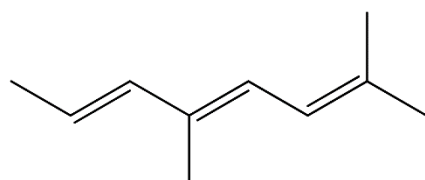
Camphene



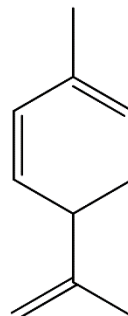
α-Longipinene



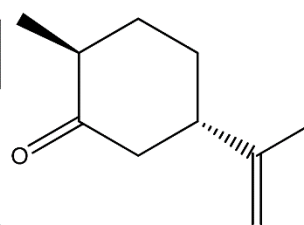
2,4,10-Thujadiene



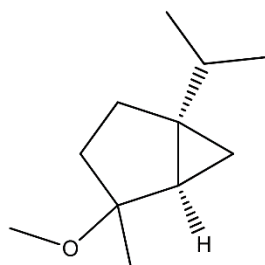
alloocimene



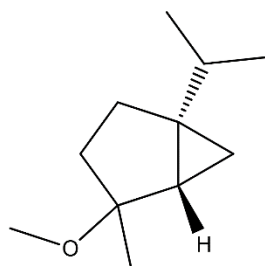
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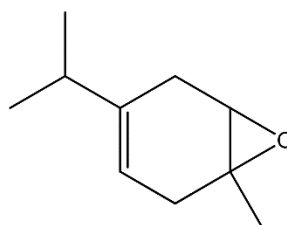
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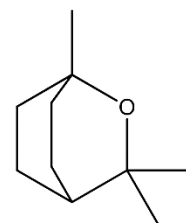
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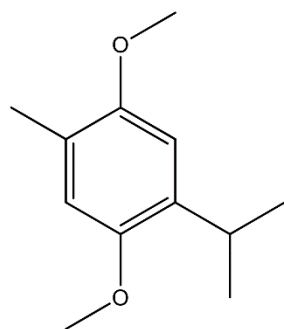
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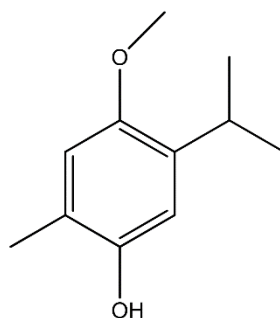
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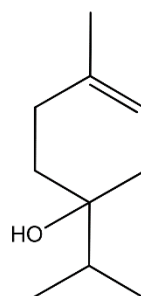
1,8-Cineole/Eucalyptol



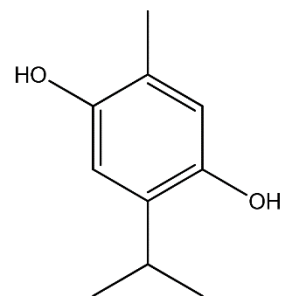
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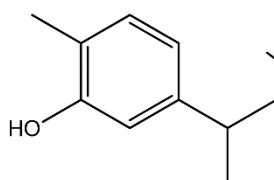
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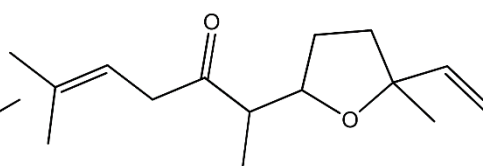
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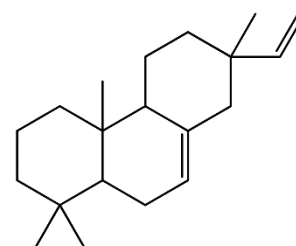
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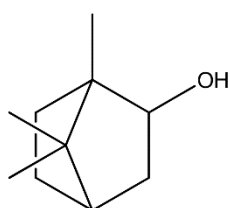
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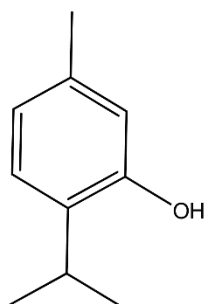
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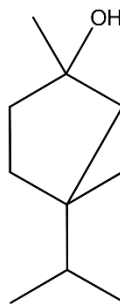
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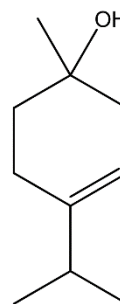
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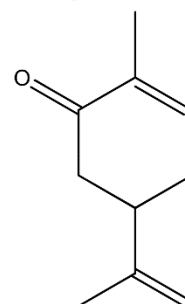
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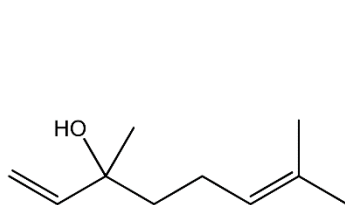
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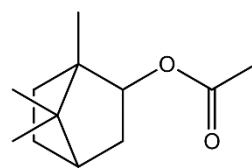
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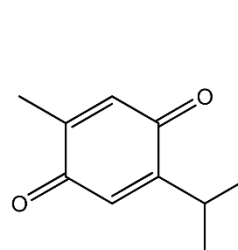
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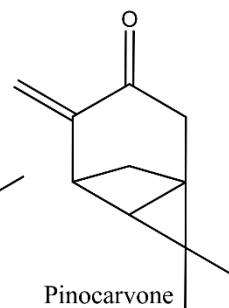
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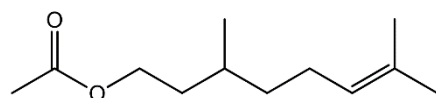
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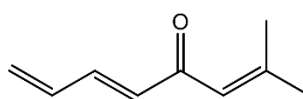
Thymoquinone



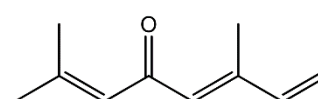
Pinocarvone



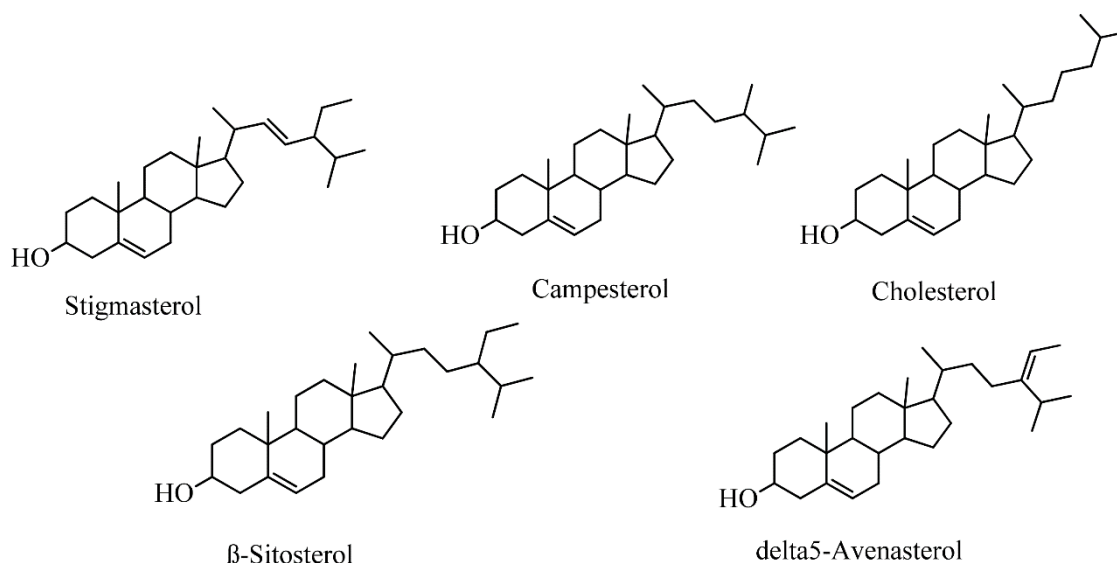
Citronellyl acetate



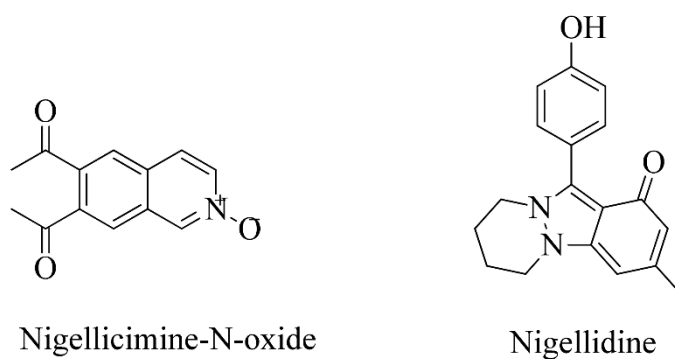
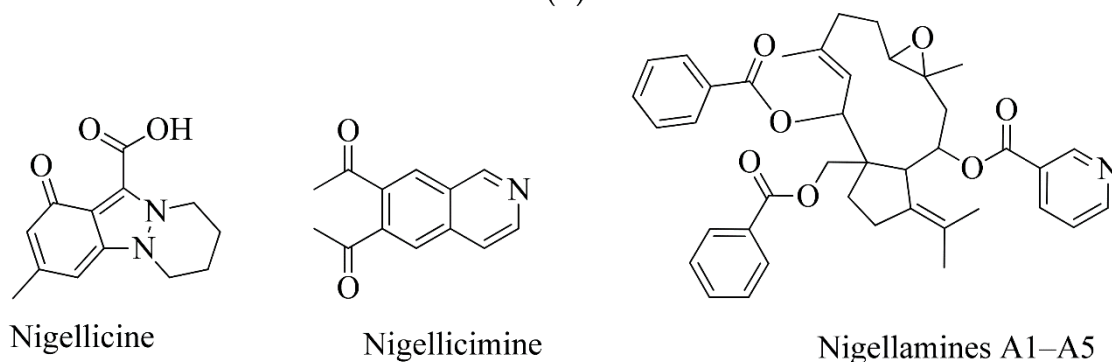
(E)-Tagetenone
(A)



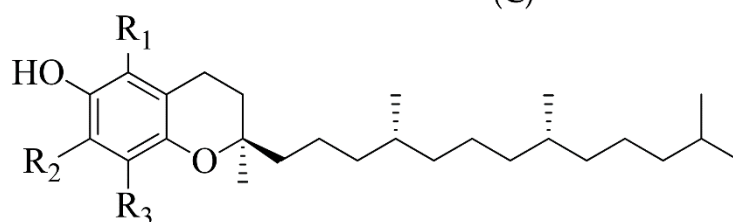
(e)-Ocimenone



(B)

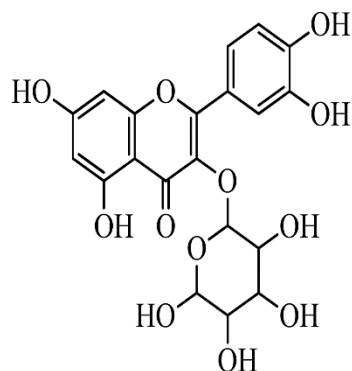


(C)

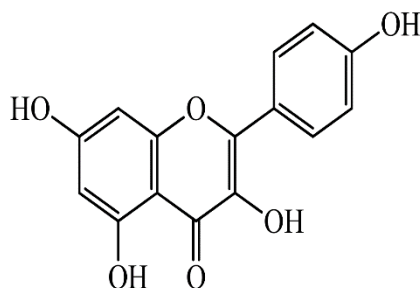


α -Tocopherol: $R_1=R_2=R_3=CH_3$; β -Tocopherol: $R_1=R_3=CH_3$, $R_2=H$
 γ -Tocopherol: $R_2=R_3=CH_3$; $R_1=H$; δ -Tocopherol: $R_1=R_2=H$, $R_3=CH_3$

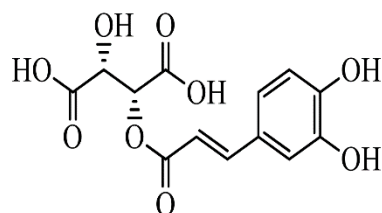
(D)



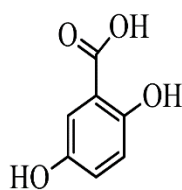
Quercitrin



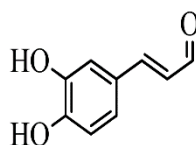
Kaempferol



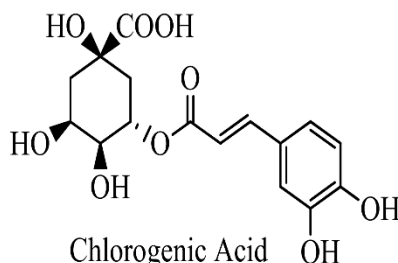
Caftaric acid



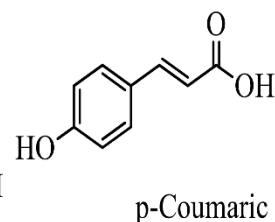
Gentisic acid



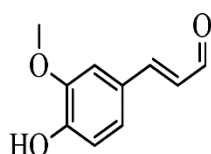
Caffeic acid



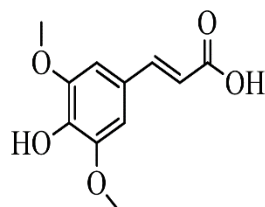
Chlorogenic Acid



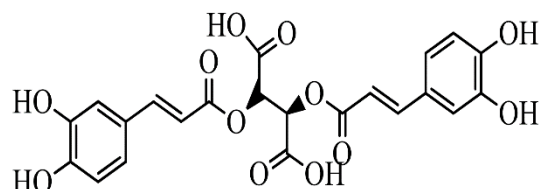
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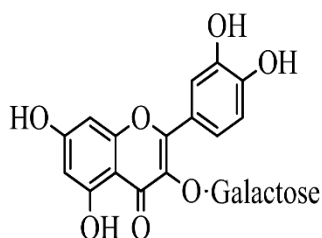
Ferulic acid



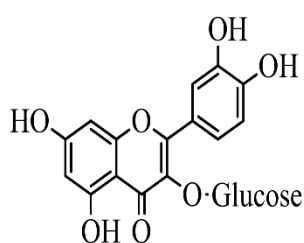
Sinapinic acid



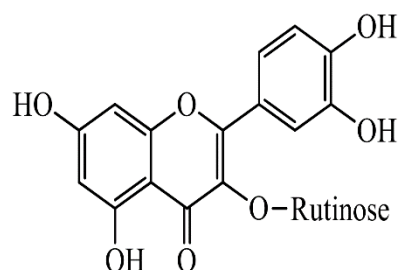
Chicoric acid



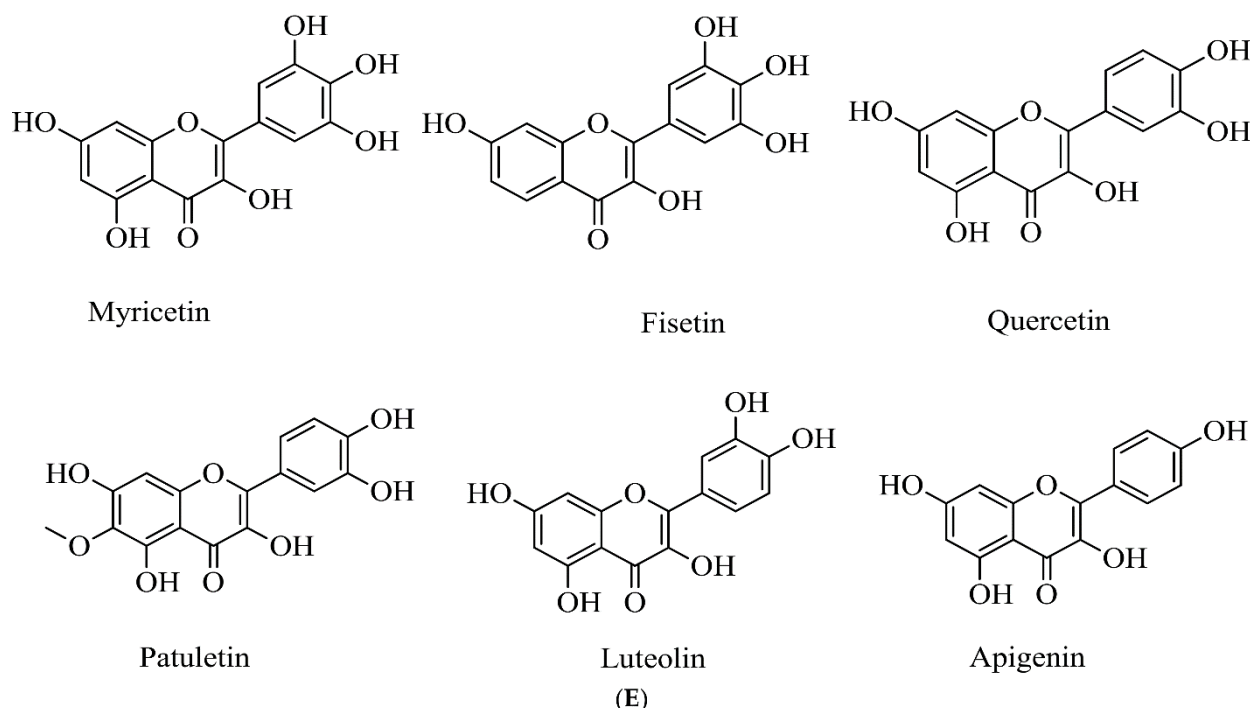
Hyperoside



Isoquercitrin



Rutin



(Hannan, Abdul, Ataur Rahman *et al.*, 2021)

2) Phytosterols

The oil derived from has various sterols, the utmost abundant of which is -sitosterol (44-54%) (Figure 3B). Stigmasterol is the secondary level of abundant sterol in nigella seeds, accounting for 16.57-20.92% of all entire sterols [19]. The oil too has lower levels of 7-stigmasterol, 7-avenasterol, campesterol, and cholesterol. Because of its high sterol content, NS is an fruitful genuine medication for decreasing blood cholesterol and helps to put a big stop on cardiovascular disease (Cheikh-Rouhou *et al.*, 2008).

3) Alkaloids

The alkaloids of nigella seeds can be divided into two groups based on their skeletons: isoquinoline alkaloids like nigellicimine and nigellicimine-N-oxide, and pyrazole or indazole alkaloids like nigellidine and nigellicine (Figure 3C). Furthermore, alkaloid nigelamines A1-A5 from nigella seed, which pertain to the diterpene family, have been demonstrated to have significant lipid metabolism-promoting action (Amin and Hosseinzadeh, 2016).

4) Tocopherols

Tocopherols are powerful natural antioxidants that neutralise radicals that cause damage and prevent lipid peroxidation in plasma membranes. Tocopherols are classified into four isomers: alpha (α), beta (β), gamma (γ), and delta (δ), whichever characterised by the placement of the methyl group on the chromanol ring (Figure 3D). Among the different tocopherols, -tocopherol has the highest level, reaching from 8.57 to 34.23 ppm (Kiralan *et al.*, 2014). Extraction procedures may have an impact on the concentration of tocopherol isomers. Variations in the concentration of tocopherol isomers in black cummin take place caused by differences in farmed areas, maturation span, and repository circumstances (Pourahmadi, 2009).

5) Polyphenols

HPLC-UV-MS was used to identify 19 polyphenols from seeds, as evidenced in (Figure 3E) (Perez-Vizcaino *et al.*, 2009). Caftaric acid, gentisic acid, caffeic acid, chlorogenic acid, p-coumaric acid, ferulic acid, sinapic acid, cichoric acid, hyperoside, isoquercitrin, rutin, myricetin, fisetin, quercitrin, quercetin, patuletin, luteolin, kaempferol, and apigenin are some examples. Quercetin and kaempferol were occurring in the highest concentrations in nigella seed, with 105.55 0.12 and 12.15 0.04 g/g dry weight of plant stuff, sequentially. Kaempferol, as an antioxidant polyphenol, helps to put a stop on oxidative cell damage, whereas quercetin protects against a diversity of ailments for example, osteoporosis, lung cancer, and cardiovascular difficulties. Furthermore, kaempferol is helpful to reduced arteriosclerosis symptoms by blocking LDL oxidation and platelet production in the human blood (Anand David, Arulmoli and Parasuraman, 2016) (Singh *et al.*, 2005).

6) Other various components

Nigella seed is gaining popularity and flowering as an embellished natural substance due to the presence of several other chemical constituents, including specific carbohydrates (rhamnose, xylose, and arabinose), glycerolipids (monoacylglycerols, diacylglycerols, and triacylglycerols), phospholipids (phosphatidylinositol, phosphatidylcholine, and phosphatidylglycerol).

The Therapeutic Effects of Nigella Seeds on Human Health and Disease Management

The health advantages of nigella seeds and its bioactive constituents extend to nearly each & every physiological system, through the neurological system to the integumentary system, and in addition metabolic problems and many malignancies also.

1) Antioxidant activities

The antioxidant parcels of nigella seeds contribute significantly to its health advantages. A five- time review of modern studies concentrated on their antioxidant conditioning in cell- grounded in vitro and in vivo models is offered then. As a possible source of natural antioxidants, nigella reduced the position of reactive oxygen species (ROS) while adding antioxidant enzymes and composites similar as glutathione (GSH), as demonstrated in multiple studies (Kazemi, 2014) (Singh *et al.*, 2014). El- Gindy *et al.* set up a significant increase in human blood TAC and a drop in malondialdehyde (MDA) in rabbits given 600 mg/ kg of nigella seeds (El-Gindy *et al.*, 2020). There was noted a considerable depletion in ROS and nitrous oxide product in the amygdala of Wister rats given NSO (1 mL/ kg), effectively cheapening chlorpyrifos- convinced oxidative stress (Singh *et al.*, 2005). TQ treatment redounded in the scaling down of intracellular ROS and shielding against hydrogen peroxide- convinced neurotoxicity in mortal SH- SY5Y cells by a medium that associate upregulation of antioxidant related genes (SOD and CAT), as well as signalling genes, similar as c- Jun N-terminal kinase (JNK), extracellular signal- regulated protein kinase (ERK)1/2, p53, protein kinase B (Akt) 1, and nuclear factor kappa- light- chain- enhancer of actuated B cells (NF- κ B) (Ismail *et al.*, 2016). TQ (5 mg/ kg/ day) soothed poisonous goods in adult manly rats exposed to lead acetate (2000 ppm) defiled drinking water for five weeks by stimulating conditioning of CAT, glutathione reductase (GR), glutathione peroxidase (GPx), and SOD, as well as raising GSH situations in liver Akins (Mabrouk and Cheikh, 2016). TQ treatment has also been unveiled to reduce oxidative stress labels (superoxide, hydrogen peroxide, and nitric oxide) and devaluate oxidative stress in lipopolysaccharide (LPS)/ IFN or H₂O₂- actuated BV- 2 microglia by enhancing antioxidant enzymes (SOD and CAT), GSH position, down regulating pro-oxidant genes and upregulating antioxidant genes (Cobourne-Duval *et al.*, 2016). A methodical review of five trials involving 293 mortal individualities reveals that nigella seed supplementation may have antioxidant benefits by adding SOD situations while dwindling the position of MDA and overall antioxidant capacity. With these new findings, it's possible to say that nigella seed (in the form of NSO) and its primary element TQ have implicit antioxidant parcels that bolster their anti-oxidative stress- convinced cellular pathologies. further scientific studies are demanded to probe the preventative conditioning of nigella seeds and its ingredients against oxidative stress- convinced cellular dysfunction in colourful complaint conditions.

2) Anti-Inflammatory Effects

Anti-inflammatory goods of nigella seeds and TQ are consequential pharmacological rates. Even along to antioxidant rates, recent exploration on the anti-inflammatory capabilities of nigella seeds over the former five times is stressed. In mortal pre-adipocytes with low- grade inflammation, lately uprooted NSO reduced interleukin- 6 (IL- 6) situations although hoarded NSO minimized IL- 1 situations (Singh *et al.*, 2005). There was a considerable enhancement in the pro-inflammatory cytokines IL- 6, IL- 12, and tumour necrosis factor (TNF)- in paw exudates and sera following NSO administration (400 mg/ kg) in rats with carrageenan- convinced paw edoema (Food *et al.*, 2005). likewise, in rats with paw edoema, topical operation of a attar stick containing 10 NSO significantly reduced acute and subacute inflammation with a pronounced edoema inhibition (60.64), a decreased leucocyte count (43.55 lower than control), and TNF- position (50 lower than control) on the painful part (Atta, 2003). TQ, as a strongest and important bioactive, is the primary patch responsible for nigella seed's anti-inflammatory parcels. TQ forbite pro-inflammatory factors similar as nitric oxide (NO), nitric oxide synthase (iNOS), TNF-, IL- 6, IL- 1, and cyclooxygenase (COX) 2 in LPS- stimulated murine macrophage- suchlike RAW264.7 cells, involving a medium involving the hindrance and holding back of IRAK- linked AP- 1/ NF- B pathways (Khan, 1999). TQ too increased the autophosphorylation of TANK- binding kinase 1 (TBK1), dropped interferon (IFN- and IFN-) mRNA expression, and downregulated IRF- 3 signalling pathways in LPS- stimulated murine macrophage- suchlike RAW264.7 cells (Aziz, 2018).

3) Immunomodulatory Effects

Numerous preclinical and clinical exploration have revealed that nigella seeds and TQ have immunostimulatory parcels. Sheikh *et al.* estimated the immunomodulatory effects of an ethanolic excerpt of nigella seeds on a murine macrophage cell line and discovered that the excerpt boosted macrophage population (M *et al.*, 2017). likewise, nigella seed excerpt has been demonstrated to boost the phagocytic conditioning of three category of macrophages (Hakim *et al.*, 2019). Koshak and associates set up that the unctuous TQ-rich excerpt boosted immunological response by lowering IL- 2, IL- 6, and PGE2 in primary T- lymphocytes and IL- 6 and PGE2 in primary monocytes (Koshak *et al.*, 2018). A modern study

set up that nigella seed oil painting (NSO) had an immunomodulatory effect in *S. typhimurium*-infected rats, adding the entire number of leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, and macrophages. Similarly, the susceptible reaction was protected against H9N2 avian influenza contagion (AIV- H9N2) by the oral administration of 1 IMU (Immulant, a marketable product made from Echinacea and nigella seed) after AI- H9N2 vaccination, diminishing the inflexibility of contagion in stressed-out funk (Naz, 2015). likewise, feeding nigella seed amended food to caw hens bettered vulnerable response by adding antibody response to Newcastle complaint vaccine (Khedr and Abdel-fattah, 2015). In a clinical testing on children with beta- thalassemia major, nigella seed greasepaint (2 g/ day, per zilch's (p.o.), adding with foods or drinks, for quarterly) boosted the vulnerable system by adding CD4, CD8, and WBC cell counts (Mahmoud *et al.*, 2021). likewise, NSO excerpts demonstrated immunomodulatory benefits in rheumatoid arthritis cases by changing T- lymphocyte subsets (Kheirouri, Hadi and Alizadeh, 2016).

4) Defence Against Neurological Diseases

Nigella seeds and TQ, demonstrated remedial eventuality in the treatment of a variety of neurological ails, including neurodegenerative conditions (Alzheimer's complaint(advertisement) and Parkinson's complaint (PD)), ischemic stroke and brain related injuries, fear and downswing and epilepsy. likewise, under experimental conditions, nigella seeds and TQ were demonstrated to cover against different chemical- induced neuronal damage. The antioxidative and anti-inflammatory exertion of nigella seeds and TQ are primarily responsible for their neuroprotective benefits (Farkhondehetal., 2018).

5) Prevention of Alzheimer's Disease

Alzheimer's complaint (announcement), the most common age- related neurodegenerative complaint characterised by cognitive derangement, is distinguished by the vicinity of intracellular neurofibrillary befuddlements composed of hyperphosphorylated tau protein and extracellular senile pillars composed of amyloid- beta (A) peptide (Dash *et al.*, 2021). These two crucial pathogenic emblems helps to changes in a variety of cellular and subcellular processes, similar as mitochondrial malfunction, oxidoreduction inequality, and neuroinflammation, which affect in the activation of a neurotoxic waterfall leading to cell death and dismembering synaptic connection (Hannan *et al.*, 2020) (Rahman *et al.*, 2021). These pathogenic processes ultimately lead to neurodegeneration. In Alzheimer's complaint beast models, nigella seeds and TQ were demonstrated to give neuroprotection and better complaint issues. TQ, for illustration, defended cholinergic hiPSC neurons from A1- 42 convinced neurotoxicity by restoring intracellular antioxidant situations and precluding ROS conformation, cell death, and apoptosis (Alhibshi, Odawara and Suzuki, 2019), and latterly decreased quantal size of set to release synaptic vesicle pools caused by A1- 42. likewise, in high fat/ cholesterol diet (HFCD)- convinced rats, TQ rich bit nano conflation (TQRFNE) of nigella seeds lowered brain A scrap length 1- 40 and 1- 42 (A40 and A42) through modifying APP processing enzymes similar as BACE1, PSEN1 and PSEN2 (Ismail *et al.*, 2017). TQRFNE also increased transportation exertion- convinced A declination by increasing the enzymes insulin- demeaning enzyme (IDE), low- viscosity lipoprotein receptor- related protein 1 (LRP1), and receptor for advanced glycation end-products (RAGE). TQRFNE administration to Sprague- Dawley rats bettered HFCD- fed- convinced hypercholesterolemia, cognitive disablement, and lipid peroxidation by enhancing total antioxidant status and antioxidant gene expression. TQ (10, 20, and 40 mg/ kg/ day for fourteen days) soothed cognitive deterioration in aluminium chloride (AlCl₃) and D- galactose (D- girl) generated announcement mice by lowering A product and accumulation and inhibiting seditious response via the NF- B pathway (Abulfadl *et al.*, 2018). likewise, TQ (20 mg/ kg/ day, intraperitoneally, for forty-two days) soothed D- girl/ AlCl₃- convinced cognitive poverties by decreasing oxidative stress, perfecting cholinergic function, and raising brain- deduced neurotrophic factor and Bcl- 2 situations. likewise, nigella seed oil painting has been set up to cover hippocampus pyramidal CA1 neurons from habitual brain hypoperfusion- convinced neurodegeneration (Saad *et al.*, 2018). TQ (20 mg/ kg/ day for fifteen days) enhanced memory function, reduced IFN- expression, and boosted neuronal growth- related proteins similar as doublecortin and microtubule- associated protein in A (1- 42) invested announcement mice (Elibol *et al.*, 2019). Based on these and other modern researches, it's reasonable to believe that nigella seeds and TQ could be implicant anti-AD agents. still, mortal clinical testing is wanted to restate the preclinical findings of this natural substance into patient use.

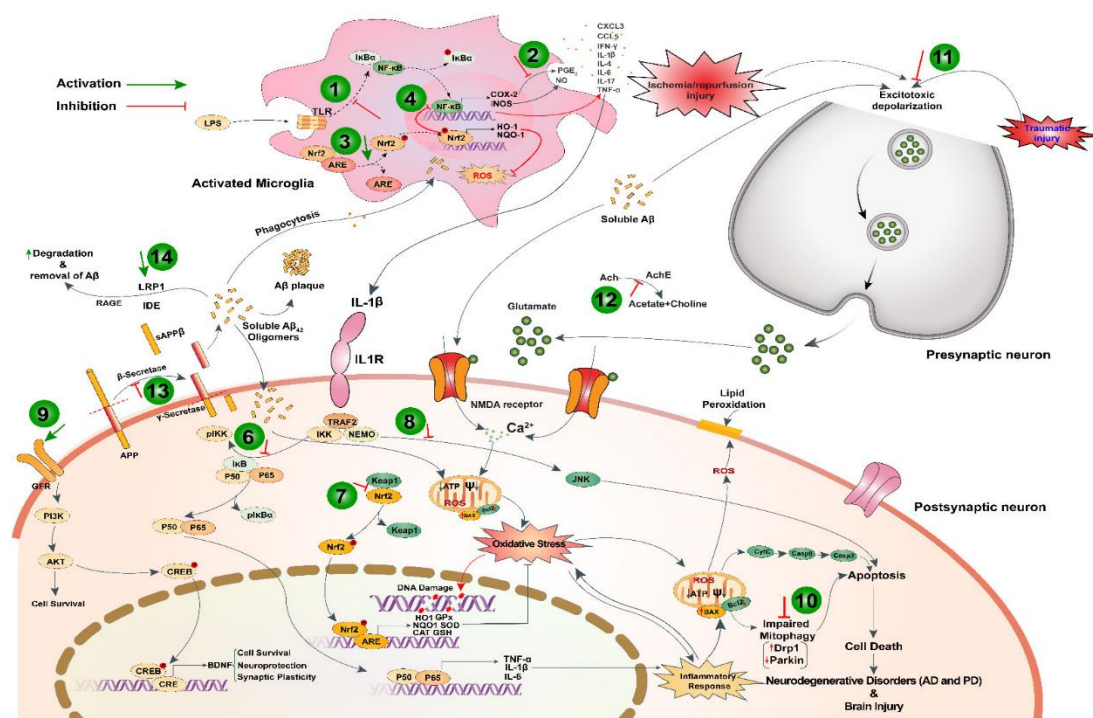


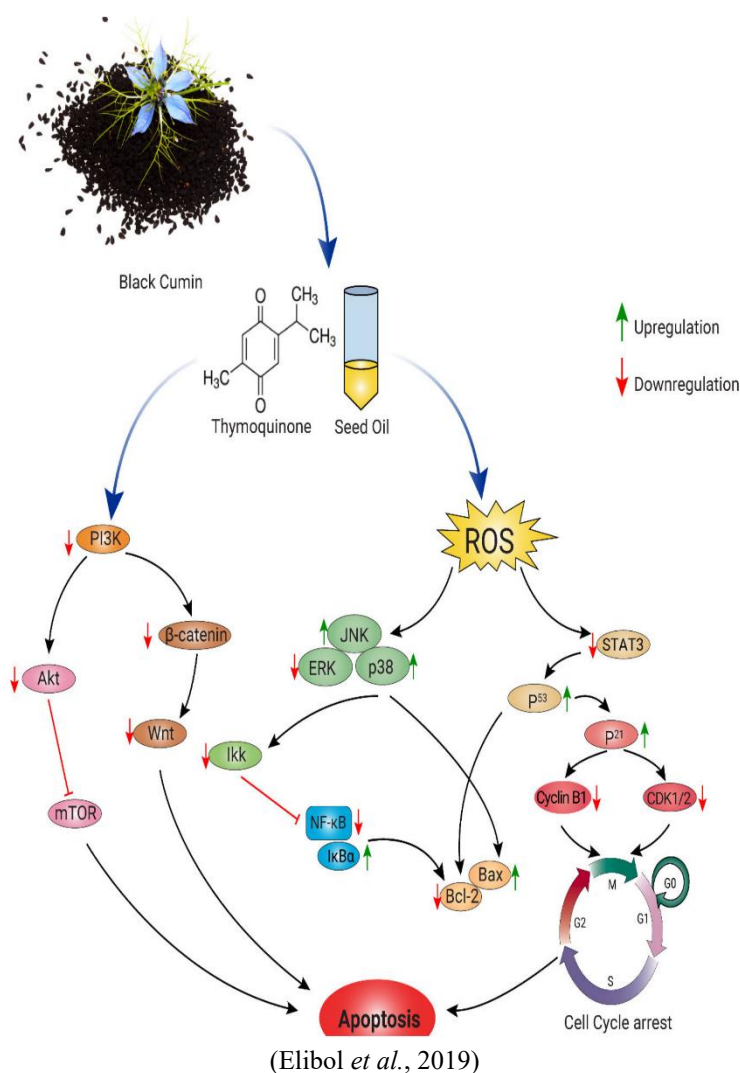
Figure 4. A schematic visual demonstrating the pathobiology of retrogressive intellect complications and post- ischemic/traumatic effects displaying plan of action of black cumin and TQ. The neuroprotective mechanisms of nigella seeds and TQ involve (1) depletion of inflammatory response via inhibition of NF- κ B signalling; (2) hindrance of COX-2 activity; (3) Activation of antioxidant defence system via activation of Nrf2/ARE pathway; (4) cross-talk between Nrf2 and NF- κ B; and (5) reduction of oxidative stress in activated microglia; (6) resilience against neuroinflammation by preventing NF- κ B signalling; (7) boosting of antioxidant defence system by cranking Nrf2 ARE pathway;(8) forestalment of apoptosis via downregulating pro-apoptotic JNK/ Erk pathway;(9) activation of BDNF-dependent pro-survival pathway via converting PI3K/ Akt signalling; and(10) induction of mitophagy in neuron;(11) attenuation of I/ R- injury via precluding excitotoxic depolarization in presynaptic outstation of neuron;(12) anticholinesterase exertion;(13)anti-amyloid genesis via blocking β - secretase exertion; and(14) A β - concurrence by upregulating IDE, LRP1, and RAGE. TLR, risk- suchlike receptor; LPS, lipopolysaccharide; NF- κ B (p50- p65), nuclear factor kappa- light- chain- enhancer of actuated B cells; Nrf2, nuclear factor erythroid 2-affiliated factor 2; ARE, antioxidant response element; I κ B, asset of NF- κ B; IKK, I κ B kinase; Keap1, Kelch-like ECH-associated protein 1; COX2, cyclooxygenase 2; iNOS, inducible isoform of Nitric oxide synthase; ROS, reactive oxygen species; HO-1, heme oxygenase- 1; NQO- 1, NAD(P) H quinone oxidoreductase 1; PGE2, prostaglandin E2; NO, nitric oxide; IL- 1 β , interleukin- 1 β ; IL1R, interleukin- 1 receptor; APP, amyloid forerunner protein; LRP1; Low- thickness lipoprotein receptor- bonded protein 1; IDE, insulin- deprecary enzyme; RAGE, Receptor for progressive glycation finish- products; JNK, c- Jun N-terminal kinases; GluN2B, N- methyl D- aspartate receptor subtype 2B; GFR, growth factor receptor; PI3K, phosphoinositide 3- kinases; Akt, protein kinase B; CREB, cAMP- reaction factor binding protein; BDNF, Brain- deduced neurotrophic procurator; Drp1; dynamin- bonded protein- 1; pang, acetylcholinesterase; Ach, acetylcholine; ψ , mitochondrial membrane eventuality. This image is modified from (Hannan *et al.*, 2021).

6) Anti-Cancer Properties

Nigella seed and its constituents are well known for their anticancer properties. According to the data, the chemical contents of nigella seeds are chemo preventive and effective at inhibiting cell proliferation and inducing apoptosis. A recent study found that treatment of nigella seed ethanolic extract (250 mg/kg; p.o. for 5 days) attenuated diethyl nitrosamine (DENa)-induced liver carcinogenesis and reduced serum AFP and VEGF levels as well as liver HGF protein in rats [94]. TQ, the main bioactive of nigella seed, has been found to control many signalling systems in cancer prevention (Figure.5) (Mahmoud and Abdelrazek, 2019). For example, Shahin et al. found that administering seed extract (150, 250, and 350 mg/kg, p.o. daily for 12 days) and TQ (20 mg/kg, p.o., three alternate days/week for 12 days) improved antioxidant status (GSH, GST, GPx, and SOD), downregulating expressions of Bcl-2, c-fos, and PCNA and by inhibiting epidermal growth factor receptor (EGFR)/extracellular signal-regulated kinase (ERK)1/2 signalling pathway (Kabil, 2018). TQ (20 and 100 mg/kg) was also shown to reduce eEF-2K expression and suppress tumour development and progression in an orthotopic TNBC xenograft mice model (Kabil, 2018).

Figure 5. Nigella seeds, TQ, and essential oil may have an anticancer mechanism that is associated with inducing cellular death and cell cycle detain by targeting numerous signaling pathways. Nigella seed and its important elements induced

cancer-cell death by modifying numerous signaling cascades, especially PI3K/Akt/mTOR, Wnt/-catenin, and NF- κ B signaling. Nigella seed and its constituents also produced DNA damage by a range of pathways, including ROS generation and consequent rise in oxidative stress and mitochondrial malfunction, that ultimately increased the Bax/Bcl-2 ratio via the c-Jun N-terminal kinase (p-JNK) pathway. Nigella seed also inhibited Cyclin B1 and CDK1/2 production through shifting the STAT3 and MAPK pathways, resulting in cell cycle arrest. MAPK, mitogen-activated protein kinase; STAT3, signal detector and activator of transcription-3; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; CDK1/2, cyclin-dependent kinase 1/2; Cyclin B1, maturation-promoting factor regulatory protein.



7) Effects on Obesity and Dyslipidemia

Obesity and dyslipidemia have a direct association with cardiovascular and cerebrovascular disease, raising the possibility of death. Nigella seed and its many preparations have been explored in order to discover new therapeutic agents from natural products for the treatment of obesity and dyslipidemia. Ahmed and colleagues found that dietary supplementation with nigella seed extracts helps to defend hyperlipidemic conditions by improving and enhancing high-density lipoproteins (HDL) and decreasing cholesterol, triglycerides, and low-density lipoproteins (LDL) levels in hyperlipidemic rats (Mahmoud and Abdelrazek, 2019). Furthermore, due to the presence of important fatty acids, nigella seed can encourage to improve dyslipidemia and its accompanying difficulties. Administration of nigella seeds in different arrangements greatly improved and enhanced lipid profile and blood sugar in several clinical trials, including those on hyperlipidemic smokers (Bhatti *et al.*, 2016), menopausal women with metabolic diseases, outpatients of metabolic syndrome (Iscan, Ozsin-ozler and Chu, no date), and patients with Hashimoto's thyroiditis. In addition to the preclinical findings, these clinical investigations indicate that nigella seeds can be a appropriate option for anti-obesity and anti-hyperlipidemic drugs. Future research should concentrate on the biochemical and molecular mechanisms of nigella seeds and formulations in order to have a deeper understanding of their anti-obesity capabilities.

8) Anti-Diabetic Properties

Diabetes mellitus is a chronic metabolic disorder characterised by long-term hyperglycaemia and abnormalities in carbohydrate, lipid, and protein metabolism in the human body, primarily prompted to a disruption in insulin secretion and/or action. Diabetes pathobiology is linked to dysregulated inflammation, increased oxidative stress due to poor redox homeostasis, and imbalanced blood lipid levels (NurTaşar ÖmerYiğiner, SelamiSüleymanoğlu, MeralYüksel, BerrakYeğen, GökselŞener, 2012). Diabetes-related consequences include neuropathy, nephropathy, and retinopathy. Traditional medicine is a comparatively low-cost health-care strategy for treating diabetes patients. As traditional remedies, nigella seeds and essential oil (NSO) offer significant anti-diabetic potential. Extracts of nigella seeds has been proven that it helps to improve disease outcomes in alloxan or streptozotocin-induced diabetic rats or mice via a mechanism that involved in reduction of oxidative stress by increasing antioxidant enzyme activity (NurTaşar ÖmerYiğiner, SelamiSüleymanoğlu, MeralYüksel, BerrakYeğen, GökselŞener, 2012), regulation of blood lipid profiles (Bensiameur-Touati *et al.*, 2017), improvement of endothelial dysfunction (Abbasnezhad *et al.*, 2019), and advancement of tissue regeneration and wound healing. Furthermore, silver nanoparticles-based green synthesis from nigella seed extract was demonstrated to improve STZ-induced diabetic neuropathy in rats by suppressing inflammatory signalling, restoring the antioxidant system, and boosting nerve growth factor (Alkhalaf, Hussein and Hamza, 2020).

Other Therapeutic Benefits

Existing research supports the pharmacological effects of nigella seeds in nearly every physiological system (Ismail *et al.*, 2016). The key pharmacological features of nigella seed and TQ that participate to their significant health benefits against a vast and huge variety of illness conditions are antioxidant, anti-inflammatory, antiapoptotic, and immunomodulatory capabilities. Several studies have shown that nigella seeds and TQ can also operate as effective natural antidotes, protecting against toxins in numerous organs such as the brain, kidney, lung, liver, heart, gastrointestinal tracts, and reproductive system. Because of their strong chelating ability (Majeed *et al.*, 2021).

Conclusion

Current study evidence demonstrates the medicinal characteristics of nigella seeds and TQ in almost each human biological system. However, the therapeutic significance of nigella seeds against numerous diseases has not been studied as thoroughly as it might have been because some chronic diseases, such as cancer, neurological disorders, and metabolic syndromes, take precedence over others. Its components can remove a number of variety of poisons that are typically found in contaminated or adulterated food. additionally, black cumin and TQ have the potential to reduce the adverse effects of various existing medications used to treat cancer and other human disorders.

Despite substantial development about the pharmacological effects of nigella seeds, this timeless medicine is still a long way from clinical application. TQ's medicinal usage is hampered by its poor bioavailability; nevertheless, techniques such as beneficial and usefull change of its structure without impairing biological function might be increase its bioavailability. Many modern investigations used nanoparticle manufacturing to increase the bioavailability and pharmacological effects of black cumin and TQ. However, because the majority of the research was done at the preclinical level, a human trial is required to put the findings into clinical application. Although nigella seed and TQ have low/no toxicity, this information is based primarily on preclinical investigations. As a result, a large-scale human trial is needed to confirm pharmacological and toxicological characteristics for potential clinical usage.

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Organization (WHO) estimated that 80 % of the earth ' s inhabitants rely on traditional medicine for their After the use of most chemical growth promoters as feed additives against pathogens and residues in tissues , scientists have searched for alternatives . In this view , medical plants and essential oils extracted from effects and the improving effect on animal and poultry performance .', (January 2007).

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