**Review Article**

***Nigella sativa* L.; A Golden Remedy: An Overview from Traditional to Recent Significance Worldwide with a special highlight on their possible use for COVID-19 therapy**

**Abstract**

*Nigella sativa* L.,a therapeutic natural herb that cures several serious ailments, so can be considered as a Golden remedy. It has been used for centuries and has a long history in different cultures. This review article has surveyed nearly all the relevant literature on *Nigella sativa* L. from 1960-2020, offering a broad range of data including the origin, taxonomy, botany, history of traditional uses in different regions then passing through their phytochemistry, pharmacology, and consumed natural pharmaceutical preparations till recent findings and their possible use in COVID-19 therapy.T he main aim of this review is to focus on the importance of *Nigella sativa* L. as a medicinal herb used widely in therapy and to correlateits phytochemical constituents with their pharmacological effects. The biological importance was attributed to Thymoquinonein the first-placepresent in the volatile oil of the seeds and other classes as sterols, triterpenes, tannins, flavonoids, cardiac glycosides, alkaloids, saponins, coumarins, volatile bases, glucosinolates and anthraquinones. Moreover, several studies confirmed its benefits in Alzheimer’s disease, as a potent antioxidant, cytotoxic, antiallergic, antimicrobial, etc. In addition to other studies which documented the use of this plant mainly the seeds and the extracted essential oil, in the production of cosmeceutical preparations, and its role as a nutritive spice in the food industry due to its very low toxicity, besides their use as fodder for farm animals.

***Keywords***: *Nigella sativa*L., Ranunculaceae, Black cumin, Thymoquinone, essential oil, immuno-stimulant.

**INTRODUCTION**

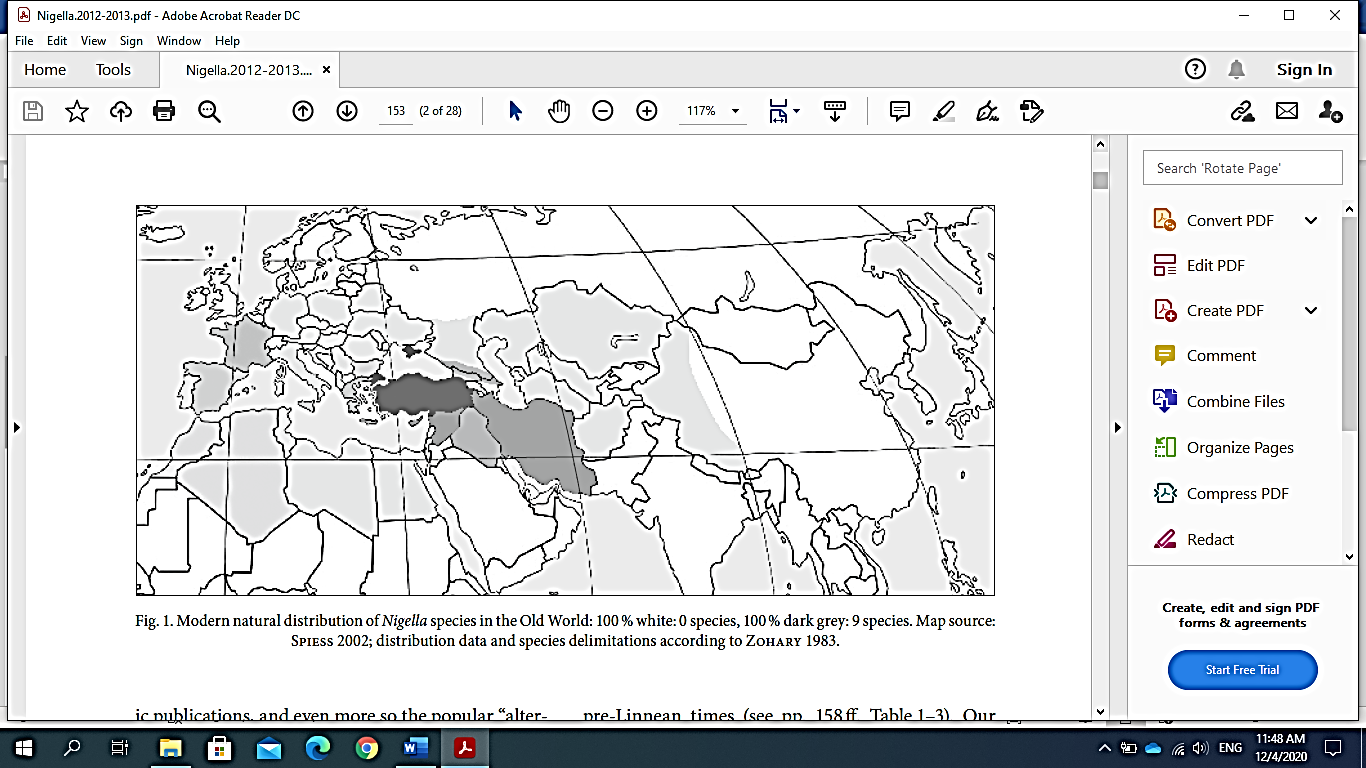
*Nigella sativa* L. (known as Black cumin), one of the members of the Ranunculaceae family, is considered recently as a “miraculous herb” for its broad pharmacological significance1, 2. *N. sativa* L. is widely distributed worldwide therefore has been recognized by different names depending on the geographical region and language. For instance, in English speaking communities it is called the black seed, black cumin, black coriander and black caraway. In India, it is termedKalaunji or Kalonji while in Greece, it is known asMelanthion or Melaspermm, in Italy named Granonero, and in Arabic as Al-HabbehAs-Sudah, HabbatAl-baraka or Kamun-Aswad3. The traditional importance of *Nigella* seeds and their essential oil returns to their ability to cure several ailments in addition to its use as a food and flavoring agent in many industries. Many herbal preparations are used clinically worldwide including black cumin as one of its constituents mainly in Africa, Arabia, South, and Southeast Asia besides Mediterranean regions1.

*N. sativa* L. has a great role in the prevention and curingaction in many intoxicated cases. Several studies showed that *N. sativa* can prevent or cure the serious toxic symptoms of many drugs including some chemotherapeutic drugs, analgesics, and antibiotics in addition toother chemicals as insecticides, organic solvents, and toxic elements4.The seeds contain a volatile oil which possesses insect repellent property. In museums, *N. sativa* L. is used to protect textiles especially linen, woolen materials, and paper-related objects from insects and microbes attack. Seeds can be scattered between folds of linen and woolen clothes and at the manuscript storage for protection5.

Recently, *Nigella sativa* L. seeds, powder and volatile oil, are considered as a promising natural remedy that has been active against the SARS-CoV-2 virus and COVID-19 disease through several mechanisms 6. It is used in the treatment of patients with COVID-19 analyzed, as it possessess antiviral, antioxidant, anti-inflammatory, anticoagulant, immune-modulatory, broncho-dilatory, antihistaminic, antitussive, antipyretic and analgesic activities6.

**History of Medicinal Use**

*Nigella* (fennel flower) is one of the small genera belonging to family Ranunculaceae (buttercup) which includes about 15 species only7. All species of the genus *Nigella* are annual herbs with a short lifecycle, requiring open habitats to propagate. This makes many of them found frequently in anthropogeniceco systems. *Nigella sativa* L. (black cumin), is the widely distributed and probably the well-known species of the genus used as a condiment in addition to its medicinal importance. This condiment has been propagated and cultivated for thousands of years since ancient era. Today it is a frequently consumed condiment in North Africa, the Arabian Peninsula, and the Indian subcontinent while also being the object of intensive pharmacological research and reliable phytomedicine market7. The evolutionary origins of this genus are most probably in the center of species diversity, which occurs in the Aegean 7and the adjacent Western-Irano-Turanian region8, as shown inFigure (1). *N. sativa* L. may thus have come into existence somewhere in this area, Also the great popularity which*N. sativa*L. has gained in pharmaceutical literature, makes this review necessary due to the high amount of published literature generating the impression that the plant is of significant importance economically and medicinally or generally in the pharmaceutical industry.



**Fig. (1):**Modern natural distribution of *Nigella* species in the Old World: **100 % white**: 0 species, **100 % dark grey**: 9 species 7. Map source: Spiess 2002; distribution data and species delimitations according to 8.

**Distribution and Taxonomic Consideration of *Nigella sativa* L.**

The botanical classification of the plant according to the International Code of Nomenclature (ICN) for Algae, Fungi and Plants 9 is documented to be as follows:

**Kingdom:***Plantae*

**Subkingdom:***Tracheobionta*

**Superdivision:***Spermatophyta*

**Phylum:***Magnoliophyta*

**Class:***Magnoliopsida*

**Order:***Ranunculales*

**Family:***Ranunculaceae*

**Genus:***Nigella*

**Species:***sativa*9

**Table 1.** The Latin synonyms and Common names of*N.sativa*seeds L.

|  |  |
| --- | --- |
| Latin synonym / Common name | References |
| Latin synonyms | |
| *Nigella cretica* Mill. | 10 |
| *Nigella truncata* Viv. |
| *Nigella indica* Roxb. ex Flem. |
| Common names | |
| Kalonji | 11 |
| Habat-ul-Sauda | 1 |
| Black Cumin | 12 |
| Black caraway |
| Black onion seed |
| Fennel Flower |
| Nutmeg Flower |
| Roman Coriander |
| Black seed |
| Damascena |
| Devil in-the-bush |
| Wild Onion Seed |

**Genetic Issues**

The genetic diversity of *Nigella sativa* L. herb using random amplified polymorphic DNA(RAPD) markers was studied, where samples were collected from different geographical regions including India, Pakistan, Saudi Arabia, Egypt, Oman, Syria, Tunisia, and Turkey. It was found that there is a marked genetic diversity depending on the geographical source. This was attributed to the ability of *N. sativa* L. to adapt itself to different environmental parameters in these regions. The strains obtained from India and Pakistan were found to be very close to each other genetically. On the other hand, those obtained from Egypt and Oman were far different from those obtained from India, Pakistan, Saudi Arabia, Syria, and Tunisia13.

**Phytochemical characteristics**

The volatile oil of *N. sativa* L.  mainly  consists of monoterpenes, but after seed maturation,Thymoquinonebecomes the most active ingredient in the seeds and oil14. Seed coats are the only place where volatile oil components and Nigellidine and Nigellicine alkaloids can be found. Other molecules, such as dopamine, are found in the inner seed tissues, and other constituents are dispersed in the inner seed. 14.

**Volatile oil constituents**

The volatile oil of *N.sativa* L. is a pale yellow liquid with a significant aromatic odor and taste. The volatile oil is readily soluble in organic solvents such as ether, chloroform and ethanol but sparingly soluble in water15.It is isolated by simple extraction with diethyl ether, then the organic solvent is evaporated under reduced pressure. The volatile oil content of *N. sativa* L. is about 0.4%-0.5% w/w15. Besides, Soxhlet extraction method of the seeds with petroleum ether can be carried out to yield35% of the volatile oil which on steam distillation yielded a higher amount 1.5%16. The chemical constituents of the (Table 2, Figure 2) are mainly monoterpenes including:*p*-cymene (2.8 %), *α*-thujene (0.4%), Thymoquinone (6.1%), Carvacrol (traces), *α*-Longipinene (traces), Longifolene (0.6 %), Thymohydroquinone (1.6%), Palmitic acid, ethyl ester (traces), Linoleic acid methyl ester (0.5%), Linoleic acid, ethyl ester (traces),Oleic acid ethyl ester (traces), Oleic acid (traces), Linoleic acid (43%), Linoleic acid, butyl ester (5.7%), Oleic acid, butyl ester (4.5%), Glyceryl palmitate (1.6%), Glyceryl linoleate (21.9%). Besides, sterols as *β*- sitosterol.

**Table 2.** The chemical composition of the volatile oil of*N.sativa* L. seeds.

|  |  |  |
| --- | --- | --- |
| Chemical Groups/Compounds | Estimated Content (%) | References |
| Monoterpenes | | 17, 18 |
| *p*-cymene | 2.8 |
| *α*-thujene | 0.4 |
| Thymoquinone | 6.1 |
| Carvacrol | Traces |
| *α*-Longipinene | Traces |
| Longifolene | 0.6 |
| Thymohydroquinone | 1.6 |
| Palmitic acid, ethyl ester | Trace |
| Linoleic acid, methyl ester | 0.5 |
| Linoleic acid, ethyl ester | Trace |
| Oleic acid, ethyl ester | Trace |
| Oleic acid | Trace |
| Linoleic acid | 43.9 |
| Linoleic acid, butyl ester | 5.7 |
| Oleic acid, butyl ester | 4.5 |
| Glyceryl palmitate | 1.6 |
| Glyceryl linoleate | 21.9 |
| Sterols | |
| *β*-Sitosterol | 1.3 |
| Total | 90.9 |



**Fig. (2):** Chemical Structures of *N.sativa*L.volatile oil constituents: Thymol **(A)**, Thymoquinone **(B)** and Dithymoquinone**(C)**,*p*- Cymene **(D)**,Carvacrol **(E)**,Thymol **(F),** Limonene **(G)**, Carvone **(H)**, *α*-pinene**(I)**.

**Alkaloids**

**-** The seeds of *N.sativa*L. contain 2 classes of alkaloids (Table 3, Fig. 3);Isoquinoline alkaloids, such as Nigellidine19, Nigellimine and Indazole alkaloids as Nigellicine20, Nigellimine-*N*-oxide21.





**Fig (3): Structures of Alkaloids isolated from *N.sativa* seeds**

Nigellimine N-oxide **(A)**,Nigellicine**(B)**,Nigellimine**(C)**,Nigellidine**(D)**.

**Flavonoids**

- Some flavonoids22 were isolated and identified from the aerial parts of *N. sativa*L. as hederagenin, flaccidoside III, catechol, quercetin-3-gentiobioside, magnoflorine, nigelflavonoside B, nigelloside, quercetin sphorotrioside, kaempferol-3,7-diglucoside, kaempferol 3-*O*-rutinoside, rutin. Also,quercetin-3-*O*-*α*-*L*-rhamnopyranoside 1, quercetin-7-*O*-*β*-*D*-gluco- pyranoside were identified23.

**Sterols**

Sterols listed in Table. 3 are considered from the main secondary metabolites of *N.sativa* L. 18as Cholesterol, Campesterol, Campestanol,Stigmasterol,Sitosterol, Stigmastanol, ∆5-avenasterol, ∆7-stigmasterol, ∆7-avenasterol, Lophenol, Obtusifoliol, 24-methyllophenol, Cycloeucalenol, Gramisterol, 24-ethyllophenol,Citrostadienol, Triucollol,Faraxerol, *β*-amyrin, Butyrospermol, Cycloartenol and 24- methylenecycloartanol**TriterpenoidalSaponins**

Triterpenoidal saponins is the main class of saponins isolated from*N.sativa*L. (Table.3, Fig.4). Saponins isolated from the alcoholic extract of the seeds of *N.sativa* as Sativosides A and B 24, in addition to 3-*O*-[*α*-l-rhamnopyranosyl-(1→2)-*α*-*l*-arabino-pyranpsyl-hederagenin, 3*β*,23,28-trihydroxyolean-1-2-ene-3-*O*-*α*-*l*-arabinopyranoside (1→4) -*α*-rhamno-pyranosyl-(1→4)-*β*-*d*-glucopyranoside, 3-*O*-*α*-*l*-rhamno-pyranosyl-(1→2)-*α*-*l*-arabino-pyranpsyl]-28-*O*-*β*-*d*-gluco-pyranosyl-hederagenin22, 25,3-*O*-[*β*-*d*-xylo-pyranosyl-(1→3)-*α*-*l*-rhamno-pyranosyl-(1→2)-*α*-*l*-arabino-pyranosyl]-hederagenin26, Tauroside E, Sapindoside B23.



**R1***β*-D- Xyl (1→3)-*α*-L- Rha1 (1→2)-*α*-L-Ara,

**R2***α*-L-Rha II (1→4)-*β*-D- Glu II (1→6)-*β*-D-Glu I

**Fig.4: TriterpenoidalSaponins isolated from the seeds of *N.sativa*L.**

Sativosides A and B (**A** &**B**)

**Table 3.** Active Constituents of Different classes isolated from *N. sativa* L.

|  |  |  |
| --- | --- | --- |
| Chemical Group | Compound | References |
| Isoquinoline alkaloids | Nigellimine, Nigellimine-*N*-oxide | 21 |
| Indazole alkaloids | Nigellidine, Nigellicine | 19 |
| Phenolic compounds | Stearic acid, Linoleic acid,Palmitic acid, Oleic acid, Arachidic acid, Eicosadienoic acid. | 22 |
| Sterols | Cholesterol, Campesterol,Campestanol,Stigmasterol,Sitosterol, Stigmastanol, ∆5-avenasterol, ∆7-stigmasterol, ∆7-avenasterol,  Lophenol, Obtusifoliol,24-methyllophenol,  Cycloeucalenol,Gramisterol,24-ethyllophenol,  Citrostadienol,Triucollol,Faraxerol, *β*-amyrin,  Butyrospermol, Cycloartenol,24- methylenecycloartanol | 18, 27 |
| Triterpenoidal Saponins | α- hederin, Sativosides A and B  3-*O*-[*α*-l-rhamnopyranosyl-(1→2)-*α*-l-arabino-pyranosyl-hederagenin  3*β*,23,28-trihydroxyolean1-2-ene-3-*O*-*α*-l-arabinopyranoside (1→4) -*α*-rhamnopyranosyl-(1→4)-*β*-*d*-glucopyranoside, 3-*O*-*α*-l-rhamnopyranosyl-(1→2)-*α*-l-arabinopyranpsyl]-28-*O*-*β*-*d*-glucopyranosyl-hederagenin  Tauroside E  Sapindoside B | 24 |
| Flavonoids | hederagenin, flaccidoside III, catechol, quercetin-3-gentiobioside, magnoflorine, nigelflavonoside B, nigelloside, quercetin sphorotrioside, kaempferol-3,7-diglucoside, kaempferol 3-*O*-rutinoside, rutin. Also, quercetin-3-*O*-*α*-*L*-rhamnopyranoside 1, quercetin-7-*O*-*β*-*D*-gluco- pyranoside | 22 |

**Nutritive value of *N.sativa*L. seeds**

The seeds of N. sativa L. contain a high percent of nutrients including proteins (26.7%), fats (28.5%), carbohydrates (24.9%), crude fibers (8.4%) and total ash (4.8 %). Besides, vitamins and minerals like Cu, P, Zn and Fe as well as carotenes metabolized by the liver to vitamin A, C, thiamine, niacin, pyridoxine and folate28, 29. Roots and shoots are reported to contain Vanillic acid 28.The seeds are also reported to contain a reasonable amount of fixed oil rich in saturated and unsaturated fatty acids. The saturated fatty acids include mainlypalmitic and stearic acids mainly where their amount reaches 30% or less while the unsaturated fatty acids contain linoleic acid (50-60%), oleic acid (20%), eico-dadienoic acid (3%) and di-homo-linoleic acid (10%).

**Biological Activities of Extracts Confirmed by Scientific Research**

The applications of *N. sativa* L. confirmed by scientific experiments and the pharmacological action profile of this species highly recommended in modern phytotherapy are summarised in Table 4 with their suggested mechanism of action.

**Table 4.** Pharmacological profile of *N.sativa* L. seeds and their suggested mechanism

|  |  |  |  |
| --- | --- | --- | --- |
| Activity | Mechanism of action | Compounds Supposed to be Responsible | Ref. |
| Allergic Diarrhea | * inhibition of the cyclooxygenase and 5- lipoxidase pathways. * regulation of the toll-like receptor 4/NF êB pathway. | Thymoquinone | 30 |
| Allergic Rhinitis | * reduced the level of allergen induced lung remodeling which proved to have strong therapeutic effect. | Black seed oil | 31 |
| Alzheimer's disease | - ↓ TBARS & 5-LOX levels - ↑ GSH extent and SOD action - Causes disaggregation of Aβ peptide - prevents declining of neurons - Slows | Thymoquinone | 32 |
| Analgesic | - inhibition of lipo- oxygenase and/or cyclo-oxygenases | Thymoquinone | 33 |
| Anti-hyperlipidemic | - regulate cholesterol synthesis through regulation of HMG-CoA reductase, Apo-A1, Apo-B100 and LDL-receptor genes; enhancing the efficiency of liver cells to remove LDL from the blood circulation; also contributing to decrease dietary cholesterol absorption; and increasing the primary bile synthesis. | Thymoquinone migellamine  flavanoids  sterols  soluble fiber (mucilage)  polyunsaturated fatty acids | 34-36 |
| Anti-cancer | - inhibition of cell proliferation, apoptosis induction through dependent-pathway and P53 independent, antioxidant activity and glutathione alternation. | Thymoquinone Saponins  *α-*hederin | 37-40 |
| Anti-diabetic | - regulating liver enzymes activity associated with glucose metabolism.  - reducing gluconeogenesis.  - antioxidant activity; preservation.  - proliferation of pancreatic beta cells. activating adenosine monophosphate kinase. | Thymoquinone | 22, 41-43 |
| Anti-inflammatory | - indirect activation of the supraspinal mu (1)- and kappa opioid receptor subtypes | Thymoquinone  Saponins | 24, 44-46 |
| Anti-microbial activity | - presence of active compounds with anti-microbial activity | Thymoquinone  Thymohydroquinone melanin | 47, 48 |
| Antioxidant | improve scopolamine-induced cognitive impairment and reduced the AChE activity and oxidative stress of the rat’s brain | Phenolic compounds | 22, 49-51 |
| Anti-ulcer | - | Black seed oil Thymoquinone | 44 |
| Anthelmintic | - decrease in glutathione-S-transferase and superoxide dismutase activity and reduced glutathione (GSH) level  -inhibition of Cathepsin L (Cat L) gene expression in thymoquinone treated worms. | Thymoquinone | 46, 52 |
| Asthma/bronchodilatory | - increase in peak expiratory flow (PEF), forced expiratory volume in one second (FEV1), maximal expiratory flow (MEF), maximal mid expiratory flow (MMEF), and specific airway conductance. | Black seed oil Thymoquinone | 53 |
| Cytotoxic | - Inhibition of cell growth in cancer cell lines: MCF7 | Black seed oil Thymoquinone | 54 |
| Dieuretic | - natriuretic and kaluretic effect | Black seed oil Thymoquinone | 55 |
| Hepato-protective | * antioxidant activity | Black seed oil Thymoquinone | 44 |
| Immunomodulatory/ Immuno-protective | - increasing macrophage activity and lymphocyte numbers.  - Inhibition of inflammatory processes.  - strengthening the immune response, especially in T cells. | Thymoquinone  *α*-linoleic acid  Stearic acid | 44, 56-58 |
| Pancreatic carcinoma | - Inhibition of cell growth in cancer cell lines | Thymoquinone | 44 |
| Reproductive system | - Prevention of cell death and loss of tissue weight or volume of sexual cells by inhibiting cyclooxygenase and lipo-oxygenase enzymes and reduce the harmful effects of free radicals. | Black seed oil Thymoquinone | 59, 60 |
| Arthritis | - anti-inflammatory processes by preventing the production of eicosanoids such as thromboxane B2 and leukotriene B4 via suppressing COX and 5-lipoxygenase in addition it inhibits the leukotriene C4 synthase activity | Thymoquinone | 44, 61-63 |
| Neuroprotective | - substantial anti-inflammatory and antioxidant potential | Thymoquinone | 64 |
| Wound healing activity | - Enhancing the proliferation of fibroblasts and promoting the level of beta-FGF. | Thymoquinone | 65 |

**Natural preparations containing *N. sativa*L. and their uses**

The combination *N. sativa* L. ointment and the oral administration of the crude powder of the seeds exhibited effective anti-psoriatic activity 50.

**Pharmaceutical Preparations including*N. sativa*L. and TQ**

Thymoquinone is the main ingredient of *N. sativa* L. essential oil, it is of limited use in therapy due to its poor water solubility, high instability in aqueous solution and pharmacokinetic drawbacks. TQ was combined with polymeric solubilizers for developing polymeric micelles which led to a bio-enhancement 66.

***N. sativa* L. seeds in Veterinary Medicine**

Since *Nigella sativa* L. seeds and oil are added as a healthy and nutritive constituent in farm animal formulations, Nigella sativa L. supplementation has a positive impact on animal production parameters. *N. sativa* L. is a good source of proteins, carbohydrates, fatty acids, and a variety of bioactive principles, and it's used in animal feed because of its medicinal properties. *N. sativa* L. is a plant that has a variety of uses.. Feed consumption, mortality rate, digestibility, active and reproductive performances, milk yield and composition, egg compositional characteristics, blood chemistry parameters, health status, and carcass traits of broiler chickens, laying hens, rabbits, ruminants and pseudo-ruminants are all improved by*N.sativa*L.67. Another study found that supplementing broiler diets with black cumin seeds (1%) increased body weight, feed conversion ratio, and carcass yield after a 6-week growing span, suggesting that *N.sativa* L. (1%) may be used as a natural growth promoter material in broiler diets. 68.

*N.sativa* L. had a major impact on growing lambs as well, with improved overall nutrient consumption, digestibility, and growth efficiency parameters when fed to growing lambs 69.*N. sativa* L. seeds in a study on 40-week-old White-Leghorn birds, significantly improved egg yield, egg mass, and egg shell thickness70.

**Drug interactions and Toxicity**

Many human clinical studies stated that the simultaneous administration of *N. sativa*L. extracts and/or its essential oil with the conventional treating drug improved its activity and declined significantly its side effects. Many studies revealed the protective effect of *N. sativa* L. and intoxication activity against different chemical agents 4, 71. It possesses ameliorative effects against several drugs intoxication as 71.Chemical war victims from mustard gas inhalation taking *N. sativa* L. extract required less salbutamol and corticosteroids72.Asthma patients using *N. sativa* L. decoction decreased the use of all the treating drugs as inhaled corticosteroids: beclomethasone or fluticasone inhalers and theophylline, and beta-agonists73. In another study, the use of *N.sativa*L. seeds helped in reducing acute opiate withdrawal symptoms, craving and relapses through an open study including 50 persons addict to opioids. This study continued for 12 weeks with a daily dose of *N sativa* L. seeds of 250-500 mg for 3 times74.Some clinical studies were carried out one of which was on 40 females suffering from rheumatoid arthritis using anti-rheumatic drugs as methotrexate, hydroxychloroquine, diclofenac, and folic acid for therapy. It was revealed that when *N.sativa* L. seeds oil administered as an adjuvant therapy a significant decrease in the disease score and less morning stiffness occurred 75.In a 21 patients’ study with non-ulcer *Helicobacter pylori* dyspepsia taking 2 grams of seed powder in combination with omeprazole daily for 4 weeks was significantly effective in eradicating the *H. pylori* in 66.7%76. On the contrary, *N. sativa*L. extract-phenobarbitone combination must be avoided as concomitant use of the herb during treatment with phenobarbitone showed undesirable drug interactions77.

Moreover, several i*n vitro* and *in silico* studies were carried out on the effect of *N. sativa* L. and volatile oil constituents in the presence of certain drugs.An *in vitro* study on the anticancer effect of Oxaliplatin and/or Gemcitabine against pancreatic cancer which increased significantly after adding 3 mg thymoquinone reducing local invasion and nodal metastasis reduced pancreatic cancer cell growth78.The use of Gentamicin with 50 mg/L thymoquinone in drinking water for 8 days completely reversed its kidney toxicity and the increase in serum creatinine, BUN, TBARs, and total nitrate/nitrate and decreases in kidney glutathione, glutathione peroxidase, catalase, and ATP levelsin rats79.Doxorubicin induced cardiotoxicity indicated by the increase in serum lactate dehydrogenase and creatine phosphokinase levels phosphokinase was prevented with 5 days of pretreatment and 2 days of parallel treatment with 10 mg/kg daily of thymoquinone in rats. This protection is due to the *in vitro* superoxide radical scavenger potency and inhibition of lipid peroxidation possessed by thymoquinone80.The hepatotoxicity caused by acetaminophen was prevented by 5 days of 2 mg/kg/day of thymoquinone in mice. This *in vitro* study was carried out through measuring the level of certain liver enzymes which returned to the normal levels upon the addition of Thymoquinone in therapy81.When the seed oil was given at 880 mg/kg for 2 weeks before a 1 ml dose of ethanol, it significantly reduced formation of stomach ulcers by increasing mucosal glutathione levels and mucin and decreasing mucosal histamine in rats82. Thymoquinone given at 20 mg/kg reduced ethanol-induced stomach ulcers and the associated lipid peroxidation and glutathione depletion in rats83.

Furthermore, *N. sativa* L. andits main constituent Thymoquinone could protect some tissues against most drugs overdose including analgesics, anti-cancers, immune-suppressives, antibiotics, antiretrovirals, and antiseizures 71. Several mechanisms are involved in *N. sativa*L. antidotal effects including antioxidant, anti-inflammatory, free radical scavenging, improvement in the disturbed levels of biochemical markers, modulation of antioxidant defense systems, inhibition of apoptosis and regulatory effects on genes expression , and different signaling pathways 71.

***Nigella sativa* L. and COVID-19**

*Nigella sativa* L. was reported to have antiviral activity either separately or in combination with other herbs. A herbal preparation that consists of Extracts of (*Anthemis hyaline* DC., *Nigella sativa* L., and *Citrus sinensis* (L.) Osbeck) was found to decreased the replication of CoVvirus, as it increased IL-8 level,expression of the genes TRPA1, TRPC4, TRPM6, TRPM7, TRPM8 and TRPV4 changed significantly84.

Several studies recommended *N.sativa*L. as an adjuvant therapy with repurposed drugs including Chloroquine, Hydroxychloroquine, Remdesivir and Favipiravirused to manage patients with COVID-1953.Various randomized controlled trials, case reports, pilot studies, *in vitro* and *in vivo* investigations confirmed that *N.sativa*L. possesses antiviral, antioxidant, anti-inflammatory, immunomodulatory, broncho-dilatory, anti-histaminic, anti-tussive activities related to Coronavirus and signs of COVID-1953.

The main active constituents revealed *in silico* affinity with SARS-CoV-2 enzymes and proteins. They possess high to moderate affinities where they potentially inhibit SARS-CoV-2 replication and attachment to host cell receptors. These constituents include: nigelledine, *α*-hederin, hederagenin, thymo-hydroquinone, and thymoquinone 85. Besides, Nigellidine and α-hederin have been identified as potential inhibitor of SARS CoV-2 6.

Finally, *N. sativa* L. may be used as an adjuvant treatment alongside repurposed chemical drugs for the treatment of COVID-19, which nearly diminishes the side effects of other medications by lowering their doses. However, further randomised controlled trials are required to validate the potential and benefits of *N. sativa* L. seeds and essential oil as an alternative herbal therapy for SARS CoV-2.

**Conflict of Interest**

The author declares that there is no conflict of interest.

**References**

1. Ahmad A, H. A., Mujeeb M, , A review on therapeutic potential of Nigella sativa: A miracle herb. *Asian Pac J Trop Biomed.* **2013,***3* (5), 337-352.

2. EI-Dakhakhny, M., Egyptian Nigella sativa. *Arzneimittel-Forsch* **1965,***15*, 1227-1229

3. E.B., E. S. A. a. A., Some Biological and Pharmacological Effects of the Black Cumin (Nigella sativa): A Concise Review. *American Journal of Research Communication* **2018,***6* (3).

4. S.S., E., The preventive and curative role of Nigella sativa in poisoning cases. *J Clin Exp Tox.* **2018,***2* (2), 18-24.

5. De, S., Controlling Biological Infestations in Museums by Medicinal Plants. In *Medicinal Plants: Biodiversity, Sustainable Utilization and Conservation*, Khasim, S. M.; Long, C.; Thammasiri, K.; Lutken, H., Eds. Springer Singapore: Singapore, 2020; pp 271-283.

6. P., M. N. a. M., Prophetic Medicine-Nigella Sativa (Black Cumin Seeds) – Potential Herb for COVID-19? *Journal of Pharmacopuncture* **2020,***23* (2), 62-70.

7. Heiss A.G., S. H., De Zorzi N. and Jursa M., Nigella in the Mirror of Time A Brief Attempt to Draw a Genus’ Ethnohistorical Portrait. *Offa* **2012/13,***69/70*, 147-169.

8. M., Z., The Genus Nigella (Ranunculaceae), A Taxonomic Revision. *Plant Systematics and Evolution* **1983,***142*, 71-107.

9. Sharma NK, A. D., Jhade D, Gupta S., Medicinal and Pharmacological Potential of *Nigella sativa*: A Review. *Ethnobotanical leaflets* **2009,***11*.

10. Reference taxon from World Plants in Species & ITIS Catalogue of Life. In *Encyclopedia of Life*, 2000.

11. Singh BR, S. D., Bhardwaj M, Vadhana P, Saraf A, Rajendran VKO, Pawde A, Gupta VK and De UK, Antimicrobial Activity of Kalonji Oil and its Comparison with Methanolic and Aqueous Extracts of Nigella sativa (Kalonji) Seeds. *Nat Prod Ind J.* **2017,***13* (2), 107.

12. A., C., Encyclopedia of Medicinal Plants DK Publishing: New York, NY, 1996; p 237. 237.

13. Sudhir S. P., K. A., Malakar J., Verma H. N., Genetic Diversity of Nigella sativa from Different Geographies Using RAPD Markers *American Journal of Life Sciences* **2016,***4* (6), 175-180

14. Botnick I., X. W., Bar E.,Ibdah M., Schwartz A., Joel M.D.,Lev E.,Fait A. and Lewinsohn E., Distribution of Primary and Specialized Metabolites in Nigella sativa Seeds, a Spice with Vast Traditional and Historical Uses. *Molecules* **2012,***17* (9), 10159-10177.

15. EI-Alfy, T. S., El-Fatary, H. M. and Toama, M. A. , Isolation and structure assignment of an antimicrobial principle from the volatile oil of *Nigella sativa* L. seeds. *Pharmazie* **1975,***30*, 109-111.

16. Rathee, P. S., Mishra, S. H. and Kaushal, R. , Antimicrobial activity of essential oil, fixed oil and unsaponified matter of Nigella sativa L. *Indian J. Pharmac.* **1982,***44*, 8-10.

17. Singh, S.; Das, S. S.; Singh, G.; Schuff, C.; de Lampasona, M. P.; Catalán, C. A. N., Composition, In Vitro Antioxidant and Antimicrobial Activities of Essential Oil and Oleoresins Obtained from Black Cumin Seeds (<i>Nigella sativa</i> L.). *BioMed Research International* **2014,***2014*, 918209.

18. Gad A.M., E.-D. M. a. M. M. H. M. M., Studies On The Chemical Constitution OF Egyptian Nigella Sativa L. Oil. *Planta Med* **1963,***11* (2), 134-138.

19. ur-Rahman A., M. S., Hasan S.S., Choudhary M.I., Ni CZ, Clardy J., Nigellidine — A new indazole alkaloid from the seeds of Nigella sativa. *Tetrahedron Letters* **1995,***36* (12), 1993-1996.

20. ur-Rahman A, M. S., Cunheng H, Clardy J., Isolation and structure of determination of nigellicine, a novel alkaloid from the seeds of Nigella sativa. *Tetrahedron Lett* **1985,***26*, 2759-62.

21. ur-Rahman A., M. S., Ahmad S., Chaudhary I., and ur-Rehman H. , Nigellimine N-oxide -A New Isoquinoline Alkaloid From The Seeds Of Nigella sativa *Heterocycles* **1985,***23* (4).

22. Parveen A., F. M. A. a. K. W. W., A New Oleanane Type Saponin from the Aerial Parts of Nigella sativa with Anti-Oxidant and Anti-Diabetic Potential. *Molecules* **2020,***25* (2171).

23. Elkhayat, E. S.; Alorainy, M. S.; El-Ashmawy, I. M.; Fat'hi, S., Potential Antidepressant Constituents of Nigella sativa Seeds. *Pharmacogn Mag* **2016,***12* (Suppl 1), S27-31.

24. Elbandy M., K. O., Kwon DY., and Jung-Rae Rho, Two New Antiinflammatory Triterpene Saponins from the Egyptian Medicinal Food Black Cumin (Seeds of Nigella sativa). *Bull. Korean Chem. Soc.* **2009,***30* (8).

25. Ansari A.A., H. S., Kenne L., Ur-Rahman A and Thomas W. , Structural Studies On a Saponin Isolated from Nigella sativa *Phytochemistry* **1988,***21* (12), 3971-3919.

26. Taskin M.K., C. O. A., Abou-Gazar AH, Khan IA, and Bedir E., Triterpene Saponins from Nigella sativa L. *Turk.J.chem.* **2005,***29*, 561-569.

27. R.B., S., Sterols in the seed oil of Nigella sativa. *Planta Med.* **1973,***24* (4), 375-7.

28. M.S., A.-J., Chemical composition and microflora of black cumin (Nigella sativa L.) seeds growing in Saudi Arabia *Food Chem.* **1992,***45*, 239-242.

29. A., M., The Chemical Constituents and Pharmacological Effects of Nigella sativa- A Review. *Journal of Bioscience and Applied Research* **2018,***4* (4), 389-400.

30. Duncker S.C., P. D., Martin-Paschoud C., Moser M., Mercenier A., Nutten S., Nigella sativa (Black Cumin) Seed Extract Alleviates Symptoms of Allergic Diarrhea in Mice, Involving Opioid Receptors. *Plosone* **2012,***7* (6), e39841.

31. Alsamarai AM, A. S. M. a. A. A., *Evaluation of Therapeutic Efficacy of Nigella sativa (Black Seed) for Treatment of Allergic Rhinitis* 2012.

32. Sharaf R., E. M. N., Mahran L. , Neuroprotective effect of thymoquinone against lipopolysaccharide-induced Alzheimer’s disease in an animal model. *European Geriatric Medicine* **2014,***5* (1), S83-S158.

33. B, I. T. a. A.-R., Evaluation of the Analgesic Effects of Nigella sativa Ethanolic Extracts on Experimentally Induced Pain in Albino Mice. *British Journal of Pharmaceutical Research* **2016,***10* (5), 1-7.

34. Boskabady MH, M. N., Takaloo L. , Antiasthmaticeffect of Nigella sativa in airways of asthmatic patients. *Phytomedicine* **2010,***17* (10), 707-713.

35. Ibrahim RM, H. N., Mahmud R. , A randomised controlled trial on hypolipidemic effects of Nigella sativa seeds powder in menopausal women. *J Transl Med* **2014,***12*, 82.

36. Kaatabi H, B. A., Lebda FM. , Favorable impact of Nigella sativa seeds on lipid profile in type 2 diabetic patients. *J Family Community Med* **2012,***19* (3), 155-161.

37. Bano F, W. M., Baig N, , Antiobesity, antihyperlipidemic and hypoglycemic effects of the aqueous extract of *Nigella Sativa* seeds (Kalongi). *Pak J Biochem Mol Biol.* **2009,***42* (4), 136-140.

38. Badary OA, T. R., Gamal El-Din AM Thymoquinone is a potent superoxide anion scavenger. *Drug Chem Toxicol* **2003,***26* (2), 87-98.

39. Gali-Muhtasib H, R. A., Schneider-Stock R. , Thymoquinone: a promising anti-cancer drug from natural sources. *Int J Biochem Cell Biol* **2006,***38* (8), 1249-1253.

40. Adamska A. , S.-H. J. a. O. J., Alpha-Hederin, the Active Saponin of Nigella sativa, as an Anticancer Agent Inducing Apoptosis in the SKOV-3 Cell Line. *Molecules* **2019,***24*, 2958.

41. Pari L, S. C., Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin– nicotinamide induced diabetic rats. *Life Sci* **2009,***85* (23-26), 830-834.

42. Wienkötter N, H. D., Schütte U. , The effect of nigellone and thymoquinone on inhibiting trachea contraction and mucociliary clearance. *Planta Med* **2008,***74* (2), 105-108.

43. Al-Hader A, A. M., Hasan Z. ; 96-100., Hypoglycemic effects of the volatile oil of Nigella sativa seeds. *Pharm Biol* **1993,***31*.

44. Khan M.A., A. M., Chemical composition of Nigella sativa Linn: Part 2 Recent advances. *Inflammopharmacology* **2016,***24*, 67-79.

45. Abdel-Fattah AM, M. K., Watanabe H Antinociceptive effects of Nigella sativa oil and its major component, thymoquinone, in mice. *Eur J Pharmacol* **2000,***400* (1), 89-97.

46. Ullah R, R. A., Zafeer MF, Rehman L, Khan YA, Khan MA, Khan SN, Khan AU, Abidi SM. , Anthelmintic Potential of Thymoquinone and Curcumin on Fasciola gigantica. *PLoS One.* **2017,***12* (2), e0171267.

47. ZH., K., Spectacular black seeds (Nigella sativa): Medical importance review. *Med J Babylon* **2013,***10* (4), 1-9.

48. Toama MA, E.-A. T., El-Fatatry HM. , Antimicrobial activity of the volatile oil of Nigella sativa Linneaus seeds. *Antimicrob Agents Chemother* **1974,***6* (2), 225-226.

49. Hosseini M., M. T., Karami R., Rajaei Z., Sadeghnia H.R., and Soukhtanloo M., Effects of the hydro-alcoholic extract of Nigella sativa on scopolamine-induced spatial memory impairment in rats and its possible mechanism. *Chinese Journal of Integrative Medicine* **2015,***21* (6), 438-444.

50. Jawad H.A., A. Y. I., Khalil A., Evaluation of efficacy, safety and antioxidant effect of Nigella sativa in patients with psoriasis: A randomized clinical trial. *Journal of Clinical and Experimental Investigations* **2014,***5* (2), 186-193.

51. Pop RM., B. L., Buzoianu A.D., Chedea V.S., Ancut S., Socaci A., Pecoraro M. and Popolo A., Evaluation of the Antioxidant Activity of Nigella sativa L. and Allium ursinum Extracts in a Cellular Model of Doxorubicin-Induced Cardiotoxicity. *Molecules* **2020,***25* (5259).

52. Agarwal R, K. M., Shrivastava R. 1979 Nov;17(11):1264-5. PMID: . Antimicrobial & anthelmintic activities of the essential oil of Nigella sativa Linn. *Indian J Exp Biol.* **1979,***17* (11), 1264-5.

53. P., M. N. a. M., Prophetic Medicine-Nigella Sativa (Black cumin seeds) – Potential herb for COVID-19. *J Pharmacopuncture* **2020,***23* (2), 62-70.

54. Khurshid, Y.; Syed, B.; Simjee, S. U.; Beg, O.; Ahmed, A., Antiproliferative and apoptotic effects of proteins from black seeds (Nigella sativa) on human breast MCF-7 cancer cell line. *BMC Complementary Medicine and Therapies* **2020,***20* (1), 5.

55. Toma CC, O. N., Vlase L, Mogoșan C and Mocan A., Comparative Studies on Polyphenolic Composition, Antioxidant and Diuretic Effects of Nigella sativa L. (Black Cumin) and Nigella damascena L. (Lady-in-a-Mist) Seeds *Molecules* **2015,***20*, 9460-9574.

56. Umar S, Z. J., Umar K. , Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. *J. Chem Biol Interact.* **2012,***197* (1), 40-46.

57. Swamy S, T. B., Cytotoxic and immunopotentiating effects of ethanolic extract of Nigella sativa L. seeds. *J. Ethnopharmacol.* **2000,***70* (1), 1-7.

58. Yehuda S, C. R., Modulation of learning, pain thresholds, and thermoregulation in the rat by preparations of free purified alpha-linolenic and linoleic acids: determination of the optimal omega 3-to-omega 6 ratio. *Proc Natl Acad Sci USA* **1993,***90* (21), 10345-10349.

59. Al-Sa'aidi JAA, A.-K. A., Al-Zobaydi NFH. , Effect of alcoholic extract of Nigella sativa on fertility in male rats. *Iraqi J Vet Sci* **2009,***23*, 123-128.

60. Ng Cho Ping, H. N., Hasan Adli DS. , Effects of Nigella sativa (Habbatus sauda) oil and nicotine chronic treatments on sperm parameters and testis histological features of rats. *Evid Based Complement Alternat Med* **2014,***2014* (18293).

61. Khabbazi, A.; Javadivala, Z.; Seyedsadjadi, N.; Malek Mahdavi, A., A Systematic Review of the Potential Effects of Nigella sativa on Rheumatoid Arthritis. *Planta Med* **2020,***86* (07), 457-469.

62. Houghton PJ, Z. R., de las Heras B, Hoult JR. , Fixed oil of Nigella sativa and derived thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. *Planta Medica* **1995,***61*, 33-36.

63. S., M. M. T., Inhibition of 5-lipoxygenase and leukotriene C4synthase in human blood cells by thymoquinone. *J. Enzyme Inhib. Med. Chem.* **2004,***19*, 431-436.

64. Cascella M., B. S., Barbieri A., Dissecting the potential roles of Nigella sativa and its constituent thymoquinone on the prevention and on the progression of Alzheimer's disease. *Frontiers in Aging Neuroscience* **2018,***10*, 16.

65. O.A., A.-Z., Using Nigella sativa oil to treat and heal chemical induced wound of rabbit skin  *JKAU: Sci* **2009,***21* (2), 335-346.

66. Maria Camilla Bergonzi , M. V., Giulia Marroncini , Emanuela Barletta and Donatella Degl’Innocenti Thymoquinone-Loaded Soluplus®-Solutol® HS15 Mixed Micelles: Preparation, In Vitro Characterization, and Effect on the SH-SY5Y Cell Migration. *Molecules* **2020,***25*, 4707.

67. Longato E., M. G. a. P. P. G., NUTRITIONAL AND ZOOTECHNICAL ASPECTS OF NIGELLA SATIVA: A REVIEW. *The Journal of Animal & Plant Sciences* **2015,***25* (4), 921-934.

68. Guler T., B. D., O. N. Ertas and Çiftçi M., The Effect of Dietary Black Cumin Seeds (*Nigella Sativa* L.) on the Performance of Broilers *Asian-Aust. J. Anim. Sci.* **2006,***19* (3), 425-430.

69. BS, O., The Inclusion of Black Cumin Meal Improves Growth Performance of Growing Awassi Lambs. *Vet. Sci.* **2020,***7* (40).

70. Akhtar MS, N. Z. a. A. A., Effect of Feeding powdered Nigella sativa L. seeds on poultry egg production and their suitability for human consumption. *Vetrinariski Arhiv* **2003,***73* (3), 181-190.

71. Tavakkoli A., A. A., Razavi B.M., Hosseinzadeh H., Black Seed (Nigella Sativa) and its Constituent Thymoquinone as an Antidote or a Protective Agent Against Natural or Chemical Toxicities. *Iranian journal of pharmaceutical research (IJPR)* **2017,***16 (Supp;.)*, 2-23.

72. Francis Brinker, N. D., *Updates and Additions for Herbal Contraindications & Drug Interactions plus Herbal Adjuncts with Medicines*. 4th ed.; 2016.

73. Boskabady MH, J. H., Sajady M The possible prophylactic effect of Nigella sativa seed extract in asthmatic patients. *Fund. Clin. Pharmacol.* **2007,***21*, 559-566.

74. Yarnell E, A. K., Nigella sativa holy herb of the Middle East. *Altern. Compl. Ther.* **2011,***17* (2), 99-105.

75. Haghighi M, K. A., Toliat T Comparing the effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis. *Arch. Iran. Med.* **2005,***8* (4), 267-271.

76. Salem EM, Y. T., Bamosa AO Comparative study of Nigella sativa and triple therapy in eradication of Helicobacter pylori in patients with non-ulcer dyspepsia. *Saudi J. Gastroent.* **2010,***16* (3), 207-214.

77. Joseph L., P. R. a. R. S., Drug Interaction analysis-Nigella sativa L.seed (Black Cumin) ethanolicextract on antiseizure activity of Phenobarbitone sodium. *Asian Journal of Medical Sciences* **2020,***11* (2), 18-20.

78. Psaltopoulou T, K. R., Haidopoulos D Olive oil intake is inversely related to cancer prevalence: A systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies. *Lipids Health Dis.* **2011,***10*, 127.

79. Sayed-Ahmed MM, N. M., Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats. *Clin. Exp. Pharm. Physiol.* **2007,***34*, 399-405.

80. Banerjee S, K. A. W. Z., Antitumor activity of gemcitabine and oxaliplatin is augmented by thymoquinone in pancreatic cancer. *Cancer Res.* **2009,***69* (13), 5575-5583.

81. Nagi, M. N.; Almakki, H. A.; Sayed-Ahmed, M. M.; Al-Bekairi, A. M., Thymoquinone supplementation reverses acetaminophen-induced oxidative stress, nitric oxide production and energy decline in mice liver. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* **2010,***48* (8-9), 2361-5.

82. El-Dakkakhny M, B. M., El-Halim MA Effects of Nigella sativa oil on gastric secretion and ethanol induced ulcer in rats. *J. Ethnopharm.* **2000,***72*, 299-304.

83. Arslan SO, G. E., Armutcu F, The protective effect of thymoquinone on ethanol-induced acute gastric damage in the rat. *Nutrit. Res.* **2005,***25*, 673-680.

84. Refaey, M. S., and M. A. Fayed TRADITIONAL TO RECENT APPROACHES IN HERBAL MEDICINE THERAPY OF COVID-19. *Universal Journal of Pharmaceutical Research* **2020,***5* (5), 71-84.

85. Koshak, D. A. E.; Koshak, P. E. A., Nigella sativa L as a potential phytotherapy for coronavirus disease 2019: A mini review of in silico studies. *Current Therapeutic Research* **2020,***93*, 100602.