



# **Black Cumin Seed (Nigella sativa) in Inflammatory Disorders: Therapeutic Potential and Promising Molecular Mechanisms**

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Abstract: Inflammation is an essential defense mechanism against harmful stimuli. However, uncontrolled inflammatory mechanisms culminate in disturbed responses that contribute to multiple serious diseases. Besides common synthetic drugs, there is a growing interest in optimizing the use of natural products as therapeutic or protective supplements against inflammatory disorders. Black cumin seed (BCS), or Nigella sativa (Family Ranunculaceae), is widely used as a health-supportive herb in the Middle East, Far East and West Asia. BCS is a rich source of phytochemicals, and studies have reported its promising effects against a variety of metabolic, proliferative, respiratory, and neurological disorders associated with disrupted inflammatory pathways. This review presents an updated comprehensive assessment of BCS's effects against various inflammatory disorders and highlights the role of BCS's bioactive constituents in inflammation and oxidative stress pathways. Moreover, it outlines the future possibilities for enhancing therapeutic activity through efficient pharmaceutical formulations. Thorough analysis of international research studies published between the years 1998 and 2023 reveals the promising anti-inflammatory potential of BCS's bioactive constituents through modulating inflammation and crucial oxidative stress players in inflammatory disorders. Thus, the bioactive constituents of BCS can be further boosted by updated technologies such as nano-incorporation for the improved management of inflammatory diseases.

Keywords: cytokines; inflammation; oxidative stress; natural products; nano formulations

# 1. Introduction

Inflammation is a vital and complicated process in the body used to defend against numerous chemical, biological, and physical stimuli [1]. The concept of inflammation has developed from being described basically as a burning sensation to an intense understanding of its pathology and contributing molecules. Inflammation varies in accordance with different stimuli and their consequent inflammatory responses [2]. Prolonged exposure to inflammation creates a state of chronic inflammation which involves complicated processes of macrophage and cytokine release and the emergence of a high-oxidative-stress status, which in turn can cause irreversible cellular, genetic, and epigenetic disruptions. Such alterations are now established as being highly involved in the pathogenesis of different diseases. Consequently, trying to modify inflammatory status and the implicated inflammatory molecules through anti-inflammatory agents is a therapeutic target that can improve the management of inflammation-related pathologies. This review discusses the inflammation process and the most prominent molecules involved in inflammation. Moreover, it highlights the promising potential of black cumin seed constituents as powerful inflammatory modulators in various disorders. Finally, supporting research for using



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**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). nano-formulations of black cumin seed as a future approach for optimized therapeutic applications is also included.

#### 2. Methods

The studies included in the current article were obtained from several databases and websites, such as Elsevier, Springer, Wiley online library, Google Scholar, PubMed, MDPI, Science Direct, ResearchGate and Hindawi. All possible data were collected up until 2023. Examples of inflammatory disorders were classified and different synonyms of black cumin seed such as '*Nigella sativa*', 'black seed', 'black cumin', 'thymoquinone' and 'nigella oil' were used. Both in vivo and in vitro studies were included. All studies were peer reviewed and published in the English language or were translated into English.

# 3. Inflammation: Different Types and the Involved Key Players

## *3.1. Types of Inflammation*

## 3.1.1. Acute Inflammation

Acute inflammation is a self-limited process that lasts for a few hours to a few days. It is associated with plasma proteins and fluid perfusion (edema) and leukocyte arrival (mainly neutrophils and later macrophages) at the inflammation site. The inflammation process starts with vascular changes, followed by cellular and molecular recruitment [3]. The immune cells control inflammation by producing anti-inflammatory mediators. The recruitment of monocytes, macrophages and dendritic cells critically clears remnant cell debris and antigens [4]. When the immune system eliminates the harmful stimuli, the inflammation ends. However, if these stimuli are not removed successfully, the inflammation turns into a chronic phase [5].

## 3.1.2. Chronic Inflammation

Uncontrolled inflammation due to extended exposure to stimuli or an improper inflammatory response for a long time, results in chronic inflammation. Inflammation is characterized by the infiltration of lymphocytes and macrophages mononuclear cells, vascular proliferation, fibrosis, and the progression of tissue damage [6]. Persistent inflammation causes extreme pro-inflammatory mediators and cytokine production that can contribute to systemic inflammatory response syndrome (SIRS), sepsis and multiple organ failure. Several studies linked chronic inflammation to several diseases such as type 2 diabetes mellitus [7], arthritis and joint diseases [8], chronic obstructive pulmonary disease (COPD) [9], neurodegenerative diseases [10], multiple sclerosis [11], inflammatory bowel disease [12] and more (Figure 1).

Inflammatory reactions frequently begin with the detection of foreign stimuli by pattern recognition receptors (PRRs) on the cell surface, which then activate several inflammatory pathways. As a result, inflammatory mediators are produced, and inflammatory cells are recruited. The PRRs can identify different molecules such asPAMPs (pathogen-associated molecular patterns) andDAMPs (danger associated molecular patterns). These receptors are expressed on immune cells and other non-immune cells. They contain many classes, such as receptors for advanced glycation end products (RAGE), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and Toll-like receptors (TLRs). Crucial intracellular signaling pathways are activated through these receptors, followed by inflammatory cytokine and chemokine release [13].



**Figure 1.** Interrelationship between Inflammation and oxidative stress. TNF- $\alpha$ : Tumor necrosis factor alpha; IL-1: Interleukin-1; ROS: Reactive oxygen species; NF- $\kappa$ B: Nuclear factor-kappa B; AP-1: activator protein-1; Nrf2: Nuclear factor erythroid 2-related factor 2; TGF- $\beta$ : transforming growth factor-beta; IL-10: Interleukin-10.

#### 3.2. Signaling Pathways Involved in the Inflammation Process

## 3.2.1. Mitogen-Activated Protein Kinase (MAPK) Pathway

Many extracellular stimuli can cause the MAPK pathway to be activated, such as growth factors, pathogens, toxins cytokines, and stress signals. The extracellular-signal-regulated kinases ERK1/2 and ERK5, p38 MAP kinases, and c-Jun N-terminal kinases (JNKs) comprise the signaling families of mammalian MAPKs. The MAP kinase pathways have been implicated in a wide range of pathological illnesses, including cancer and other diseases [14,15].

## 3.2.2. Nuclear Factor Kappa B (NF-кB) Pathway

The NF- $\kappa$ B pathway plays a crucial role in the regulation of immunity, inflammation, and cell survival. Five proteins, namely p105/p50 (NF-B1), p100/52 (NF-B2), p65 (RelA), RelB and c-Rel, compensate the NF-B transcription factors in mammals. NF- $\kappa$ B activation occurs through at least two different pathways; T- and B-cell receptors, pathogenrelated molecules, and pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 stimulate the "canonical" pathway, while the tumor necrosis factor (TNF)-family cytokines (LT $\beta$ , CD40L, BAFF, and RANKL except for TNF- $\alpha$ ) activate the "alternative" NF- $\kappa$ B pathway. The noncanonical NF-B regulates the adaptive immune system concomitantly with the canonical NF-B pathway, whereas canonical NF-B plays a major role in immune responses. NF- $\kappa$ B directly regulates inflammation by increasing the production of inflammatory cytokines, chemokines, and adhesion molecules [16,17]. 3.2.3. The Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) Pathway

The JAK-STAT pathway is another important pathway that regulates many cellular events. Cytokines are a major activator of this pathway. STAT is phosphorylated by JAK and moves to the nucleus to influence specific gene expressions [18]. All STATs except for STAT4 localize to the mitochondrion and enhance oxidative phosphorylation and membrane permeability, while STAT3 can move to the endoplasmic reticulum and resists excessive apoptosis induced by oxidative stress. Dysregulation of JAK-STAT in humans can contribute to diseases such as cancer and autoimmune diseases [19,20].

### 3.3. Key Inflammatory Molecules

- Tumor necrosis factor alpha (TNF-α): is a potent pro-inflammatory cytokine that is crucial for the immune system's function during inflammation, cell proliferation, differentiation, and apoptosis. TNF-alpha exerts its effects through TNF-alpha receptor I, expressed almost in all kinds of cells, while TNF-alpha receptor II is only expressed in immune system cells, fibroblasts and endothelial cells [21].
- Nitric oxide (NO): is involved in physiological processes such as neurotransmission, vasodilation, platelets aggregation and adhesion, host defense, and immune regulation. In pathological conditions, NO acts as a cytotoxic agent especially in inflammatory diseases. Upon immunological stimulation, NF-κB stimulates inducible nitric oxide synthase (iNOS, also called NOS2), which synthesizes NO. Overproduction of NO causes high oxidative stress and cell death [22].
- Prostaglandin E2 (PGE2): The cell membrane's phospholipids and phospholipase A2 (PLA2) release arachidonic acid (AA). AA is the main precursor for prostanoids which are converted into Prostaglandin H2 (PGH2) by cyclooxygenase (COX) and peroxidase. PGH2 is then transformed by Prostaglandin E (PGE) synthase into Prostaglandin E2 (PGE2) [23]. PGE2 acts as a vasodilator to promote the migration of white blood cells to the site of inflammation causing edema. Additionally, it increases the pain response and acts as a fever mediator [24,25]. Therefore, the inhibition of cyclooxygenase enzyme suppresses prostanoid synthesis and decreases vasodilatation, vascular permeability, and the recruitment of immune cells in inflammation.
- Interleukin-1 $\beta$  (IL-1 $\beta$ ), as a member of the Interleukin 1 (IL-1) family, is a pivotal pro-inflammatory mediator. It is usually linked to acute and chronic inflammation, where the levels of NOS2, COX-2, adhesion molecules, IL-6 and TNF- $\alpha$  are elevated with IL-1 $\beta$  overexpression [26].
- Interleukin-6 (IL-6): is a main pro-inflammatory member of the IL-6 family. It is involved in acute and chronic inflammation. NF-κB and activator protein 1 (AP-1) are important transcription factors for IL-6. IL-6 is capable of inducing differentiation in T-helper cells and B cells. Elevated IL-6 levels were observed in autoimmune diseases, inflammatory diseases and cancer [27].
- Interleukin-17 (IL-17): is produced by a subset of T-helper cells known as Th17 cells as a primary source as well as other immune cells including natural killer T cells, gammadelta T cells, microglia, mast cells, neutrophils, and others. IL-17 is involved in host defense mechanisms through releasing antimicrobial peptides (AMPs), chemokines, and proinflammatory cytokines. On the other hand, it may be implicated in the pathogenesis of autoimmune disorders [28].

## 3.4. Chronic Inflammation and Oxidative Stress: A Vicious Cycle

Chronic inflammation triggers a status of oxidative stress leading to the excessive release of reactive oxygen species (ROS), which opposes the body's antioxidant defense mechanisms and causes cellular damage. In turn, excessive oxidative stress caused by reactive species triggers an inflammatory response, which produces more free radicals, which can lead to further oxidative stress and chronic inflammation, creating a vicious cycle (Figure 1). Chronic inflammation due to oxidative stress has been shown to be involved

520

in several conditions, including cancer, diabetes, cardiovascular disease, arthritis, and neurodegenerative disorders [29].

## 4. Natural Herbs as Anti-Inflammatory Agents

Natural herbs have been used for centuries in folk medicine for the treatment of various diseases, including inflammatory disorders. Many of these herbs have been shown to possess anti-inflammatory properties with few side effects compared with synthetic drugs. Scientific research is ongoing to further explore their potential health benefits. Among the promising constituents in natural herbs with anti-inflammatory activity are resveratrol in grapes [30], quercetin in citrus fruits [31], curcumin in turmeric [32], epigallocatechin-3-gallate in green tea [33], gingerol in ginger [34], allicin in garlic [35], 1,8-cineole in eucalyptus [36] leaves and thymoquinone in black cumin seed [37]. Black cumin seed has been extensively studied for its potential health benefits. In this review, we highlighted the updated studies of black cumin seed in inflammatory disorders and its different pharmacological formulations.

## 4.1. Black Cumin Seed

Black cumin seed, or *Nigella sativa* Linneaus (*N. sativa*), is an annual flowering herb belonging to the Ranunculaceae family. It is widely distributed in Middle Eastern and Southeast Asian countries [38]. Black cumin seed (BCS) and its oil are used in many therapeutic and cosmetic applications. Traditionally, they are used as a spice, appetizer and food additive, a source of energy and an immune stimulant, a carminative and bowel movement regulator, as well as an analgesic and antipyretic supplement. Additionally, they are used in many respiratory conditions such as the common cold, coughing and asthma. BCS is used to treat dyslipidemia, obesity, diabetes and hypertension as well [39,40]. Women use BCS to relieve menstrual discomfort and as a galactagogue herb [40]. They also use it for skin and hair beauty purposes [41]. Moreover, BCS is used to support the general health of the neurons, stomach, intestines, kidneys, and liver. *N. sativa* has gained attention as a potential therapeutic agent due to its diverse pharmacological properties [42].

#### 4.2. Chemical Constituents

Many compounds have been identified and quantified in black cumin seed by using different techniques such as high-performance liquid chromatography (HPLC) [43], gas chromatography [44] and thin-layer chromatography (TLC) [45]. BCS is a rich source of carbohydrates (24.9%), fats (28.5%), of which the essential (volatile) oils constitute about 0.4–2.5%, while the fixed oil, which is rich in saturated and unsaturated fatty acids, constitutes about 26–34%, proteins (26.7%), fibers (8.4%), ash (4.8%), vitamins (1.8–3.7%), minerals (3.7–7%) and water [38]. Thymoquinone (TQ) is a putative phytochemical compound of the BCS (Figure 2). It constitutes around 30–48% of the volatile oil. Table 1 demonstrates different compounds that have been identified in BCS.



Figure 2. The molecular structure of thymoquinone.

Group	Compounds
Proteins (Amino acids)	Cysteine, methionine, glutamate, aspartate, arginine, alanine, valine, glycine, isoleucine, leucine, tyrosine, lysine, proline, threonine, serine, phenylalanine
Carbohydrates	Arabinose, glucose, rhamnose, xylose
Sterols	Cholesterol, campesterol, $\beta$ -sitosterol, stigmasterol, 5-avenasterol
Terpenes and Terpenoids	Thymoquinone, thymohydroquinone, dithymoquinone, thymol, p-cymene (7–15%), longifolene, limonene, longifolene, α-pinene, citronellol, carvone, 4-terpineol (2–7%), carvacrol (6–12%), t-anethole
Fatty acids	Stearic acid, palmitic acid, oleic acid (20%), linoleic acid (50–60%), eicosadienoic acid (3%), eicosanoic acid, dihomolinoleic acid, tetradecanoic acid
Alkaloids	Nigellidine, nigellicine, nigellicimine, nigellicimine-n-oxide
Tocols	$\alpha$ - tocopherol, $\gamma$ -tocopherol, $\beta$ -tocotrienol (Vit. E)
Saponin	α-hederin, hederagenin
Cumarins	7-oxy-coumarin, 7-hydroxy-coumarin, 6-methoxy-coumarin
Polyphenols	Apigenin, caffeic acid, caftaric acid, chlorogenic acid, cichoric acid, gentisic acid, ferulic acid, fisetin, hyperoside, isoquercitrin, kaempferol, luteolin, myricetin, p-coumaric acid, patuletin, quercitrin, quercetin, rutin, sinapic acid
Steroidal glycosides	Stigma-5,22-dien-3-β-D-glucopyranoside, 3-O-[β-Doxylopyranosyl-(1-2)-α-L-rhamnopyranosyl-(1-2)-β-D-glucopyranosyl]-11-methoxy-16, 23-dihydroxy-28-methylolean-12-enoate, 3-O-[β-D-xylopyranosyl-(1-3)-α-L-rhamnopyranosyl-(1-4)-β-D-glucopy-ranosyl]-11-methoxy-16- hydroxy-17-acetoxy hederagenin
Phospholipids	Phosphatidylinositol, phosphatidylglycerol, phosphatidylcholine
Minerals	Calcium, copper, iron, potassium, magnesium, manganese, phosphorus, sodium, selenium, zinc
Vitamins	Folic acid, riboflavin, niacin, Vit. A, Vit. C, thiamin, pyridoxine

Table 1. The different compounds identified in black cumin seed [40,44,46–48].

### 4.3. Safety and Toxicological Profile of Black Cumin Seed

Studies that evaluated the toxicity of BCS typically described it generally as a safe therapeutic plant as it has a broad safe margin [49–51]. In animal models, TQ exerted a median lethal dose (LD50) of 2.4 g/kg in acute oral administration in mice, while in sub-chronic administration, a cytoprotective effect was revealed in mice that received 0.01, 0.02, and 0.03% of TQ in their drinking water, with no signs of toxicity or morbidity [52]. Oral administration of BCS oil for 3 weeks at 2 mL/kg showed a hepatic and renal-protective effect in rats [53]. Different forms of BCS showed LD50 values of 3020, 3371, and 1853 mg/kg for aqueous extract, fixed oil and volatile oil, respectively, in mice [54]. BCS extracts in water, methanol, and chloroform at oral doses of 6, 9, 14, and 21 g/kg did not cause substantial morbidity or mice death [55]. BCS powder integrated in rats pellets at doses of 0.01, 0.1, and 1 g/kg administered daily for 28 days did not cause any toxicity or alteration in liver function markers [56]. BCS fixed oil had LD50 values of 28.8 mL/kg orally and 2.06 mL/kg intraperitoneally in mice after being delivered in single doses [51]. Rats tested for the chronic toxicity of BCS fixed oil (2 mL/kg orally for 12 weeks) showed no histological changes in the kidneys, liver, heart or pancreas or any alteration in liver enzymes as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT). Moreover, a significant elevation in hemoglobin and hematocrit values was observed along with a marked decrease in glucose, serum cholesterol, triglyceride, platelet and leukocyte values [51]. However, BCS oil doses should be carefully adjusted, as some histological changes were observed in rats' kidneys and livers after one month of administering oral BCS oil at doses of 15 and 25 mL/kg [57].

In humans, the clinical utilization of BCS has also provided evidence of its safety. For example, BCS oil administration for 8 weeks reduced blood pressure and showed no adverse effects on healthy candidates [58] or in hypertensive patients [59]. BCS and TQ were both well tolerated and showed no side effects considering the management of dyslipidemia [60]. Despite the lack of information regarding the maximum tolerable dose of TQ, it was reported that adult patients with solid tumors tolerated TQ oral doses of up to 2600 mg/day [61]. BCS oil was well tolerated by both adults and children when given at doses of 40 mg/kg. However, children who received high doses of BCS oil (80 mg/kg) experienced gastrointestinal side effects. Therefore, BCS oil is recommended to be used in children at weight-appropriate doses and given after meals [62].

# 4.4. Therapeutic Activity of Black Cumin Seed in Inflammatory Disorders

The health benefits of BCS have been largely attributed to its powerful anti-inflammatoryantioxidant properties (Figure 3). A summary of updated studies that reported the efficiency of using BCS constituents in in-vivo and in-vitro models for a variety of inflammationrelated disorders is represented in Table 2.



**Figure 3.** Most prominent effects of black cumin seed related to key molecules involved in inflammation and oxidative stress.  $\uparrow$  increase;  $\downarrow$  decrease.

Table 2. Studies of BCS's therapeutic effects in inflammation-related disorders.

Disorder	TQ/BCS Formula	Model	<b>Improved Parameters</b>	Ref.
Neuro-inflammation	TQ (10 μM)	BV-2 cells	↓ NO2– and iNOS ↓ IL-6, IL-12, p40/70 ↓ Granulocyte colony-stimulating factor ↓ CCL12/MCP-5 and CCL2/MCP-1	[63]
Cognitive impairment (Alzheimer's disease)	BCS (100, 200, and 400 mg/kg) i.p. TQ (10, 20, and 40 mg/kg) i.p.	Rats	↓ MDA ↑ SOD ↓ AChE - Ameliorate learning and memory impairments	[64]

Disorder	TQ/BCS Formula	Model	Improved Parameters	Ref.
Parkinson's disease	TQ (5 and/10 mg/Kg) orally	Rats	↓ MDA, Nitrite levels ↑ SOD ↓ loss of substantia nigra pars compacta neurons - Improved the rotational Behavior	[65]
	TQ (7.5 and 15 mg/kg) Orally	Rats	↑ Tyrosine hydroxylase, dopamine, and parkin levels ↓ Dynamin-related protein-1 - Enhance the motor functions	[66]
	BCS oil (500 mg twice a day for 8 weeks) orally	Diabetic patients	↑ HDL-C levels ↓ MDA and hs-CRP, TC, L DL-C ↓ Triglycerides and FBG levels	[67]
Diabetes mellitus	TQ (20 mg/kg)	Pregnant mice and their offspring	↓ Body weight ↓ BGL, ↑ Insulin ↓ LDL-C, TC, MDA ↑ IL-2, IL-4, IL-7, ↓ IL-6, IL-1β and TNF-α	[68]
Myocardial infarction	TQ at (10 and 20 mg/kg) orally	Rats	$\uparrow$ GSH and TAC ↓ TNF-α and NF-κB ↓ Metalloproteinase 9 ↓ Cytochrome-C and Caspase 3 and 9	[69]
	TQ (20 mg/kg) orally		$\uparrow$ GSH, GPx, SOD, CAT, BCL-2 ↓ IL-6, IL-1β, and TNF-α MDA ↓ BAX, Caspase-3 ↓ Troponin I and LDH	[70]
Ulcerative colitis	BCS oil (2.0 mL/kg)	Mice	↑ CAT, SOD ↑ GSH, GPx ↓ IL6, MDA, NO ↓ CRP, MPO	[71]
Rheumatic arthritis	TQ at (10 mg/kg) i.p.	Rats	$\downarrow$ IL-1, TNF-α, NF-κB $\downarrow$ TLR4 and TLR2 $\downarrow$ CRP	[72]
- Liver injury	TQ (12.5 μM)	(LX-2) hepatic stellate cells	↑ LKB1 and AMPK phosphorylation ↓ Collagen-I, α-SMA, TIMP-1 ↑ MMP-13 ↑ (PPAR-γ) expression	[73]
	TQ (20 or 40 mg/kg) orally	Mice	↓ Serum aminotransferase ↓ Hepatic triglyceride ↓ Collagen-I, α-SMA ↑ SIRT1 ↑ LKB1 and AMPK phosphorylation	
	TQ (25, 50 mg/kg) Orally	Rats	$\downarrow$ Hydroxyproline and MDA $\uparrow$ SOD and GPx	[74]
Pancreatitis	TQ (5 mg/kg) i.p.	Rats	↓ IL-1β ↑ TAC ↓ TOS - Ameliorate histopathologic findings	[75]

# Table 2. Cont.

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Disorder	TQ/BCS Formula	Model	Improved Parameters	Ref.
Lung Injury	TQ (5 or 10 mg/kg) i.p.	Rats	↓ PGE2, TGF-β, IFN-γ ↑ IL-4 ↓Epithelial damage emphysema scores of lung tissue ↓ Eosinophil, neutrophil, and monocyte% ↑ lymphocyte%	[76]
Asthma	TQ (1, 10, and 30 mg/kg) i.p.	Rats	↓ IL-6 and TNF-α in BALF ↓ MDA in lung tissue ↓ Total WBCs in BALF ↓ Lymphocyte Eosinophil, Monocyte, Neutrophil ↓ Evans blue dye	[77]
Gingivitis	BCS oil (diluted with water 50%) Rinsing	Gingivitis patients	↓ IL-6 ↓ Colony-forming units ↓ Pathogenic bacteria	[78]
Psoriasis	BCS (ointment, powder, capsule, combination of ointment and capsule)	Psoriatic patients	↓ Psoriasis Area and Severity Index score ↓ MDA - Cure of psoriatic lesions	[79]
Atopic dermatitis	TQ (10 mg/kg dissolved in ethanol/distilled water) orally, TQ (5 μmol in 0.2 mL acetone) topical	Mice	↓ IgE level ↓ IL-4, IL-5 ↓ IFN-γ	[80]

 $\uparrow$  increase;  $\downarrow$  decrease; i.p.: Intraperitoneal injection; IL: interleukin; CCL12/MCP-5: chemokine (C-C motif) ligand 12/monocyte chemoattractant protein-5; CCL2/MCP-1: chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1; MDA: malondialdehyde; SOD: superoxide dismutase; CAT: catalase; AChE: acetylcholinesterase; hs-CRP: high-sensitivity C-reactive protein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BGL: blood glucose level; TC: total cholesterol; TNF- $\alpha$ : tumor necrosis factor-alpha; GSH: reduced glutathione; GPx: glutathione peroxidase; TAC: total antioxidant capacity; TOS: total oxidative stress; NF- $\kappa$ B: nuclear factor-kappa B; LDH: lactate dehydrogenase; Bax: bcl-2-associated X protein; BCL-2: B-cell lymphoma 2 protein;  $\alpha$ -SMA: alpha-smooth muscle actin; TIMP-1: tissue inhibitor of metalloproteinase 1; MMP-13: matrix metalloproteinase-13; SIRT1: sirtuin 1; LKB1: liver kinase B1; PGE2: prostaglandin E2; TGF- $\beta$ : transforming growth factor-beta; BALF: bronchoalveolar lavage fluid; IgE: immunoglobulin E; IFN- $\gamma$ : interferon-gamma; AMPK: AMP-activated protein kinase.

## 4.4.1. Rheumatic Arthritis (RA)

Rheumatic arthritis is a chronic autoimmune disease that affects the joints and other parts of the body. It causes inflammation and swelling in the joints, leading to pain, stiffness, and difficulty in movement [81]. Over time, RA can cause significant joint damage, leading to disability. In 2019, a study performed by Cinzia Nasuti et al., on the healing impact of BCS oil (at oral doses of 0.91 mL/kg and 1.82 mL/kg) on arthritic rats showed a marked inhibition of the arthritis score, the percentage inhibition of paw edema and disease progression. In addition, inflammatory markers such as C-reactive protein (CRP) and interleukin 6 were significantly lowered [82]. A clinical study that recruited 40 rheumatic arthritic females revealed the significant therapeutic activity of BCS oil (500 mg of BCS oil capsules twice/day for a month after a month of placebo intake), which was reflected by the improved activity score in swollen joints, pain and morning stiffness [83]. Another study for the effect of BCS oil (500 mg capsules twice a day for 8 weeks) on 23 rheumatic arthritic female patients showed that the disease activity score was significantly lower in the BCS oil group, with a remarkable decrease in serum nitric oxide (NO) and malondialdehyde (MDA) relative to the baseline and elevated protective IL-10 levels [84]. Moreover, one gram of BCS oil given orally to 23 rheumatic arthritic females for 8 weeks caused a significant decrease in CRP levels and CD8+, together with the alleviation of disease activity scores of 28 joints compared with baseline and placebo groups [85]. In addition, pre-treatment of

rheumatoid arthritis synovial fibroblast cells with TQ inhibited the production of IL-6, IL-8, and the adhesion molecules: Intercellular Adhesion Molecule 1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1) and Human Cadherin-11 (Cad-11). TQ is considered a potential therapy for RA by inhibiting apoptosis-regulated signaling kinase 1 (ASK1) and the consequent activation of p38 and JNK [86]. The histological indices of joint inflammation and paw weight were both significantly lowered by TQ in pristane induced arthritis in rats [87].

#### 4.4.2. Inflammatory Bowel Disease and Ulcerative Colitis

Ulcerative colitis is a chronic idiopathic disease that affects the large intestine and rectum, causing inflammation and ulcers in the inner lining area, leading to inconvenient symptoms such as abdominal pain, diarrhea, and rectal bleeding [88]. Thymoquinone at a rectal dose of 100 mg/kg was found to reduce fecal inflammatory bowel disease (IBD) biomarkers such as calprotectin, hydroxyproline, and lactoferrin, as well as oxidative stress index (OSI) and total oxidant status (TOS) levels in rats treated with dextran sulfate sodium (DSS) [89]. In line with these findings, TQ was found to have powerful anti-inflammatory activity in HT-29 cells and an ulcerative colitis mouse model at doses of 10 and 20  $\mu$ M and 20 and 40 mg/kg, respectively. It reduced the gene expression and protein levels of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , COX-2, and iNOS and decreased the myeloperoxidase (MPO) activity. Furthermore, it regulated the phosphorylation of NF-KB and MAPK proteins. Likewise, TQ reduced IL-8 and C-X-C Motif Chemokine Ligand 1(CXCL-1) levels and increased the expression and protein levels of peroxisome proliferator- activated receptor gamma (PPAR- $\gamma$ ) modulator, while it also enhanced the disease activity index (DAI) score and altered the histopathological findings caused by DSS [90]. Another study revealed that more favorable clinical illness scores, macroscopic assessment, and weight gain were noticed in rats treated with 2 mL/kg BCS oil, with a lower extent of bowel damage, apoptosis, and histopathologic findings. Additionally, significantly lower MDA and MPO levels with high activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) were observed [91].

# 4.4.3. Neurodegenerative Disorders

# Alzheimer's Disease (AD)

Alzheimer's disease is the most common dementia-causing factor, characterized by the gradual loss of neurons and synapses in the brain [92]. Several factors are thought to contribute to its development, including genetics, lifestyle, and age [93]. Azar Hosseini et al., showed that BCS oil exerted an anti-inflammatory effect in LPS-induced microglial neuroinflammation. BCS oil markedly decreased IL-1 $\beta$ , IL-6, TNF- $\alpha$ , PGE2, and iNOS levels while elevating IL-10 and arginase-1 (Arg1) levels [94]. Moreover, rats treated orally with 3 mL/Kg BCS oil for 6 weeks showed decreased inflammatory and oxidative stress markers by regulating the levels of MDA, caspase 3, TNF- $\alpha$ , acetylcholinesterase (AChE), GPx, catalase (CAT), and SOD, along with improved histopathological changes in the brain such as congestion, hemorrhage, degeneration, and edema in emamectin benzoate-induced neurotoxicity [95]. In the same context, the anti-oxidant activity of the hydro-alcoholic extract of BCS was suggested to improve learning and memory capabilities in neonatal and juvenile rats [96]. BSC oil also improved behavioral test assessments when administered at a dose of 2 mL/kg for 4 weeks in mercuric chloride-induced neurotoxicity when used alone or combined with ginger [97]. Moreover, hydro-alcoholic extract treatment of BCS resulted in better memory performance and decreased levels of AChE activity and MDA in scopolamine-treated rats [98]. In another study, BCS oil used in combination with virgin olive oil and an aqueous extract of roasted date seeds revealed high prophylactic and therapeutic efficiency against CuSO<sub>4</sub>-induced AD [99]. Meanwhile, a low dose of BCS (500 mg per day for four weeks) was sufficient to reduce anxiety, maintain mood, and positively enhance cognition in healthy participants compared to a placebo [100]. Thymoquinone administration for 2 weeks at different doses was recently found to counteract cognitive impairment and morphological abnormalities in D-Gal/aluminum chloride-induced AD in

rats by decreasing the levels of pro-inflammatory cytokines such as TNF- $\alpha$  and IL1- $\beta$  and the mRNA expression of NF- $\kappa$ B, TLR-2, TLR-4, MyD88, TRIF and IRF-3, while reducing amyloid- $\beta$  formation and accumulation in rat brain striata [101]. Meanwhile, Abulfadl et al., reported that TQ administration to treat D-gal- and AlCl<sub>3</sub>-induced neurotoxicity significantly enhanced the levels of SOD, total antioxidant capacity (TAC), brain-derived neurotrophic factor (BDNF), B-cell lymphoma 2 protein (BCL-2) and acetylcholine (Ach) immunoreactivity and lowered the levels of AChE activity, MDA, NO as well as TNF- $\alpha$ immunoreactivity [102]. TQ was also found to inhibit I $\kappa$ B and p65 subunits in an LPSinduced microglia inflammation model, and thus inhibit NF- $\kappa$ B activation. Additionally, its anti-inflammatory activity was confirmed via the activation of Nrf2/ARE signaling pathway [103].

#### Parkinson's Disease (PD)

Parkinson's disease is a progressive neurodegenerative disorder that affects movement, muscle control, and balance [104]. Mice orally treated with 200 mg/kg of hydroalcoholic BCS for 12 days exhibited improved muscle stiffness in a Parkinson's model [105]. Furthermore, the ethanolic extract of BCS significantly reduced the decline in climbing capacity and lengthened life in a PD genetic model of Drosophila in a dose-dependent manner [106]. Additionally, BCS ethanolic extract was significantly able to increase reduced Glutathione (GSH) and total protein levels and reduce the levels of thiobarbituric acid reactive substances (TBARS) and nitrites in rats treated with chlorpromazine [107]. The oral administration of 0.2 mL of BCS oil for 6 weeks exerted a marked neuroprotective effect in extrapyramidal symptoms (EPS) such as behavior in rats receiving haloperidol, improving the motor functions and enhancing the histopathological findings with the decreased alteration of microglia and astrocyte activities [108].

#### 4.4.4. Respiratory Diseases

#### Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease is a progressive inflammatory lung disease that causes difficulty in breathing, coughing, and wheezing. A major cause of COPD is the persistent inflammation brought on by long-term exposure to harmful particles or gases such as cigarette smoke [109]. A clinical study compared COPD patients that were divided into a control group, who received medications only, and the experimental group, who received medications only, and the experimental group, who received medications and encapsulated BCS oil for three weeks. The BCS oil group showed a significant decrease in TBARS, protein carbonyl (PC), IL-6 and TNF- $\alpha$ , while a significant enhancement was observed in pulmonary function tests, vitamins levels such as vitamin C and E, and antioxidant markers such as GSH, GPx, CAT, SOD [110]. Furthermore, the chemotaxis of neutrophils triggered by N-Formylmethionyl-leucyl-phenylalanine (fMLP) and the migration of random cells was found to be inhibited by an essential oil from BCS in a dose-dependent manner, in addition to its effect on human neutrophil elastase (HNE) secretion [111].

## Asthma

Oral administration of BCS oil capsules for four weeks as an adjuvant therapy led to an improvement in the asthma control test (ACT) score and pulmonary function tests along with a marked decrease in blood eosinophil count compared to the placebo group [112]. Moreover, BCS oil administration for eight weeks orally as an adjunctive therapy at a dosage of 15–30 mg/kg/day in asthmatic children revealed an enhancement in IFN- $\gamma$ /IL-4 levels with no significant differences in the Th1 and Th2 cell number or the Th1/Th2 ratio when compared to control [113]. Meanwhile, Koshak and colleagues showed that BCS suppressed the release of pro-inflammatory mediators (IL-2, IL-6, PGE2) in human T-lymphocytes, monocytes, and A549 human lung epithelial cells [114]. Moreover, BCS ethanolic extract reduced the amounts of histamine in rat peritoneal mast cells and exhibited no toxicity to mast cells [115].

## Coronavirus Disease 2019 (COVID-19)

COVID-19 emerged as a pandemic in early 2020 [116]. It was found to cause a massive disturbance in the immune system and correlate with NF-KB, IRF, and MAPK pathway activation, ending with an elevation of different proinflammatory cytokines and chemokines [117]. Black cumin seed was suggested as a supplement or treatment for COVID-19 due to its known immunomodulatory and antiviral properties [118]. BCS was hypothesized to interfere with SARS-CoV-2 receptors [119]. Using the molecular docking technique, BCS's active constituents, namely  $\beta$ -sitosterol,  $\alpha$ -hederin, nigellidine-4-O-sulfite, sterol-3-D-glucoside, nigellidine, and dithymoquinone, were reported to have binding affinity to SARS-CoV-2 Mpro [120]. Clinically, BCS was considered as a promising prophylactic herb against COVID-19 incidence [121]. Additionally, it decreased disease severity significantly when administrated with the standard COVID-19 treatment [122]. BCS oil was also shown to improve the symptoms of COVID-19 patients [123]. BCS combined with honey remedies showed accelerated viral load removal, ameliorated disease symptoms and a lower number of deaths compared to the placebo group [124]. However, there is a lack of studies that measured biochemical markers such as pro-inflammatory mediators in clinical and animal models.

#### 4.4.5. Metabolic Disorders

Metabolic disorders are a group of medical conditions that affect the metabolism of the body, leading to health problems such as obesity, diabetes, and cardiovascular disease. Many studies have shown that chronic inflammation plays a critical role in the development and progression of metabolic disorders, and vice versa [125].

#### Obesity, Diabetes Mellitus (DM) and Cardiovascular Disease (CVDs)

Essential and fixed oil of BCS was found to minimize free radicals' release and boost the antioxidant capacity and immunity in streptozotocin-induced DM rats [126]. A clinical study on obese females supplied with BCS for 8 weeks (2 g/day) together with an aerobic training program exhibited a significant decrease in the lipid profile, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and body mass index, with a significant increase in high-density lipoprotein cholesterol (HDL-C) levels and maximal aerobic capacity (max VO2) [127]. Another study on obese females who received 3 g of BCS oil for 8 weeks observed a marked reduction in their weight and waist circumference, in addition to a decline in triglycerides and VLDL compared to the placebo group [128]. Indeed, a pilot study on healthy male candidates who received 1 g/day of BCS powder for 4 weeks showed no significant changes in serum lipids or in glucose regulation, while this treatment also did not change insulin sensitivity. However, a significant correlation between the change in total cholesterol, LDL-C and their baseline levels was observed in the BCS group only [129].

## Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is a condition where there is an excessive accumulation of fat in the liver, which is not caused by alcohol consumption. The accumulation of fat in the liver can trigger an inflammatory response, leading to the recruitment of immune cells to the liver, which can cause progressive damage [130]. NAFLD patients who received BCS oil for 3 months showed a significant decrease in liver ALT and AST enzymes as well as LDL-C and triglycerides [131]. Another clinical study used 2 g of BCS for 12 weeks as a supplement in NAFLD patients, showing a marked decline in glucose and insulin levels and a remarkable rise in quantitative insulin sensitivity check index [132]. Meanwhile, using 1 g of BCS capsules twice daily for 12 weeks revealed remarkable reductions in ALT and AST and the body mass index, with 57.14% of patients reporting normal ultrasound grades when compared to the placebo group [133]. Additionally, an NAFLD patient group who ingested 2 g of BCS per day for 12 weeks showed a better reduction in inflammatory markers such as NF- $\kappa$ B, high-sensitivity C-reactive protein (hs-CRP), TNF- $\alpha$  as well as hepatic

steatosis percentage compared to the placebo patient group [134]. Another clinical study by Rashidmayvan and colleagues revealed that BCS oil consumption at 1000 mg/day for 8 weeks decreased fasting blood sugar levels, lipid profile (TC, TG, VLDL-C, LDL-C), liver enzymes (AST and ALT), hs-CRP inflammatory markers, TNF- $\alpha$  and IL-6, while it increased HDL-C levels. BCS oil showed no significant effect on insulin levels, blood pressure, and GGT in comparison to the placebo group [135].

#### 4.4.6. Anticancer Activity

Thymoquinone, as a major constituent of BCS, has shown promising antineoplastic activity against a wide variety of cancers [136], where TQ is involved in multiple biological pathways that are critically involved in proliferation, cell migration and cell cycle regulation. Emerging studies are continuously highlighting the distinguished potential of TQ against pancreatic cancer, where it significantly enhances apoptosis and decreases metastasis through modulating the NF- $\kappa$ B, tumor growth factor-B (TGF- $\beta$ ) and MAPK signaling pathways [137]. Moreover, TQ remarkably increases chemosensitivity in pancreatic cancers resistant to therapy by modulating matrix metalloproteinase enzyme (MMP-1) and NF- $\kappa$ B levels [138]. Table 3 presents updated studies that reported the efficiency of using BCS constituents in various types of cancer.

Cancer Type	TQ/BCS Formula	Model	Improved Parameters	Ref.
	BCS protein extract	MCF-7 cells	↑ BAX ↓ BCL-2 ↑ Caspase-3 ↓ Survivin	[139]
Breast cancer	TQ (50µM)	MDA-MB-231 triple negative breast cancer (TNBC)	↓ CXCR4 ↓ NF-κB	
	TQ (2 and 4 mg/kg)	Mice	↓ CXCR4 ↓ Metastases and metastatic biomarkers ↓ Osteolytic lesions	[140]
Brain cancer	TQ (10–100 µМ)	Glioma cells (U87MG, U118MG, A172)	↑ Cell cycle arrest ↑ Par-4 ↑ p53, p21, Rb ↓ Lamin B1, CDK-2 and Cyclin E	[141]
Blood cancer	TQ (1, 2, 3 μM)	HL60 cells	↑ Cell cycle arrest ↓ Cell proliferation ↑ Apoptotic activity ↑ Negative Regulators of JAK/STAT: SOCS-1, SOCS-3 and SHP-1	[142]
Lung cancer	ΤQ (25, 50, 100μΜ)	A549 cells	↑ BAX ↓ BCL-2 ↑ p53 ↑ Caspases-3 and -9	[143]
Hepatic cancer	TQ (10, 30, 50 μM)	HepG2	↑ Apoptosis ↓ Angiogenesis-related genes: VCAN, Grb2 and EZH2 expressions	[144]
Kidney cancer	TQ (20, 40 μM) (25, 50 μM)	A498 cells and Caki-1 cells	↑ Cell cycle arrest ↑ BAX ↓ BCL-2 ↓ Akt phosphorylation	[145]

Table 3. Updated studies of using BCS constituents in various types of cancer.

	Table 3. Cont.			
Cancer Type	TQ/BCS Formula	Model	Improved Parameters	Ref.
Bladder cancer	TQ (25, 50 μM)	5637 and T24 cells	↑ ROS ↑ Bax, cleaved caspase 3, PARP, cleaved poly (ADP-ribose). ↓ BCL-2, BCL-XL ↑ Beclin-1, ATG7 and LC3B proteins ↑ miR-877–5p	[146]
Prostate cancer	TQ (11.11, 22.22, 44.44 μM)	Panc-1 cells	↑ ROS ↓ MMP-9	[147]
Ovarian cancer	TQ oxime derivative (2.5–100 μM)	SKOV-3 cells CHO-K1 cells	$\uparrow$ Intracellular ROS and Ca <sup>2+</sup> $\downarrow$ GSH	[148]
	chemokine receptor typ protein 53; p21: cyclin-d 2; SOCS-1: suppressors of region 2 domain-conta EZH2: enhancer of zeste polymerase; ROS: reacti microtubule-associated 4.5. Updated and Fu Black Cumin Seed BCS oil repress for the wider use of and poor bioavaila and progressive act improvements in I formulations used Table 4. Nano-formu	pe 4; NF-κB: nuclear factor-ka lependent kinase inhibitor 1; R of cytokine signaling 1; SOCS-3 ining phosphatase-1; VCAN: e homolog 2 (histone methyltra ve oxygen species; Akt: protein protein light chain 3 beta; MMI eture Approach: Nano-Forn ents a natural source of r of BCS and particularly T ability. These drawbacks dvances of nano-formul BCS bioavailability and for incorporating BCS in alations of BCS in different	appa B; Par-4: prostate apoptosis response 4; b: retinoblastoma protein; CDK-2: cyclin-deper 3: suppressors of cytokine signaling 3; SHP-1: So versican; Grb2: growth factor receptor-boun ansferase for lysine 27 of histone 3); PARP: poly- n kinase B (PKB); ATG7: autophagy-related prof P-9: matrix metalloproteinase-9; GSH: reduced g <i>nulation for Optimized Therapeutic Appl</i> rich anti-inflammatory capacity. A big TQ is the low water solubility, photos s have been thoroughly tackled by the ations, leading to remarkable and co stability. Table 4 illustrates some of n a variety of therapeutic applications.	p53: tumor ident kinase rc homology d protein 2 -ADP ribose tein 7; LC3B glutathione. <i>lications of</i> challenge ensitivity the current ontinuous the nano
Disorder	Nano Formula	Model	Improved Parameters	Ref.
Alzheimer's disease	BCS oil- pDNA-chitosan-PLGA nanoparticles	N2a cell	<ul> <li>Promoted neurite outgrowth (that is important for the regrowth or repair of nervous tissues or cells</li> </ul>	[149]
Huntington's disease	Encapsulated Thymoquinone	Rats	<ul> <li>Enhanced the behavioral tests</li> <li>↓ MDA, Protein carbonyls, and Nitrite         ↑ SOD, CAT,         ↑ GST, GPx, GR, GSH         ↑ Vitamin C and E         ↑ SDH         ↓ AChE activity     </li> </ul>	[150]
Diabetic neuropathy	Silver nanoparticles of aqueous BCS extract	Rats	↓ Glucose level ↑ Serum insulin ↓ Advanced glycation ↓ TNF-α, NF-κB ↓ Serum Aldose reductase ↓ MDA, NO ↑ GSH ↑ Nitrotyrosine	[151]
Anti-bacterial	GO-PEG Nanoparticles of BCS Extract	Agar well diffusion for Staphylococcus aureus, Escherichia coli	- Destroying the bacteria by: interfering with the cell wall integrity, damaging nucleic acid elevating cell wall permeability.	[152]

## Table 4. Cont.

Disorder	Nano Formula	Model	Improved Parameters	Ref.
Hepato-toxicity, Renal toxicity	Silver nanoparticles of aqueous BCS extract	Mice	↓ The hepatosomatic index ↓ Serum levels of ALT, AST, ALP, MDA ↑ Total protein ↓ Creatinine - No change in renal somatic index	[153]
Neuro-endocrine tumors	Copper nanoparticles of BCS aqueous extract) in 2 concentrations	Adrenal phaeochro-mocytoma cells	↑ Cell viability ↓ Apoptosis index ↑ Mitochondrial membrane potential ↓ IL1α, IL1β, IL6, TNF-α ↓ Caspase-3	[154]
Chronic Lung Injury	PLGA Nanoparticles with loaded Thymoquinone	Rats	↓ Serum IL-10 ↓ TGF-β1 - Amelioration of histopathological changes and ultrastructure findings	[155]
Pulmonary Fibrosis	PLGA-PVA Nanoparticles with loaded Thymoquinone	Rats	↓ Serum IL-10 ↓ TGF-β1 ↓ iNOS - Amelioration of histopathological changes and Ultrastructure findings	[156]
Psoriasis	Ethosomal vesicles loaded with TQ	Rats	↑% Drug activity ↑% Orthokeratosis	[157]
Breast Cancer	Silver nanoparticles of aqueous BCS extract	MCF-7 cells Ab	$\downarrow COX-2 \\ \uparrow BAX \\ \downarrow BCL-2$	[158]

 $\uparrow$  increase;  $\downarrow$  decrease; TNF-α: tumor necrosis factor-alpha; MDA: malondialdehyde; NF-κB: nuclear factor-kappa B; NO: nitric oxide; GSH: reduced glutathione; GST: glutathione S-transferase; GPx: glutathione peroxidase; GR: glutathione reductase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; IL-: interleukin; TGF-β1: transforming growth factor-beta 1; iNOS: inducible nitric oxide synthase; SDH: succinate dehydrogenase; AChE: acetylcholinesterase; COX-2: cyclooxygenase-2; BCL-2: B-cell lymphoma 2 protein. BAX: BCL-2-associated X protein; GO: graphene oxide; PEG: polyethylene glycol.

#### 5. Conclusions

Inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, asthma, diabetes, and neurodegenerative diseases have received increased interest due to their adverse consequences. In this review, we briefly discussed the possible health benefits of various forms of black cumin seed (BCS) and thymoquinone (TQ) in these conditions. Their potential therapeutic effects were attributed to their anti-inflammatory and antioxidant activities. BCS modulates pro-inflammatory molecules such as IL-1 $\beta$ , IL-2, IL-6, IL-12, IL-8 TNF- $\alpha$ , COX-2, iNOS, PGE2, MDA, and MPO, anti-oxidant enzymes such as SOD, CAT, GSH, GPx, and AChE, as well as adhesive molecules such as ICAM-1, VCAM-1, and Cad-11. BCS regulates the blood pressure, lipid profile and blood glucose levels in a favorable manner. The anticancer activities of TQ were proven in different types of cancers. However, more studies are required to investigate the role of black cumin seed constituents other than TQ. Combinations of BCS with other remedies have exerted more beneficial effects. Finally, recent studies have shown that BCS and TQ nano-formulations are important approaches to enhance the outcomes of their biocompatibility and efficiency.

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