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Review Article

Action of Bioactive Compounds on Inflammation Via Nuclear Factor-Kappa B In Chronic Noncommunicable Diseases - Insights for Neuropsychiatric Disorders

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Abstract

The transcriptional factor called NF-kB factor is responsible for modulating the inflammatory process and its deregulated activation is related to the genesis and progression of NCDs, due to the activation of genes encoding inflammatory proteins. NCDs have been growing sharply in recent years around the world and generate too much burden on health systems, and it is of paramount importance to reduce their incidence. The BC present in fresh foods have shown great potential in inhibiting the NF-kB cascade. The aim of the study was to verify, through a literature review, BC suppressors of NF-kB. 47 articles were found, 26 with *in vitro* experiments, 7 *in vivo* with murine and 13 reviews and 1 clinical trial of the post-genomic era. Literature review has shown that ECGC, Curcumin, Resveratrol, Gingerol, Sulfuraphanes, Quercetin, Capsaicin and Omega III were able to suppress NF-kB by inhibiting IKK kinase and consequent inhibition of phosphorylation/degradation of IkB-α kinase, inhibition of translocation of the p65 subunit to the cell nucleus and suppression of NF-kB activating ROS.

Keywords: NF-kB and Inflammation; Bioactive Compounds and NF-kB; Phenolic Compounds and NF-kB; Eicosapentaenoic Acid and NF-kB; Bioactive Compounds and Inflammation

Abbreviations

ARE: Antioxidant Response Elements; AGE: Advanced Glycation Product; AMPK: Adenosine Monophosphate Active Kinase; ADHD: Attention Deficit Hyperactivity Disorder; BC: Bioactive Compounds; CRF: Corticotropin-Releasing Factor; DHA: Docosahexaenoic Acid; DMII: Type II Diabetes Mellitus; EPA: Eicosapentaenoic Acid; EC: Epicatechin; EGC: Epigaltochin; ECG: Epicatechin-3-Gallate; EGCG: Epigallocatechin-3-Gallate; GR: Glucocorticoid Receptor; IL-1β: Interleukin 1 Beta; IL-2: Interleukin 2; IL-6: Interleukin 6; IL-7: Interleukin 7; INF-y: Interferon Gamma; IkB: Ikappa B Kinase; IkB-α: Ikappa B Kinase Alpha; IkB-β: Ikappa B Kinase Beta; IkB-y: Ikappa B Kinase Gamma; IBD: Inflammatory Bowel Diseases; LPC: Lysophosphatidylcholine; LPS: Lipopolysaccharides; MCP1: Monocyte Chemotactic Protein; Nrf2: Nuclear Factor Related to Erythoid Factor Two; NF-kB: Nuclear Factor Kappa B; NCDs: Chonic Non-Communicable Diase; OCD: Obsessive-Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species; SAH: Systemic Arterial Hypertension; SFA: Saturated Fatty Acids; STAT: Signal Transducer and Activator of Transcription; STAT1: Signal Transducer and Activator of Transcription 1; SIRT: Sirtuin; SIRT1: Sirtuin 1; TNF-α: Tumor Necrosis Factor Alpha; VIGITEL: Department of Surveillance of Chronic Diseases by Telephone Survey; WHO: World Health Organization

Introduction

Gene expression occurs in two stages, transcription and translation that are regulated by transcriptional factors that increase or decrease the expression of a gene. Transcriptional factors bind the promoter region of the gene to attract and position ribonucleic

polymerase acid at the correct location for the beginning of transcription and subsequent cytoplasm translation by ribosomes [1,2].

The transcriptional factor NF-kB is responsible for the regulation of several biological processes, one of them is the induction of inflammatory processes that are related to the genesis of several NCDs, such as neoplasms, SAH, DMI, dyslipidemias, IBD, arthritis, neurological diseases, psychiatric diseases and respiratory diseases [3].

NCDs represent the main factor of premature death in the world according to a WHO report. The WHO report found that 70% of deaths worldwide are due to NCDs, about 38 million deaths annually, of which 16 million are premature and 28 million occur in [4].

In Brazil, according to VIGITEL 2021 survey, NCDs have been on the rise since 2006, generating a very high burden for the Union. In 2013 alone, 974,641 hospital admissions were performed, with a cost of R$1,848,627,410.03 [5,6].

Countries with dietary patterns rich in fruits, vegetables, vegetables, extra virgin olive oil, fish, oilseeds have been showing in epidemiological studies lower incidence of NCDs, these results have boosted in vitro and *in vivo* research on the gene-nutrient relationship [7-9].

The scientific literature has been relating the low consumption of BC present in food, as well as excessive consumption of calories and SFA with the genesis of NCDs, however the higher consumption of BC has shown the ability to modulate genes that encode proteins involved in NCDs [7-10].

Given the relationship of transcriptional factor NF-kB in the genesis of NCDs, as well as the high mortality rate related to such diseases, the present study aims to review BC and their dietary sources that inhibit the cascade of transcriptional factor NF-kB.

Materials and Methods

This is a systematic review conducted based on the following research question "Which BC act positively in the modulation of the transcription factor NF-kB? And by what mechanisms BC act in suppressing this transcriptional factor?" The selection of articles and writing of the review occurred between the years 2019 and 2022 and used as initial selection criteria publications of the post genomic era that verified the effects of bioactive compounds under the cell signaling cascade of NF-kB directly or indirectly.

The articles were selected through search in the *databases of the Scientific Electronic Library Online* (SciELO), *National Center for Biotechnology Information* (PuBMed) and the search site *Google Scholar* (G.S.). The following descriptors and their combinations in Portuguese and English were used: bioactive compounds, suppression of NF-kB, green tea, curcumin, resveratrol, gingerol, sulforaphanes, capsaicin, quercetin and omega III.

This review included *in vitro,* and *in vivo* trials published in Portuguese and English between 2000 and the end of 2022, which evaluated mechanisms for suppression of the transcription factor NF-kB and its impact on inflammation and obesity. After all eligibility criteria were established, 47 studies were selected that contemplate this review article.

Results and Discussion

Forty-three articles were selected, of which 26 are *in vitro* studies in cells of different tissues, 7 with *in vivo* assays with murine, 13 reviews of the scientific literature and 1 clinical trial discussing the effects of BC in the transcriptional factor NF-kB cascade.

The BC found were organized in topics demonstrating their mechanism of action in the NF-kB cascade and are presented briefly in table 1, located at the end of the results and discussions.

NF-kB and inflammation

Shoelson., *et al*. describe the transcriptional factor NF-kB being composed of a family of five subunits, NF-kB1/p105-p50 (NF-kB1 gene), NF-kB2/p100-p52 (NF-kB2 gene), RelA/p65 (RELA gene), RelB (RELB gene) and c-Rel (REL gene), which are responsible for regulating various biological processes. One of these processes is the induction of inflammatory processes by activating several genes that encode and later translate into pro-inflammatory cytokines, such as Interleukins (IL-1β, IL-2, IL-6, IL-7), TNF-α, IFN-y, among others, and this process is of paramount importance for life maintenance, however when activated unregulated is related to the genesis of NCDs [11].

Transcriptional factor NF-kB is sequestered in the cytoplasm by inhibitory proteins of the IkB family - (IkB-α, IkB-β and IkB-ϒ

– main NF-kB inhibitor proteins) - that prevent translocation to the cell nucleus of the transcriptional factor NF-kB, regulating inflammation processes. However inflammatory inducers such as ROS, LPS, AGE, SFA and the adipocytes' own cytokines trigger the action of the Enzyme IKK kinase that phosphoryl to IkB-α proteins, which is later ubiquitinated and degraded by the proteosome complex 26S, resulting in the release of NF-kB, allowing the translocation of the p65 subunit of NF-kB to the cell nucleus, triggering the inflammatory process [11].

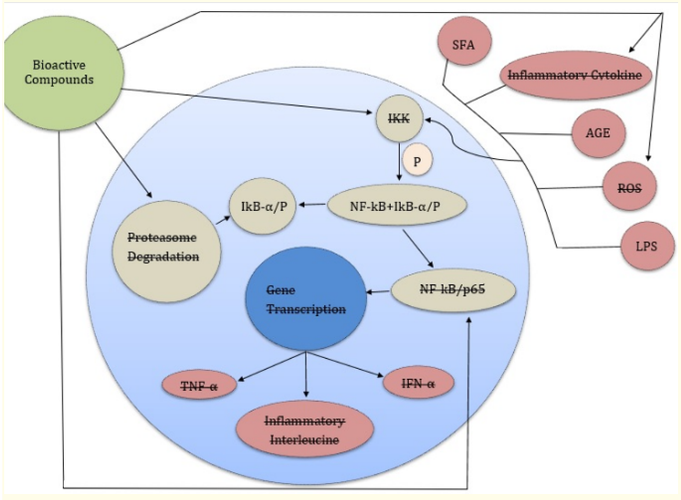

Figure 1: NF-kB suppression mechanism by BC. The NF-kB cascade is activated by inflammatory cytokines/LPS/SFA/AGE/ROS that activate IKK kinase responsible for phosphorylate the IkB-α inhibitor protein that is subsequently degraded by the proteasome, leaving nf-kB free for translocation to the cell nucleo. BC act in multiple ways, inhibiting inflammatory cytokines/ROS, inhibiting IKK kinase activity, inhibiting the translocation of the p65 unit to the cell nucleus and inhibiting the degradation of IkB-α protein by proteasome.

Source: Prepared by the authors, 2020.

Epigalocatekin-3-galate and NF-kB

Catechins, such as EC, EGC, ECG and EGCG, are BC found in black tea, white tea and green tea. However, EGCG, catechin with greater therapeutic potential, is found to be more abound in green tea, derived from *the plant Camellia sinensis (L.) Kuntze*, which has its use associated, according to scientific literature, with the reduction of cardiovascular diseases, cancers, hyperglycemia and reduction of body fat [12]. EGCG acts by inhibiting the activity of the Enzyme IKK kinase, in the signaling pathway of the transcription factor NF-kB, consequently there is no phosphorylation of the IkB-α protein, which is responsible for the suppression of NF-kB [3,13].

Mechanisms that Yang., *et al*. *in vitro* research shed light after stimulating cells with TNF-α treated with EGCG, were the suppression of NF-kB by inhibition of IKK kinase [14]. Jiang., *et al*. similarly demonstrated that foamy cells of macrophages exposed to TNF-α had the NF-kB cascade inhibited by EGCG [15]. Similar results occurred with Joo., *et al*. and Lagha and Grenier *in the exposure of macrophages in vitro to* LPS treated with EGCG, evidencing inhibition of the NF-kB cascade [16,17].

In a review study on EGCG and neurodegenerative diseases Payne., *et al*. found that BC would be able to inhibit phosphorylation of the IkB-α protein and suppress ROS that end up suppressing the signaling of transcription factor NF-kB acting preventively in this disease [18].

Curcumin and NF-kB

Curcumin, belonging to the curcuminoid family, is a phenolic acid found in turmeric and mustard, used for centuries in traditional Chinese medicine and Ayurveda to treat various disorders, such as: epigastric pain, flatulence, dysentery, ulcers, jaundice, arthritis, acnes, skin and ophthalmologic infections [19-21].

In the signaling pathway of the transcription factor NF-kB curcumin stabilizes the ROS due to its hydroxyl and methoxy group, besides preventing phosphorylation of the IkB-α protein by suppressing the IKK, inhibiting the activation of NF-kB [3,13].

The aforementioned mechanism was elucidated by Bachmeier., *et al*. *in vitro* research with mammary cancer cells of humans MDA-MB-23, in which the researchers reported the induction of apoptosis due to the suppression of transcriptional factor NF-kB by inhibition of phosphorylation of the IkB-α protein using curcumin [22]. A similar result was described in the study by Marquardt., *et al*. in Huh7 cells of hepatocellular carcinoma after three-day treatment with 3mcg of curcumin [23].

Other positive results were demonstrated by Kim., *et al*. after treating KBM-5 cells of chronic myeloid leukemia with different doses of curcumin and subsequently inducing the activation of NF-kB with TNF-α, the researchers found that NF-kB activation was suppressed proportionally with the dose of curcumin used [24]. Shakibaei., *et al*. after exposing human articular chondrocytes *in vitro* for 72h to IL-1β and TNF-α and subsequently treating them with curcumin, they found the suppression of NF-kB due to inhibition of phosphorylation of the IkB-α [25].

Fusar-Poli., *et al*. in a review of the use of curcumin in depression concluded that curcumin, suppressing NF-kB, was able to

significantly reduce depressive and anxious symptoms in populations of depressive patients with and without underlying clinical conditions [26]. Results that are supported in meta-analysis that included depressive patients [27] and were extended in Lopresti to other psychiatric pathologies such as PTSD, OCD, bipolar disorder, psychotic disorder and autism [28].

In a review about the use of medicinal plants in the treatment of endometriosis Meresma., *et al*. they verified that curcumin was able to inhibit the translocation of NF-kB in endometriotic lesions in murine [29].

Resveratrol and NF-kB

Resveratrol found in red wine, grapes, nuts, peanuts and cocoa is a phenolic compound of the stilbenoid class formed by two phenolic rings connected by a double bond, presenting in two isoforms: *Trans* and *Cis* [3,19,30].

Resveratrol has a great anti-inflammatory potential, antioxidant and antitumor and is related to the inhibition of NF-kB, through the super expression of SIRT1 that acts by deacetylating the p65 subunit of the NF-kB complex preventing the expression of inflammatory genes, besides acting preventing phosphorylation of the IkB-α protein and its degradation by proteosome 26S inhibiting the NF-kB pathway [31,32].

Ma., *et al*. verified the effect of resveratrol on the NF-kB cascade in an *in vitro* study with [33]. Gonzales and Orlando found that adipocytes that received TNF-α with 20mcg of resveratrol had the translocation of NF-kB and phosphorylation of the IkB-α protein [34].

Another *in vitro* study in H9C2 myoblastic cells conducted by Bagul., *et al*. found that the use of resveratrol increased the expression of SIRT1 which consequently deacetylated the p65 subunit preventing the expression of inflammatory genes [35].

In a systematic review on resveratrol Parsamanesh., *et al*. showed that it may decrease the production of MCP1 activated by TNF-α by suppressing NF-kB transcription in adipocytes. In the same study he suggested that the effects of LPC on enzymatic function, secretion of pro-inflammatory cytokines and expression of the p65 subunit were strongly diminished by resveratrol [36].

In a review study of resveratrol in psychiatric disorders Shayganfard found that inflammation is related to symptoms of these pathologies, but the use of resveratrol was able to suppress NF-kB and increase SIRT, improving the prognosis of these diseases [37]. One study concluded that it reverses the increase in adrenal gland index and CRF levels, and rescued the differential expression of GR in the hypothalamus, hippocampus and amygdala in murine with PTSD-like behavior [38] and can be considered an effective treatment for depression in animal models at doses between 10- 80 mg/kg/day, although higher doses have the most significant effects. In humans, it did not improve cognitive performance, but increased stamina with less fatigue and improved mood [39].

Gingerol and NF-kB

Ginger originates from East Asia, widely used in traditional medicine as an anti-inflammatory agent to treat pathologies such as arthritis, rheumatism, muscle, infections and hypertension, besides having an antiemetic [40-42]. Its pharmacological effects are related to Gingerol, its main BC, which acts on the classical IKK/IKB/NF-kB cascade by AMPK-activated kinase activation that increases SIRT expression by inhibiting nuclear translocation of NF-kB [43,44].

Fan., *et al*. verified the effects of gingerol on the NF-kB cascade in an *in vitro* study with MG63 cells similar to osteoblasts. In this study, inflammation was induced in cells with TNF-α and later treated them with gingerol, observing the inhibition of nuclear translocation of the p65 subunit of the NF-kB complex and consequent reduction of inflammatory proteins with the use of BC [45].

Hashem., *et al*. fed murine on a high-fat diet for eighteen weeks to induce obesity and a pro-inflammatory state verified by p65 and resistin levels, subsequently administered 200mg of ginger extract/kg body weight for two weeks and found that the p65 level reduced 85.91%, attributed by AMPK-SIRT activation by gingerol. The authors also verified the decrease in SFA and TNF-α, NF-kB inducers, by the same mechanism [46]. A murine study suggests that gingerol suppresses the super activation of astrocytes, through which it contributes to improved cognitive capacity [47].

In a systematic review study on the effects of ginger on cardiovascular diseases Roudsari., *et al*. reported that prior treatment with gingerol significantly decreases the production of NF-kB and cardiac caspase3 in cardiotoxicity induced by doxorubicin *in vivo* [48].

Sulforaphanes and NF-kB

Sulforaphanes are glucosinolates compounds and are related to decreased risk of NCDs due to their great anti-inflammatory and antitumor potential. Its main food sources are cruciferous vegetables, such as cabbage, cabbage, broccoli, cauliflower, arugula, chard, watercress, turnip, radish, mustard, among others [49].

These BC act indirectly and directly in the suppression of transcriptional factor NF-kB. Indirectly sulforaphanes induce Nrf2, which [50-52].

The aforementioned mechanism was verified by Bai., *et al*. in a study with diabetic murine. In this study, the use of 0.5mg/kg/day of sulforaphanes was able to inhibit diabetic cardiomyopathy due to Nrf2 activation, suppressing the inflammatory processes involved in the pathology [49]. Corroborating these findings, Negi., *et al*. verified that the same sulforaphane dosage used by Bay., *et al*. was able to improve murine diabetic neuropathy through the same activation mechanism of Nrf2 [53].

Another study conducted by Zhou., *et al*. found that the use of sulforaphane in murine induced to hepatic steatosis provided an increase in Nrf2 and consequent increase in ARE that suppressed ROS/NF-kB, showing significant improvement in the hepatic condition of the murine [54].

Yang., *et al*. worked with a lineage of retinal pigmented cells immortalized and pretreated with 5μM of sulforaphanes for 6 hours that were subsequently exposed to blue light, the researchers found that NF-kB had its nuclear translocation inhibited [55], was reported to prevent the progression of Alzheimer's disease, Parkinson's disease, cerebral ischemia, Huntington's disease, multiple sclerosis, epilepsy and psychiatric disorders by promoting neurogenesis or inhibiting oxidative stress and neuroinflammation [56].

Quercetin and NF-kB

Quercetin is a BC of the flavonoid class most commonly found in fruits, vegetables and vegetables with abundant amounts in onions, broccoli, cabbage, spinach, pears, apple, strawberries, grapes, blueberries, raspberries, cherries, blackberries and others. The great antioxidant and anti-inflammatory potential of quercetin present in foods is described in the literature [19].

In the signaling pathway of the transcription factor NF-kB, quercetin acts by suppressing NF-kB by inhibiting the phosphorylation of the IkB-α protein by IKK kinase, in addition to blocking the translocation of the p65 subunit to the cell nucleus [57].

In an *in vitro* study, Granado-Serrano., *et al*. treated HepG2 hepatoma cells with 50μM of quercetin and verified inactivation and lower binding capacity of NF-kB from 15 minutes of treatment remaining up to 18 hours, post quercetin [58]. The potential of quercetin was also verified by Zhang., *et al*. who verified lower binding capacity of NF-kB and phosphorylation of IkB-α protein after using quercetin in CACO-2/SW-620 colon cancer cells, suppressing NF-kB activation in cytochrome [59].

A study conducted by Youn., *et al*. found that quercetin increased the expression of genes encoding for IkB-α protein, which instill the activation of NF-kB, as well as suppress genes encoding for NF-kB itself and IKK kinase in H460 lung cancer [60].

Sul and Ra induced inflammatory process in A549 lung cells stimulated by LPS pretreated with quercetin and verified that this prevented the degradation of the IkB-α preventing the translocation of NF-kB [61].

In the nervous system it has been linked to lower astrocytes function in neurodegenerative and cerebrovascular diseases [62,63].

Capsaicin and NF-kB

Capsaicin, BC primarily found in red peppers, has great antitumor and anti-inflammatory potential, blocking phosphorylation of the IkB-α protein and the subsequent translocation of the p65 subunit to the cell nucleus [64,65].

The aforementioned mechanism was verified by Guo., *et al*. after treating squamous cell carcinomas of the esophagus with capsaicin and verifying the suppression of translocation from the p65 subunit to the cell nucleus, demonstrating its antitumor potential [66]. Lee., *et al*. presented similar results with HuCCT1 cholangiocarcinoma cells, also treated with capsaicin, in which, equally, NF-kB suppression was suppressed by the aforementioned mechanism [67].

In line with these findings, Shin., *et al*. after stimulating epithelial cells of the salivary glands with LPS and pre-treating them with 10mcg of capsaicin verified that BC inhibited phosphorylation of the IkB-α protein by suppressing NF-kB [68], demonstrating its great therapeutic potential in the NF-kB cascade.

Zhao., *et al*. pretreated a J-2 intestinal epithelium cell line with 100μM capsaicin and induced inflammatory process with LPS and found that NF-kB/p65 phosphorylation was moderately reduced compared to the control group, but significant with the group that only received LPS [69].

In a study that used the induction of beta-amyloid pathology in murine, mimetizing Alzheimer's disease, capsaicin was able to reduce the cascade of inflammatory events, phosphorylation of tau and beta-amyloid formation, reducing cognitive degradation related to these events [70].

Omega 3 and NF-kB

Omega 3 essential fatty acid, found primarily in oily fish, has anti-inflammatory, antioxidant and antitumor potential, suppressing genes related to NF-kB synthesis and increasing the expression of genes related to glutathione synthesis, inactivating the action of ROS that consequently activate the NF-kB cascade [3,71,72].

A study conducted by Zhao., *et al*. verified the reduction of translocation from the p65 subunit to the cell nucleus, as well as lower phosphorylation/degradation of IkB-α protein in monocytic THP-1 cells pretreated with EPA and subsequently stimulated by LPS [73]. Similarly, Ndoul., *et al*. after incubating for 24 hours THP1 macrophages, with 50 μM of omega 3, verified the suppression of genes related to NF-kB and the increase of genes related to glutathione, directly and indirectly suppressing NF-kB [71].

Ghosh-Choudhury., *et al*. verified inhibition of translocation from subunit p65 to the cell nucleus, as well as NF-kB inactivation in MDA-MB 231 breast carcinoma cells treated with omega 3, showing therapeutic potential in the NF-kB cascade [74].

Djuricic and Calder in their work to review omega 3 in human health evidenced the inhibition of phosphorylation of the IkB subunit preventing the cellular translocation of NF-kB [75].

Borsini., *et al*. verified that inflammatory process activated by NF-kB, decreases neurogenesis and increases cellular apoptosis, which affects the brain pathways in depression and its symptoms, however pretreatment with omega 3 metabolites (EPA derivatives - 5-hydroxyeicapentaenoic acid (dose: 3000 pg/μl); 18-hydroxyeicapentaenoic acid (dose: 8000 pg/μl) and 17(18)-epoxyeictetraenoic acid (dose: 0.08 pg/μl)/DHA derivative - 4-hydroxydocosahexaenoic acid (dose: 3000 pg/μl); 20-hydroxydocosahexaenoic acid (dose: 3000 pg/μl) and acid 19(20)-epoxyidocosapentaenoic acid (dose: 0.3 pg/μl)) in the progenitor cell line of the multipotent human hippocampus HPC0A07/03C prevented the increase of STAT1, NF-kB, IL6 and INF- y [76].

In the same study, the researchers evaluated the effects of omega 3 in 22 patients with major depressive disorder treating them with EPA acid (dose: 3.0 g/day) or DHA (dose: 1.4 g/day) for 12 weeks and found an increase in the metabolites mentioned above in the plasma of patients. These indices had an inverse correlation with those obtained in the Hamilton Depression Scale [76]. Results corroborated by the findings of the study by Liao., *et al*. showing improvement of depressive symptoms with treatment [77], and also, in ADHD it was possible to observe improvement of attention and general cognitive performance with the use of Omega-3 [78].

Conclusion

The present study allows to highlight the activity of BC on the NF-kB cascade, inhibiting through multiple mechanisms, such as: inhibition of IKK kinase, inhibition of phosphorylation/degradation of IkB-α protein, translocation of the p65 subunit to the cell nucleus and reduction of NF-kB activating ROS in *in vitro and* in vivo models in murine. As well, they highlight the preventive and therapeutic potential, low cost for populations at risk around the world, as therapeutic alternatives with low incidence of adverse effects for clinical and neuropsychiatric NCDs.

Bioactive Compound	Source	NFkB Supression Mechanism	Authors/Year/ Study
EGCG	Green tea (*camelia sinensis).*	IKK kinase inhibition Phosphorilation/degradation of quinase IkB-α inhibition ROS inhibition	Yang., *et al.*/2001/*in vitro* Jiang *et al.*/ 2012/*in vitro* Joo., *et al.*/2012/*in vitro* Lagha e Grenier/2016/*in vitro* Payne., *et al.*/2021/review
Curcumin	Tumeric Mustard	Kinase IKK inhibition ROS stabilization by hydroxil and metoxil groups donation NF-kB translocation	Bachmeier., *et al.*/2007/*in vitro* Shakibaei *et al.*/ 2007/*in vitro* Kim *et al.*/ 2012/*in vitro* Marquardt., *et al.*/2015/*in vitro* Al-Karawi *et al*/ 2016/clinical trial Lopresti/2017/review Fusar-Poli., *et al.*/2019/review Meresma *et al.*/ 2021/review
Resveratrol	Red wine Grapes Nuts Peanuts Cocoa	Phosphorilation/degradation of quinase IkB-α inhibition Inhibition of subunidade p65 translocation to the cellular nucleus	Gonzales e Orlando/2008/*in vitro* Ma., *et al.*/2015/*in vitro* Bagul., *et al.*/2015/*in vitro* Li., *et al.*/2018/*in vivo* Farzaei., *et al.*/2018/review Shayganfard/2020/review Parsamashe., *et al.*/2021/review
Gingerol	Ginger	Inhibition of subunity p65 translocation to the cellular nucleus	Fan., *et al.*/2015/*in vitro* Hashem., *et al.*/2017/*in vivo* Zhang., *et al.*/2018/*in vivo* Roudsari., *et al.*/2021/review
Sulfora-phanes	Cruciferous vegetables	ROS inhibition by Nrf2 activation Phosphorilation/degradation of quinase IkB-α inhibition NF-kB nuclear translocation inhibition	Negi., *et al.*/2011/*in vivo* Bay., *et al.*/2013/*in vivo* Zhou., *et al.*/2014/*in vivo* Huang/2019/review Yang., *et al.*/2021/*in vitro*
Quercetin	Berries Broccoli Onions Cherries Cabbages Raspberries Apples Blueberries Strawberries Pears Grapes	Kinase IKK inhibition Inhibition of subunity p65 translocation to the cellular nucleus Phosphorilation/degradation of quinase IkB-α inhibition	Granado-Serrano., *et al.*/2010/*in vitro* Youn., *et al.*/2013/*in vitro* Zhang., *et al.*/2015/*in vitro* Dajas., *et al.*/2015/review Sul e Ra/2021/*in vitro* Han/2021/*in vitro*

Capsaicin	Red peppers	Phosforilation/degradation of kinase IkB-α inhibition Inhibition of subunity p65 translocation to the cellular nucleus	Shin., *et al.*/2013/*in vitro* Lee., *et al.*/2014/*in vitro* Gou., *et al.*/2019/*in vitro* Wang *et al*/2020/*in vivo* Zhao., *et al.*/2021/*in vitro*
Omega III	Fat rich fishes	Supressing genes related to NFkB Activating genes related to glutathione, supressing ROS formation. Phosforilation/degradation of kinase IkB-α inhibition	Zhao., *et al.*/2004/*in vitro* Ghosh., *et al.*/2009/*in vitro* Ndou *et al.*/ 2016/*in vitro* Chang., *et al.*/2017/review Lial., *et al.*/2019/review Borsini., *et al.*/2021/*in vitro* Djuricic e Calder/2021/review

Table 1: Summary of the articles researched.

Conflict of Interest

The authors declare that there is no conflict of interests.

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