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The effects of phytochemicals and herbal bio-active compounds on tumour necrosis factor-α in overweight and obese individuals: a clinical review

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Abstract

Obesity is abnormal fat accumulation in the body which acts as a risk factor for various cardiometabolic states. Adipose tissue in excess can release inflammatory factors, including TNF-α and IL-6, and suppress adiponectin production. TNF-α increases the levels of IL-6 and acute phase reactants such as C-reactive protein (CRP). Inflammation has a crucial role in developing and progressing various cardiometabolic diseases and a wide range of obesity-related complications. It has been shown that TNF-α has a significant role in the development of insulin resistance. Recently, a growing body of evidence has focused on herbal medicine, phytochemicals and natural bioactive compounds as inexpensive, relatively easy accessible agents with low adverse effects to reduce inflammatory markers such as TNF-α and simultaneously decrease insulin resistance, glucose intolerance, and dyslipidemia in obesity. The main focus of the current review is to summarize the results of the studies, which assessed the effects of phytochemicals and herbal bio-active compounds on serum TNF-α in subjects with overweight or obesity. This review suggests that herbal medicine have favorable effects on the reduction of TNF-α concentration; however, the results were not uniform for different products. Among the reviewed plants, ginger, ginseng, resveratrol, and flaxseed had more promising effects.

Keywords: Herbal medicine; phytochemicals; Inflammation; Obesity; tumour necrosis factor α; TNF-α

Abbreviations: TNF-α: tumour necrosis factor α, IL: and interleukin, CRP: C reactive protein, NF-κB: nuclear factor kappa light chain enhancer of activated B cells, CVDs: cardiovascular diseases, NAFLD: non-alcoholic fatty liver diseases, IFNγ: Interferon-gamma, MCP-1: monocyte chemoattractant protein-1, TLR4: toll-like receptor 4, IRF: interferon-regulatory factor, CAPE: caffeic acid phenethyl ester, NO: nitric oxide, BMI: body mass index:

BMI, iNOS: nitric oxide synthesis, CNS: central nervous system, COX: cyclooxygenase, NC: nano-curcumin, ALA: α-linolenic acid, CHD: coronary heart diseases, AGE: aged garlic extract, CAD: coronary artery disease, KRG: Korean red ginseng, GSO: grape seed oil, MCI: mild cognitive impairment, EGCG: epigallocatechin gallate, PCOS: polycystic ovary syndrome.

Obesity and inflammation

Obesity is the abnormal fat accumulation that acts as a risk factor for various diseases (Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017; Karczewski et al., 2018). Adipose tissue is stimulated by extra macronutrients and release various inflammatory agents such as tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6), as well as suppress adiponectin production, predisposing to oxidative stress and inflammation. TNF-α increases the level of IL-6. Enhancement in IL-6 results in the stimulation of the liver to increase acute-phase proteins synthesis and secretion such as C-reactive protein (CRP), fibrinogen, serum amyloid A, and α1-antichymotrypsin (Figure 1) (Ellulu et al., 2017; Karczewski et al., 2018; Tanaka, Narazaki, & Kishimoto, 2014). It has also been shown that IL-6 might increase free fatty acids (Popko et al., 2010). It is confirmed that inflammation has a substantial role as a risk factor in developing and progression of cardiovascular diseases (CVDs) such as coagulation, atherosclerosis, insulin resistance, hypertension, metabolic syndrome, type 2 diabetes and non-alcoholic fatty liver diseases (NAFLD)(Ellulu et al., 2017; Karczewski et al., 2018). Inflammation could also contribute to the development and progression of non-cardiovascular diseases, including psoriasis, rheumatoid arthritis, psychological disorders such as anxiety and depression, asthma, neurodegenerative diseases, cancer, and renal diseases (Ellulu et al., 2017). Chronic systemic inflammation and immune system activation are considered the main factors associated with developing and progressing these pathologies related to obesity (Ellulu et al., 2017; Shoelson, Herrero, & Naaz, 2007). It has been shown that glucose and fat consumption cause a significant increase in the inflammatory factors by increasing oxidative stress and transcription factors, including nuclear factor (NF-κB), activating protein-1, and early growth response-1 (Shoelson et al., 2007). On the other hand, calorie restriction, fasting or reduction in macronutrient intakes

results in a significant decrease in oxidative stress and inflammatory markers (Shoelson et al., 2007). Reduction of inflammatory markers in obese individuals can decrease the risks of CVDs and poor outcomes mediated by obesity-related inflammation (Ellulu et al., 2017; Karczewski et al., 2018).

Obesity, Immune function, TNF-α, free fatty acids and insulin resistance

During obesity, in adipose tissue or liver, macrophage infiltration causes chronic systemic inflammation resulting in the activation of immune cells. Macrophages are classified into two kinds; (i) classically activated (M1) macrophages that are related to microbicidal activity, (ii) alternatively activated (M2) macrophages that are related to antiparasitic and allergic responses (Tateya, Kim, & Tamori, 2013). M2 macrophages have a role in IL-4 and IL-10 secretion, which is associated with insulin sensitivity; however, proinflammatory cytokines are secreted through M1 macrophages causes insulin resistance (Figure 2) (Tateya et al., 2013). M2 macrophages are activated in a lean state by Treg cells, TH2 cells, natural killer T cells, or eosinophils through the secretion of IL-4 or IL-10. Conversely, neutrophils or mast cells, TH1 cells, and B cells play a significant role in inducing M1 macrophages activation in the obese state by the elevated levels of TNF-α and interferon-gamma (IFNγ). Hypertrophied adipocytes increase the section of TNF-α and free fatty acids, which lead to the activation of M1 macrophages. Insulin resistance in obesity through the infiltration of macrophage and the activation of the immune cells is well established, and the role of TNF-α in this pathway is well-known. During the progression of obesity, TNF-α expression is increased in adipose tissue, although attenuation of insulin resistance is occurred in the TNF-α deactivation (Gokhan S Hotamisligil, Shargill, & Spiegelman, 1993). It has also been shown that TNF-α inhibits insulin receptor tyrosine kinase

activity, which leads to suppression of insulin signaling (Gökhan S Hotamisligil et al., 1996). Thus, it can be hypothesised that increases in the TNF-α concentration in adipose tissue, which defined as inflammation, is the foundation of systemic insulin resistance (Tateya et al., 2013). The infiltration of macrophages primarily produces TNF-α into the adipose tissue. TNF-α is the major pro-inflammatory cytokine, and as an adipokine activates proinflammatory signal cascades (Gokhan S Hotamisligil et al., 1993; Uysal, Wiesbrock, Marino, & Hotamisligil, 1997). Likewise, TNF-α inhibits the signalling of the insulin receptor; altogether, it seems that this molecule is a primary mediator between adipose tissue inflammation and insulin resistance (Weisberg et al., 2003; H. Xu et al., 2003). Moreover, free fatty acids are typically raised in obesity since pro-inflammatory cytokine TNF- causes an increase in lipolysis in the adipose tissue (Tateya et al., 2013). These free fatty acids serve as ligands for the toll-like receptor 4 (TLR4) complex, which is necessary for innate immune cells for intruding pathogens recognition and triggering a suitable immune response (Shi et al., 2006). Free fatty acid-induced TLR4 signaling activated by FFA causes activation of M1 through the transcriptional factors, including AP1, NF-κB, and interferon-regulatory factor (IRF) family members (Poltorak et al., 1998; Shi et al., 2006). Activation of the above transcriptional factors drives M1 activation, which all occurs by TNF-α (Tateya et al., 2013).

Reduction of TNF-α, why phytochemicals?

Lifestyle modification, mainly focusing on a healthy diet and physical activity, is considered a first-line strategy to prevent and treat obesity, resulting in reduced inflammatory factors. However, several challenges and poor adherence to this approach resulted in a lack of effectiveness of this therapy (Bagherniya, Nobili, Blesso, & Sahebkar, 2018). Another option is

anti-inflammatory drugs which are the specific agents for reduction of TNF-α are not wholly acceptable due to several limitations such as their side effects (Antoni & Braun, 2002; Rainsford, 2007; Scheinfeld, 2004; Tateya et al., 2013; Vane & Botting, 2003). Thus, future studies are warranted to find an appropriate pharmacotherapy. Meanwhile, recently, a growing body of evidence focusing on herbal medicine, phytochemicals and natural bioactive compounds as inexpensive, readily available and accessible agents with low amounts of adverse effects to reduce inflammatory markers such as TNF-α and simultaneously decrease insulin resistance, glucose intolerance, as well as reduction of unfavorable blood lipids and apolipoproteins (Alikiaii, Bagherniya, Askari, Johnston, & Sahebkar, 2021; Alikiaii, Bagherniya, Askari, Sathyapalan, & Sahebkar, 2020; Bagherniya, Johnston, & Sahebkar, 2020; Das & Das, 2007; Ghasemian, Owlia, & Owlia, 2016; He et al., 2015; Li et al., 2016; Mahdavi et al., 2020; Talebi et al., 2020; Zareie et al., 2020). In addition, herbal medicine is being recognized as an alternative therapy for the prevention and treatment of non-communicable diseases including, hypertension (M. Houston, 2014; M. C. Houston, 2005, 2010), diabetes mellitus (Bahadoran, Mirmiran, & Azizi, 2013; Davì, Santilli, & Patrono, 2010; McCarty, 2005), NAFLD (Bagherniya et al., 2018), and CVD (Alissa & Ferns, 2012; Badimon, Vilahur, & Padro, 2010; Ramaa, Shirode, Mundada, & Kadam, 2006; Zuchi, Ambrosio, Lüscher, & Landmesser, 2010). In most of this evidence related to obesity, inflammation reduction was considered the primary mechanism mediating the beneficial effects of medicinal plants on non-communicable diseases. It seems that these natural products have favorable effects on inflammatory markers, particularly TNF-α, among overweight and obese individuals. The main aim of the current review is to summarize the results of the previous studies, in which the effects of phytochemicals and herbal

bio-active compounds on serum TNF-α among subjects who at baseline had a mean BMI of above 25 (kg/m^2) (Table 1.).

The potential mechanisms of the effectiveness of herbal bio-active compounds on inflammatory markers and their relation to obesity-related diseases are shown in figure 3.

Propolis

Propolis or bee glue is a resinous mixture produced by honey bees from diverse plants. This product is a mixture of phenols such as aromatic compounds, flavonoid, and polyphenols (Silva-Carvalho, Baltazar, & Almeida-Aguiar, 2015). Propolis has considerable beneficial effects on different conditions, including diabetes mellitus, NAFLD, atherosclerosis, oral and dental diseases, dermatological problems, allergies, gastrointestinal disorders, gynecological and neurological diseases (Farooqui & Farooqui, 2012; Pasupuleti, Sammugam, Ramesh, & Gan, 2017). Propolis with phenolic acid and flavonoid compounds has unique antioxidant activities (Kurek-Górecka et al., 2014). Moreover, propolis is popular for its immune-modulatory and anti-inflammatory effects (Borrelli et al., 2002; Ramos & Miranda, 2007). Among the very diverse constituents of the propolis, it is proposed that quercetin, caffeic acid, naringenin, and caffeic acid phenethyl ester (CAPE) are the main ingredients with anti-inflammatory properties (Mirzoeva & Calder, 1996; Ramos & Miranda, 2007). These compounds of propolis suppressed the synthesis of prostaglandins and leukotrienes in macrophages. Likewise, ornithine decarboxylase myeloperoxidase activity, tyrosine-protein-kinase and NADPH-oxidase effects were inhibited by these constituents of propolis (Miyataka et al., 1997; Ramos & Miranda, 2007). Other ingredients of propolis, such as ferulic acid, salicylic acid, galangin, and apigenin also considered as ingredients with anti-inflammatory properties (Krol et al., 1996). Propolis also inhibits nitric oxide (NO) production by macrophages which is another mechanism showing the

anti-inflammatory activity of propolis (Ramos & Miranda, 2007). A recent meta-analysis indicated that propolis supplementation significantly reduced IL-6, CRP and TNF-α levels (Jalali, Ranjbar, et al., 2020; Shang et al., 2020). In a study, overweight and obese patients with breast cancer received 250 mg propolis/ twice per day or a placebo for 3 months while being treated with chemotherapy. Results indicated that in the placebo group, serum TNF-α significantly increased, whereas, in the propolis group, there were no significant changes (Darvishi et al., 2020). In another study, 80 patients with type 2 diabetes received Brazilian green propolis 226.8 mg/day or placebo. After 8 weeks, there were no significant changes in TNF-α in the study groups (Fukuda et al., 2015). In another study conducted on patients with type 2 diabetes, Chinese propolis (900 mg/day) was used for 18 weeks, in which, at the end of the study, there were no significant differences in TNF-α between groups (Gao et al., 2018). In another study, 100 patients with type 2 diabetes randomized to receive 1000mg/day of Iranian propolis or placebo for 90 days, in which serum TNF-α significantly decreased in the propolis group compared with the placebo group (Zakerkish, Jenabi, Zaeemzadeh, Hemmati, & Neisi, 2019).

Ginger

Ginger, a member of the Zingiberaceae family, consists of several components, including gingerol, zingerone, shogaol, paradols, and β-bisabolene. This plant is used as a spice in both foods and beverages in Asian countries for thousands of years (Sahebkar, 2011; Singletary, 2010). This herb exhibits several unique beneficial effects on human health, such as its antioxidant, anti-inflammation, antimicrobial, antihypertensive, antidiabetic, cardioprotective, anticancer, chemopreventive, and gastroprotective (Ali, Blunden, Tanira, & Nemmar, 2008; Baliga et al., 2011). It is declared that most of these beneficial effects attributed to the ginger

inflammatory responses, which might be mediated through inhibition of the activity of cyclooxygenase- 1 (COX-1) and cyclooxygenase-2 (COX-2) resulted in prostaglandin synthesis suppression. In addition, the interleukins and TNF-α production in activated macrophages could be blocked by ginger (Grzanna, Lindmark, & Frondoza, 2005; Liguori et al., 2018; Thomson et al., 2002). In a recent meta-analysis, which evaluated the effects of ginger on inflammatory markers based on clinical trials, it has been shown that in comparison to the control group, ginger consumption had a significant effect on the reduction of serum CRP, IL-6 and TNF-α (Jalali, Mahmoodi, et al., 2020). In a recent RCT, results indicated that supplementation with 1.5-gram ginger/day for 12 weeks in overweight and obese patients with active rheumatoid arthritis had no significant effects on TNF-α level compared with placebo (Aryaeian et al., 2019). In another recent RCT, patients with type 2 diabetes with chronic periodontitis were asked to consume 2 grams of ginger/day or a placebo for 8 weeks. There was a significant reduction of TNF-α in the intervention group compared with placebo (Javid et al., 2019). In another study, NAFLD patients supplemented with daily 1.5 gram of ginger after 12 weeks; serum TNF-α did not change significantly compared with control patients (Rafie, Hosseini, Hajiani, Malehi, & Mard, 2020). In a previous clinical trial study, 46 obese women with diabetes were divided into four groups, including (ginger, aerobic exercise training with ginger, aerobic exercise training) to receive 1000 mg/day of ginger extract for 10 weeks. At the end of the study, no significant differences were observed on the TNF-α level in the four groups (Asadi, Banitalebi, Esfadir, & Ghafari, 2017). In an earlier study, patients with osteoarthritis received 1 gram of ginger for 3 months, in which TNF-α was significantly reduced compared with the control group (Mozaffari-Khosravi, Naderi, Dehghan, Nadjarzadeh, & Fallah Huseini, 2016).

Cinnamon

Cinnamon has been used since time immemorial as a food spice and flavoring with known medicinal properties in both traditional and modern science. Promising health benefits of cinnamon such as antioxidant, anti-inflammatory and insulin-sensitizing characteristics made it one the most popular herbs for prevention and treatment of the various pathologies (Bagherniya et al., 2018). It is asserted that cinnamon has antimicrobial, antioxidant, anti-inflammatory, antidiabetic and cardiovascular disease lowering properties (Gruenwald, Freder, & Armbruester, 2010; Rao & Gan, 2014; Sadeghi et al., 2019). In addition, its beneficial effects on some neurological diseases (Rao & Gan, 2014; Zareie et al., 2020). It shows that cinnamon with several flavonoids might have an inhibitory role in nitric oxide production through suppression of NF-*K*b activation, which mediated its anti-inflammatory effects on cinnamon (S. H. Lee et al., 2005; Rao & Gan, 2014). In addition, it may reduce the activation of Src/spleen-tyrosine-kinase-(Src/Syk-) mediated NF-*κ*B (Rao & Gan, 2014; Youn et al., 2008; Yu et al., 2012). Suppression of the production of inducible nitric oxide synthesis (iNOS), COX-2, and nitric oxide in the central nervous system (CNS) might be another pathway of anti-inflammatory effects of cinnamon (Hwang et al., 2009; Rao & Gan, 2014). A recent study using 3 grams (3*1 gram) of cinnamon for 8 weeks among patients with type 2 diabetes mellitus had no substantial effects on serum TNF-α compared with placebo (Davari et al., 2020). In another RCT, women with rheumatoid arthritis were asked to consume 2 grams (4*500 mg) of cinnamon/day for 8 weeks. There was no significant reduction in serum TNF-α with cinnamon consumption compared with placebo (Shishehbor, Rezaeyan Safar, Rajaei, & Haghighizadeh, 2018).

Quercetin

Quercetin, a plant flavonoid that is found in a wide range of plants, fruits and vegetables. It has been shown that quercetin has beneficial effects on cardiovascular health, cancers, diabetes, eye

disorders, allergic diseases, arthritis, neurological diseases, and many other diseases (Elumalai & Lakshmi, 2016; Lakhanpal & Rai, 2007; Patel et al., 2018). It is revealed that quercetin has substantial antioxidant properties (Alrawaiq & Abdullah, 2014; M. Zhang et al., 2011). Preclinical studies have shown that the production of COX and lipoxygenase, which regularly cause inflammation induction, was inhibited by quercetin (Shuang Chen, Jiang, Wu, & Fang, 2016; K. M. Lee, Hwang, Lee, Lee, & Lee, 2010). In addition, quercetin dramatically inhibited proinflammatory cytokines in cultured fibroblasts (Shuang Chen et al., 2016; Yoon, Chae, Lee, & Lee, 2012). Likewise, COX-2 and the nitric oxide and NF-κB production were suppressed by quercetin (Ramyaa & Padma, 2014). Moreover, it is shown that quercetin suppresses the secretion of TNF-α and IL-6 in LPS-stimulated macrophages (Mueller, Hobiger, & Jungbauer, 2010). A recent meta-analysis showed that in comparison to the control group, quercetin consumption had no significant effect on CRP, IL-6, and TNF-α, which included 6, 5 and 4 clinical trials, respectively (Ou, Zheng, Zhao, & Lin, 2020). In a previous crossover trial, 93 overweight or obese subjects with metabolic syndrome traits were asked to consume 150 mg quercetin/d for 6 weeks, in which serum TNF-α did not significantly change (Egert et al., 2009). In another study, 500 mg quercetin/da, and 1000 mg quercetin/day for 12 weeks had no effects on TNF-α concentration on healthy female subjects (Heinz, Henson, Nieman, Austin, & Jin, 2010). In another study, supplementation of 500mg/day of quercetin on post-myocardial infarction patients for 8 weeks showed a significant reduction of TNF-α level in the treatment group but not significantly different from the control group (F. Dehghani et al., 2020).

Curcumin

Curcumin is a bioactive compound of turmeric. Besides curcumin's various health benefits, widespread molecular targets have been shown to interact with curcumin (Esatbeyoglu et al.,

2012; A. Mohammadi et al., 2013; Panahi et al., 2012). The anti-inflammatory effects of curcumin are well recognized attributable to its effects on the activity of COX-2, lipoxygenase, and inducible nitric oxide synthase iNOS enzymes and inhibition of inflammatory cytokines (Goel, Kunnumakkara, & Aggarwal, 2008). In one study, 37 obese patients were recruited, and each of them received curcuminoids (1 g/day) or placebo and then crossed over. Each treatment period was 30 days with a 2-week wash-out interval. They found that serum levels TNFα did not alter (Ganjali et al., 2014). In another double-blind, randomized placebo-controlled trial, 84 overweight/obese patients with NAFLD diagnosed were randomized into two equal groups to receive either two 40-mg capsules of nano-curcumin (NC) per day or placebo for 3 months. Results showed that in both NC and placebo groups, the mean difference of TNF-α decreased (Jazayeri-Tehrani et al., 2019). Also, Saadati and colleagues investigated the effects of either 1500 mg curcumin or placebo on 50 overweight/obese patients with NAFLD for 12 weeks in a randomized, double-blind trial. They found that TNF-α significantly reduced in both groups at the end of the study, but there was no significant difference between them (Saadati et al., 2019). Abdolahi et al. conducted a double-blind, randomized placebo-controlled trial on 74 overweight patients with episodic migraine. They were divided into 4 groups; (a) the group treated with 2500 mg ω-3 fatty acids and 80 mg nano-curcumin supplementation, (b) the group treated with 2500 mg ω-3 fatty acid supplementation, (c) the group treated with 80 mg nano-curcumin supplementation, and (d) the control group. After 2 months of intervention, they observed a significant reduction in the serum levels of TNF-α in the combination group, but no significant changes in other groups were observed (Abdolahi et al., 2017). In a randomized, double-blind placebo-control clinical trial,l 40 overweight/obese subjects with knee Osteoarthritis were allocated randomly to receive either 1 500 mg/day pure curcuminoids or a placebo for six

weeks. At the end of the study, there were no significant differences in TNF-α levels between the two groups (Rahimnia, Panahi, Alishiri, Sharafi, & Sahebkar, 2015).

Garlic

For several thousand years BC, Garlic (Allium sativum) has been used for medicinal purposes. The beneficial effects of garlic are due to its more than 2000 active ingredients that work synergistically. The most important compounds are different enzymes, including alliinase, sulphur-containing substances, such as diallyl sulfide and alliin, and enzyme products, such as ajoenes and allicin (Majewski, 2014). The fructose-containing carbohydrates, sulfur compounds, free amino acids, protein and fibre, constitute the bulk of garlic's dry weight, and water is the major part of garlic (65%) (Rola, Dietoprofilaktyce, & Dietoterapii, 2007). It also comprises high phosphorus levels, saponins, zinc, potassium, sulfur, moderate levels of selenium and Vitamins A and C, and low levels of sodium, calcium, manganese, magnesium, iron, and B-complex vitamins. The phenolic content is also high in garlic. A high concentration of garlic inhibits cytokine production in endothelial cells (Sharifi, Sheikhi, Behdad, & Mousavinasab, 2010). The role of garlic in reducing the risk of cardiovascular disease and other inflammatory disorders have been confirmed in several studies. Evidence for the efficacy of the active components of garlic (e.g. diallyl sulfide) in lessening inflammatory factors, include IL-1β induced COX-2 upregulation, have been provided in cell culture studies (S. Dehghani et al., 2018). In a randomized, placebo-controlled clinical trial, 80 post-menopausal overweight and obese women with mild to moderate knee osteoarthritis were given either garlic (1000 mg tab twice daily), or placebo tabs, for 12 weeks. After 12 weeks, no significant changes in TNF-α concentration were observed within or between the two groups (S. Dehghani et al., 2018). In another randomized placebo-controlled trial conducted by Sharifi et al., 50 women, including

40 cases with metabolic syndrome and ten normal female controls, were recruited. They were randomly allocated to two parallel treatment groups and received either garlic tablets (1.8 g/day; two 300 mg garlic tablets three times per day), or a placebo for six weeks. At the end of the study, serum TNF α did not change in the study groups (Sharifi et al., 2010). Van Doorn and colleagues investigated the effects of garlic powder on 90 overweight and smoker subjects. Patients were randomized into three parallel groups to receive 2.1 g/d garlic powder, 40 mg/d atorvastatin or placebo. After three months of intervention, none of the variables, including TNF-α, showed significant differences between the garlic-treated and placebo groups (van Doorn et al., 2006). Also, Xu et al. conducted another study on 51 healthy obese individuals to investigate the effect of 3.6 g/d doses of aged garlic extract (AGE) or placebo on inflammation biomarkers and immune function after 6 weeks of supplementation. At post-intervention serum TNF-α in participants supplemented with AGE were significantly lower than those with placebo capsules (C. Xu et al., 2018).

Flaxseed

The properties of flaxseed as a functional food is attributed to its components α-linolenic acid (ALA), soluble and insoluble fibres such as lignans with antioxidant and estrogen-like properties (Bloedon et al., 2008; Goyal, Sharma, Upadhyay, Gill, & Sihag, 2014). Because flaxseed is a rich source of ALA, it is known for its beneficial effects on cardiovascular diseases (e.g., atherosclerosis), diabetes, metabolic syndrome, and dyslipidemia (Brant, Cardozo, Velarde, & Boaventura, 2012; Fukumitsu, Aida, Shimizu, & Toyoda, 2010; Goyal et al., 2014; Hutchins et al., 2013; Pan, Yu, Demark-Wahnefried, Franco, & Lin, 2009). Flaxseed oil, flaxseed lignan, or flaxseed supplementation markedly reduced serum TNF-α, CRP, IL-6, IL-1 β, glycosylated haemoglobin concentrations as well as increased insulin sensitivity in humans (Caughey,

Mantzioris, Gibson, Cleland, & James, 1996; Hallund, Tetens, Bügel, Tholstrup, & Bruun, 2008; Paschos et al., 2005; W. Zhang et al., 2008). In a prospective, single-blinded 42 days study, 27 overweight/obese men with cardiovascular risk factors were assigned to two groups with either low carbohydrates intake and 60g of flaxseed powder per day or low carbohydrates intake and 60g of raw rice powder per day. At the end of the study, levels of TNF-α were reduced only in the flaxseed intake group (Cassani, Fassini, Silvah, Lima, & Marchini, 2015). In a randomized, double-blind, placebo-controlled trial with 60 overweight patients with diabetes and CHD, the participants were randomized into two groups to intake either 1000 mg flaxseed oil supplement or placebo twice a day for 12 weeks. Results showed that flaxseed oil supplementation down-regulated TNF-α in patients with diabetes and CHD (Hashemzadeh et al., 2017). Paschos et al. conducted a single-blind, parallel design intervention on 35 overweight, nondiabetic, dyslipidemic men. Participants were allocated into two groups to receive either 15 ml of flaxseed oil rich in ALA or 15 ml of safflower oil per day for 12 weeks. They found no changes in plasma TNF-α in the flaxseed oil versus the control group (Paschos et al., 2007). In another study, 44 patients with coronary artery disease were randomized to 12 weeks consumption of flaxseed (30 g/day) or usual care as control. A significant reduction in plasma TNF-α was observed in the flaxseed consumption group at post-intervention compared with the control (Khandouzi, Zahedmehr, Mohammadzadeh, Sanati, & Nasrollahzadeh, 2019). Rhee and colleagues investigated the effects of 40 g/day ground flaxseed compared with wheat bran as a placebo on inflammatory biomarkers, using a randomized crossover design for 12 weeks with a 4-week washout period on 9 obese glucose intolerant participants. They found no changes in plasma TNF-α at the end of the study (Rhee & Brunt, 2011). In a single-blind clinical study, 75 overweight adolescents were divided into 3 groups to take 28 gram/day of brown flaxseed,

golden flaxseed or control in different preparations at school from Monday to Friday for eleven weeks. Although all groups showed increased levels of TNF-a, groups did not differ significantly on the values of TNF-α (Machado, de Paula, Cardoso, & Costa, 2015). In another randomized controlled study, 50 overweight and obese adults randomized to take lifestyle advice or lifestyle advice plus 30g milled flaxseed every day for 12 weeks. They investigated that in both groups (flaxseed and control), TNF-α decreased significantly but decreasing was higher in the flaxseed group (Yari, Rahimlou, & Hekmatdoost, 2019).

Ginseng

Panax ginseng Meyer root has been regularly utilized in East Asia for about 2000 years (Heo et al., 2016; M. Hong et al., 2016). Ginsenoside Rb1 is the most plentiful ginsenoside in ginseng that inhibits gene expression, encoding lipogenesis-inducing enzymes in rats diagnosed with fatty liver disease. Numerous studies have shown that ginseng might positively affect diabetes, stress, inflammatory, or hyperlipidemia (Bang et al., 2014; Heo et al., 2016; M. Hong et al., 2016; Jeong et al., 2018). Several ingredients in ginseng have anti-inflammatory effects (Im, 2020; Ratan et al., 2020). In M1-polarized macrophages and microglia, pro-inflammatory cytokine and enzyme expressions were inhibited, demonstrating the anti-inflammatory mechanism of ginsenosides (Im, 2020; Xue et al., 2020). Ginsenoside inhibited the expression of TNF-α, IL-1 and overcame TANK-binding kinase 1/IκB kinase ε/interferon regulative factor-3 and p38/ATF-2 signaling (Huang et al., 2021; Im, 2020). A previous meta-analysis, which analyzed the findings of 7 clinical trials, indicated that ginseng consumption resulted in a significant reduction in serum TNF-α (H. Mohammadi et al., 2019). In one clinical trial study, 35 patients with NAFLD were asked to take Korean red ginseng (KRG) (ginsenosides Rg1 + Rb1 6.0 mg/g; 3,000 mg/d) (intervention group), and 31 patients received placebo, and both groups

were on healthy eating with regular exercise for three weeks. There was a significant reduction of TNF-α in the intervention group compared to the control group (J. T. Hong et al., 2020). In another study, 72 diabetic patients were randomized to receive a placebo or 1500, 2000, or 3000 mg of ginseng for eight weeks. At post-intervention, TNF-α significantly decreased in 1500 and 3000 groups compared with the control group (J. W. Yoon et al., 2012).

Resveratrol

Resveratrol, a polyphenolic compound, has beneficial effects in several diseases, including CVD, diabetes, and other metabolic disorders (Saiko, Szakmary, Jaeger, & Szekeres, 2008; Shakibaei, Harikumar, & Aggarwal, 2009; Shankar, Singh, & Srivastava, 2007). Some reports imply that resveratrol plays an important role in inhibiting inflammation, oxidative stress, carcinogenesis, and ROS generation (Xing et al., 2020). Resveratrol was reported to increase the mRNA expression of cytokine genes such as COX-2, TNF-α, IL-1β, IL-8, and improve the levels of TNF-α and NF-κB mRNA. Reseveratrol reduced the activation of NF-κB and TNF-α (Xiao et al., 2021). In a double-blind, randomized controlled study, 58 patients with non-alcoholic fatty liver disease were assigned into two groups to receive a placebo or 300 mg daily resveratrol for 12 weeks. At post-intervention, resveratrol capsules significantly reduced TNF-α to a greater extent than placebo (Shihui Chen et al., 2015). In a previous clinical trial, 44 overweight or obese women were randomly assigned to receive 15% of their energy from grape seed oil (GSO) as an intervention group or 15% of their energy from sunflower oil as a control group eight weeks. At the end of the study, the TNF-α level significantly reduced in the intervention group (Irandoost, Ebrahimi-Mameghani, & Pirouzpanah, 2013). In another study, 24 obese men were randomized into two groups to receive a placebo or 500 mg daily resveratrol for four weeks. There were no demonstrable changes in TNF-α levels in both groups (Poulsen et al., 2013). In another study, 40

polycystic ovary syndrome (PCOS) patients were randomized into two groups to receive 800 mg resveratrol/day or a placebo for 40 days. Serum TNF-α was significantly reduced in the intervention group, and this reduction was marginally significant compared with the control group (p=0.056) (Brenjian et al., 2020). In another clinical trial, using 1 gram resveratrol/day for three months was associated with a significant reduction in serum TNF-α in the rheumatoid arthritis patients compared with placebo (Khojah, Ahmed, Abdel-Rahman, & Elhakeim, 2018).

Green tea

Green tea polyphenols include anthocyanins, flavonoids, catechins, and phenolic compounds (Kim, Tan, Xiao, Sun, & Qu, 2013; Sabu, Smitha, & Kuttan, 2002; Xia, Wang, Xie, Xu, & Tang, 2019). Some studies have shown green tea's remedial effects in metabolic syndromes, type 2 diabetes, and repressing lipogenesis in hepatocytes (Kim et al., 2013; Xia et al., 2019). Evidence has revealed polyphenols of green tea, such as epigallocatechin gallate (EGCG), to restrain matrix-metalloproteinase-2 and matrix-metalloproteinase-9 (Demeule, Brossard, Pagé, Gingras, & Béliveau, 2000; Hagiu, Attin, Schmidlin, & Ramenzoni, 2020). Green tea has anti-inflammatory activity by repressing the synthesis and inhibiting various proinflammatory mediators, nitric oxide synthase, peroxynitrite, reactive oxygen/nitrogen species, and COX-2 (Hagiu et al., 2020; Paquay et al., 2000; Zhong, Chiou, Pan, & Shahidi, 2012). A recent meta-analysis has shown that green tea consumption significantly reduces TNF-α according to 6 clinical trials (Haghighatdoost & Hariri, 2019). In a clinical trial, 46 obese diabetic women were randomly recruited to four groups: (i) 1500 mg/d green tea, (ii) aerobic exercise training with green tea, or (iii) aerobic exercise training, or (iv) control. After ten weeks, three times a day, there were no significant effects on TNF-α levels between the four groups (BANITALEBI, RAZAVI, NORIAN, & Bagheri, 2016). In another study, overweight middle-aged males who

consumed 500mg/day of green tea extract + endurance training had no effects on TNF-α compared with placebo and endurance training + placebo groups (Bagheri et al., 2020).

Anthocyanin

Anthocyanins are bioactive compounds belonging to polyphenols obtained in berry fruits, including blackberries, blueberries, and strawberries (Ding et al., 2020). Anthocyanins act as reactive oxygen species, free radical scavenger, and have several health benefits on obesity and diabetes (Ding et al., 2020). Studies published that foods containing anthocyanin appeared to lower inflammatory and oxidative stress biomarkers (H. Zhang et al., 2020). Anthocyanins have a vital role in reducing the electron-transfer reaction pathways, and these beneficial effects are because of their antioxidant capacity (H. Zhang et al., 2020). A recent meta-analysis study showed that dietary intervention with anthocyanins significantly reduced serum TNF-α based on the 32 randomized controlled trials (Fallah, Sarmast, Fatehi, & Jafari, 2020). In a previous clinical trial study, 11 obese and overweight women were divided into two groups to receive 500 ml/d red orange juice. After 12 weeks, there was no significant effect on TNF-α level in baseline and after 12 weeks with consumption of red-orange juice (Azzini et al., 2017). In a study, 31 patients with mild cognitive impairment (MCI) were asked to drink 250 mL fruit juice/day, which contained: a) high dose anthocyanins (201 mg); b) low dose anthocyanins (47 mg); c) control. After 8 weeks, participants in the high dose of anthocyanins had a significantly lower serum TNF-α compared with a low dose of anthocyanins and control groups (do Rosario et al., 2021). In one study, 40 subjects with mild hyperlipidemia were randomly assigned into two groups to receive two capsules. Each capsule contained 500 mg Vaccinium Arctostaphylos L. fruit extract (each capsule contained 0.8 mg of anthocyanins) or placebo for 4 weeks. Results

indicated that consumption of Vaccinium Arctostaphylos L. fruit extract did not affect TNF-α levels (Asgary, Soltani, Mirvakili, & Sarrafzadegan, 2016).

Soy

Soybean is a good source for all essential amino acids discovered in animal proteins without cholesterol and limited saturated fat (Chatterjee, Gleddie, & Xiao, 2018). Some epidemiological studies have determined that soy intake has beneficial effects on chronic diseases, including obesity, diabetes and cardiovascular disease (Ahn et al., 2018; Dukariya, Shah, Singh, & Kumar, 2020; Martínez-Sánchez, Gabaldón-Hernández, & Montoro-García, 2020; Ramdath, Padhi, Sarfaraz, Renwick, & Duncan, 2017; Woo et al., 2019). Most of the health benefits of soy proteins are their associated phytochemicals, principally isoflavones (Chatterjee et al., 2018). Some anticancer properties of soy protein with or without isoflavones show anti-inflammatory and antioxidant outcomes by inhibiting NF-κB and blocking the proinflammatory cytokines in an oxidative stress-inducible rat model (Chatterjee et al., 2018; Matemu, Nakamura, & Katayama, 2021). Soy milk digested with pepsin and pancreatin inhibited the production of IL-1β, nitric oxide, nitric oxide synthase, and COX-2 (Chatterjee et al., 2018; González-Montoya, Hernández-Ledesma, Silván, Mora-Escobedo, & Martínez-Villaluenga, 2018). A meta-analysis, which analyzed findings of 18 clinical trials, showed that soy isoflavones and soy isoflavones plus soy protein had no significant effects on serum TNF-α (Hariri, Baradaran, & Gholami, 2021). In a double-blind, randomized controlled study, 63 overweight or obese individuals were supplemented with 2500 mg soybeans daily or 2500 mg starch in the control group for 8 weeks. Results showed that the level of TNF-α was significantly reduced in both groups with no statistical difference between them (M. Lee, Sorn, Park, & Park, 2016). In a recent double-blind, randomized controlled study, 100 hypercholesterolaemic healthy individuals were asked to

consume soy supplements or allocated a placebo group. After 24 weeks of intervention, there was no significant effect on TNF-a between the two groups (Hermansen et al., 2005). In another study, thirty-one women with post-menopausal were randomized to receive three servings of soy (vanilla soymilk (244 mL) with 6 g protein) or dairy milk for 28 days matched by a single bout of downhill running. Results showed that soy and dairy milk consumption had no significant effects on the inhibition of muscle inflammation and proteolysis and did not attenuate up-regulation of exercise-induced changes (Serra, Beavers, Beavers, & Willoughby, 2012). In a previous randomized longitudinal prospective cohort study, 87 healthy women with postmenopausal were divided into two groups to receive diet and exercise for the control group or diet, exercise, and intake of a soy isoflavones extract for the intervention group. After six months of intervention, the combination of diet, exercise, and intake of soy isoflavones had a significant decrease in TNF-a levels in both groups (Placido Llaneza et al., 2011). In another study, 80 postmenopausal women were randomly recruited to two groups: Mediterranean diet and exercise for the control group, or this intervention with soy isoflavone extract for 24 months. After these interventions, results showed that the level of TNF- α significantly declined in both groups (P Llaneza et al., 2012). In a previous study, 41 men with hypercholesterolemia and women with postmenopausal were assigned to get a low-fat dairy food for the control group, and intervention group including foods including 2 soy protein phases, one high and the other low in isoflavones with the amount of 50 g and 52g soy protein daily for high-isoflavones phase, and 73 mg and 10 mg isoflavone daily for low-isoflavones phase. After three 1-month phases, there were no significant changes in TNF- α in men and women (Jenkins et al., 2002).

Conclusion and future perspective

This review attempts to clarify the effectiveness of phytochemicals and herbal bio-active compounds on serum TNF-α in overweight and obese subjects. Evidence indicates that herbal medicine has favorable effects on the reduction of TNF-α concentration. However, the results were not uniform. Among the plants, ginger, ginseng, resveratrol, and flaxseed have more promising effects than other phytochemicals and herbal bio-active compounds. Nevertheless, in almost all of the reviewed studies, TNF-α was evaluated as the primary outcome. Moreover, it is not clear that reduction in TNF-α has led to disease treatment or not. More importantly, studies are too heterogeneous regarding the low sample size and the study population, dose of the herbs, and duration of the treatment, making it difficult to draw a definitive conclusion. To accurately assess the efficacy of the phytochemicals and natural bioactive compounds on TNF-α in obese patients, larger clinical trials are warranted to determine the optimal dose and recognize the correct dosing regimen (dosing frequency and duration) to reap their full therapeutic potential.

Figure legends:

Figure 1. Schematic summary of pathways of the effects of obesity, excess intake of fat and glucose on inflammatory response and its effects on induction of obesity related diseases. TNF-α: tumor necrosis factor α, IL-6: and interleukin 6, NF-κB: nuclear factor kappa light chain enhancer of activated B cells, CRP: C reactive protein, CVDs: cardiovascular diseases, NAFLD: non-alcoholic fatty liver diseases.

Figure 2. Macrophage infiltration into adipose tissue which induced by obesity and leads to insulin resistance. (i) In lean state, neutrophils or mast cells, TH1 cells, and B cells induce most resident macrophages are M2 macrophages that contribute to insulin sensitivity by secreting IL-10. (ii) Adipocyte hypertrophy which emerges in hyperphagia and lack of exercise induces MCP-1 secretion to the circulation, causing engagement of circulating monocytes to adipose tissues. Activated M1 macrophages emerge from the infiltrated monocytes differentiate, which induce the production and secretionproinflammatorytory cytokines including TNFα, IL-6, and MCP-1. As a result, low-grade inflammation occurs in the adipose tissue and subsequently adiponectin level decreases. Insulin resistance in the liver occurs due to the inflammatory cytokine activity.

Figure 3. The potential mechanisms of the effectiveness of herbal bio-active compounds on inflammatory markers and cytokines and its relation to the obesity related diseases. Obesity, excess fat and adipose tissue increase the activity of LOX and COX-2. LOX increases the levels of LTE-4 and COX-2 increases the level of PGE2, which both are metabolites of poly unsaturated fatty acids which play a significant role in increasing inflammation. Obesity, and excess fat also increase the amounts of NF-Kb, which increases inflammatory cytokines. NF-Kb also increases the level of NO and increase the level of COX-2. These inflammatory factors significantly increase several obesity-related diseases. Herbal medicine suppresses the activity of LOX, COX-2 and NF-Kb, which resulted in a significant reduction in inflammatory markers. PG, prostaglandin; COX, cyclooxygenase; LOX, lipoxygenase; TNF-α, tumor necrosis factor-α; LT, leukotriene; NO, nitric oxide; iNOS, inducible NO synthase; NF-Kb, nuclear factor-KB; IL, interleukin.

Table 1. The effects of herbal medicine on TNF-α level in overweight and obese individuals

Author, Year	Agent	Dose/day	Duration of treatment	Subjects	Primary outcome(s)	Effects of nutraceuticals on serum TNF-α
Darvishi et al. 2020, Iran (Darvishi et al., 2020)	Propolis	500 mg	3 months	Breast cancer patints	TNF-α significantly increased though in the propolis group, it did not significantly change	No effect
Fukuda et al. 2015, Brazil (Fukuda et al., 2015)	Propolis	226.8 mg	8 weeks	T2DM	Propolis had no effect on TNF-α	No effect
Gao et al. 2018, China (Gao et al., 2018)	Propolis	900 mg	18 weeks	T2DM	Propolis had no effect on TNF-α	No effect
Zakerkish et al. 2020. Iran (Zakerkish et al., 2019)	Propolis	1000 mg	90 days	T2DM	Propolis consumption significantly decreased TNF-α compared with the placebo	Decreased
Aryaeian et al. 2019, Iran (Aryaeian et al., 2019)	Ginger	1500 mg	12 weeks	Active rheumatoid arthritis	TNF-α was significantly reduced in the intervention group, however, it was not significant compared with control group	No effect
Javid et al. 2019, Iran (Javid et al., 2019)	Ginger	2000 mg	8 weeks	T2DM patients with chronic periodontitis under non-surgical periodontal therapy	Serum TNF-α was significantly reduced in the intervention group compared with controls	Decreased
Rafie et al. 2020, Iran (Rafie et al., 2020)	Ginger	1500 mg	12 weeks	NAFLD	TNF-α did not notably change in both groups	Decreased
Asadi et al. 2017, Iran (Asadi et al., 2017)	Ginger extract	1000 mg	10 weeks	Obese diabetic women	No significant differences were observed on TNF-α level in four groups	No effect

Khosravi et al. 2016, Iran (Mozaffari-Khosravi et al., 2016)	Ginger supplementation	500 mg	3 months	Osteoarthritis patients	TNF-α significantly reduced in the ginger group compared with the placebo	Decreased
Davari et al. 2020. Iran (Davari et al., 2020)	Cinnamon extract	3000 mg	8 weeks	T2DM patients	Cinnamon had no effect on TNF-α	No effect
Shishehbor et al. 2018, Iran (Shishehbor et al., 2018)	Cinnamon	2000 mg	8 weeks	Rheumatoid arthritis patients	TNF-α significantly reduced in the cinnamon group compared with the placebo group	Decreased
Egert et al. 2009, Germany (Egert et al., 2009)	Quercetin	150 mg	6 weeks	Overweight and obsess subjects	Quercetin had no effect on TNF-α	No effect
Heinz et al. 2010, United States (Heinz et al., 2010)	Quercetin	500 mg 1000 mg	12 weeks	Female subjects	Quercetin had no effect on TNF-α	No effect
Dehghani et al. 2020, Iran (F. Dehghani et al., 2020)	Quercetin	500 mg	8 weeks	Post myocardial infarction patients	TNF-α was significantly reduced in the intervention group, but not significant compared with control group	No effect
Jazayeri-Tehrani et al. 2019 (Jazayeri-Tehrani et al., 2019)	Nano-curcumin (NC)	80 mg/day NC or placebo	3 months	Obese/over weight NAFLD patients	NC compared with placebo significantly decreased TNF-α	Decreased
Saadati et al. 2019 (Saadati et al., 2019)	Curcumin	500 mg curcumin 3 times a day or placebo	12 weeks	Obese/over weight NAFLD patients	Both Curcumin supplementation and placebo reduced serum concentrations of TNF-α	No effect
Abdolahi et al. 2017 (Abdolahi et al., 2017)	nano-curcumin	80 mg/day	2 months	Overweight patients with episodic migraine	no significant changes in both groups were observed	No effect

Rahimnia et al. 2015 (Rahimnia et al., 2015)	Curcumin	1500 mg/day	6 weeks	Overweight/ obese subjects with knee Osteoarthritis	curcuminoid-treated subjects didn't show any significant changes in serum TNF-α concentration versus placebo	No effect
Dehghani et al. 2018 (S. Dehghani et al., 2018)	Garlic	1000mg garlic tablets twice daily or placebo tabs	12 weeks	Post-menopausal overweight/ obese women with osteoarthritis	no significant changes in TNF-α concentration were observed within or between groups	No effect
Sharifi et al. 2010 (Sharifi et al., 2010)	Garlic	1.8 g/d garlic tablets two 300 mg tab three times per day) or placebo	6 weeks	Women, aged more than 18 years, including 40 women with metabolic syndrome and 10 healthy female controls	none of the inflammatory biomarkers and plasma lipid levels changed significantly between the groups	No effect
van Doorn et al. 2006 (van Doorn et al., 2006)	Garlic powder	2.1 gr/day	3 months	Overweight and smoker subjects	no significant differences showed between the garlic-treated and placebo groups in TNF-α	No effect
Xu et al. 2018 (C. Xu et al., 2018)	garlic extract	3.6 gr/day	6 weeks	Healthy obese individuals	serum TNF-α of participants consuming aged garlic extract were significantly lower than placebo	Decreased
Cassani et al. 2015 (Cassani et al., 2015)	Flaxseed powder	60 gr/day	42 days	Overweight/ obese men with cardiovascular risk factors	The levels of TNF-α was reduced only in flaxseed intake group	Decreased
Hashemzadeh et al. 2017 (Hashemzadeh et al., 2017)	Flaxseed oil	2 gr/day	12 weeks	Overweight diabetic patients with CHD	flaxseed oil supplements down-regulated TNF-α in patients with diabetes and CHD compared with placebo	Decreased

Paschos et al. 2007 (Paschos et al., 2007)	Flaxseed oil	15 ml flaxseed oil per day or placebo	12 weeks	Overweight, nondiabetic, dyslipidemic men	no changes in plasma TNF-α in the flaxseed oil versus the control group were found	No effect
Khandouzi et al. 2019 (Khandouzi et al., 2019)	Flaxseed	30 gr/day	12 weeks	Overweight patients with CAD	significant reduction in plasma TNF-α was observed in flaxseed group compared with control	Decreased
Machado et al. 2015 (Machado et al., 2015)	Flaxseed	28 gr/day Brown or golden flaxseed and placebo	11 weeks	Overweight adolescents	although all groups showed increased levels of TNF-a, groups did not differ on TNF-α levels	No effect
Rhee et al. 2011 (Rhee & Brunt, 2011)	Flaxseed	40 g/day ground flaxseed or placebo	12 weeks	Obese glucose intolerant participants	found no changes in plasma inflammatory biomarkers like TNF-α	No effect
Yari et al. 2019 (Yari et al., 2019)	Flaxseed	30 g/day milled flaxseed	12 weeks	Overweight and obese adults	TNF-α decreased significantly in flaxseed group compared with control	Decreased
Hong et al. 2020, korea (J. T. Hong et al., 2020)	Korean Red Ginseng (KRG)	(ginsenosides Rg1 + Rb1 6.0 mg/g; 3,000 mg/d)	3 weeks	NAFLD patients	TNF-α was significantly decreased in intervention group compared with the control group	Decreased
Yon et al. 2012,Korea (J. W. Yoon et al., 2012)	Ginsam extracted from Panax ginseng	1500, 2000 or 3000 mg	8 weeks	Diabetic patients	TNF-α was significantly decreased in 1500 and 3000 groups compared with the control group	Decreased
Chen et al. 2015, China (Shihui Chen et al., 2015)	Resveratrol	300 mg	12 weeks	NAFLD patients	Resveratrol capsules significantly reduced TNF-α in greater extent than placebo	Decreased
Irandoost et al. 2013, Iran (Irandoost et al., 2013)	Grape seed oil (GSO)	15% energy	8 weeks	Overweight or obese women	TNF-α level significantly reduced in intervention group	Decreased
Poulsen et al. 2013, Denmark (Poulsen et al., 2013)	Resveratrol	500 mg	4 weeks	Obese men	There was no significant difference between two groups.	No effect
Brenjian et al. 2020, Iran	Resveratrol	800 mg	40 days	polycystic ovary syndrome	Serum TNF-α significantly reduced in the intervention group	Decreased

(Brenjian et al., 2020)				(PCOS) patients		
Khojah et al. 2018, Egypt (Khojah et al., 2018)	Resveratrol	1000 mg	3 months	rheumatoid arthritis	TNF-α level significantly reduced in intervention group compared with the placebo	Decreased
Banitalebi et al. 2016, Iran (BANITALEBI et al., 2016)	Green tea	1500 mg	10 weeks	Obese diabetic women	There was no significant effects on serum TNF-α level between groups.	No effects
Bagheri et al. 2020, Iran (Bagheri et al., 2020)	Green tea extract (GTE)	500 mg	8 weeks	Overweight middle-aged males	There was no significant effects on serum TNF-α level between groups.	No effects
Azini et al. 2017, Canada (Azzini et al., 2017)	red orange juice (COJ)	500 ml/d	12 weeks	obese and overweight women	There was no significant effect on TNF-α level in baseline and after 12 weeks with consumption of COJ.	No effect
Vinicius A et al. 2021, Australia (do Rosario et al., 2021)	Anthocyanins	a) high dose anthocyanins (201 mg); b) low dose anthocyanins (47 mg) high dose anthocyanins (201 mg); b) low dose anthocyanins (47 mg)	8 weeks	Mild cognitive impairment (MCI) patients	Participants in the high dose of anthocyanins had a significant lower serum TNF-α compared with low dose of anthocyanins and control groups	Deceased
Asgary et al. 2016, Iran (Asgary et al., 2016)	Vaccinium arctostaphylos L. fruit extract (contained anthocyanins)	1000 mg Vaccinium contained 1.6 mg anthocyanins	4 weeks	Hyperlipidemia patients	TNF-α did not significantly change	No effect
Lee et al. 2016, Korea (M. Lee et al., 2016)	Soybeans	2500 mg	8 weeks	Overweight or obese individuals	TNF-α was significantly reduced in both groups with no statistical difference between them	No effect
K Hermansen et al.	Soy protein	30g	24 weeks	Hypercholesterolaemic	There was no significant difference between two groups.	No effect

2005,Denmark (Hermansen et al., 2005)				healthy individuals		
MC Serra, et al. 2012, USA (Serra et al., 2012)	Vanilla soymilk	244 ml	28 days	Post-menopausal women	The consumption of soy and dairy milk had no significant effects on the inhibition of muscle inflammation and proteolysis	No effect
P Lianeza, et al. 2011, Spain (Placido Llaneza et al., 2011)	Soy isoflavones extract	80 mg	6 months	Post-menopausal women	The combination of diet, exercise, and intake of soy isoflavones had a significant decrease in level of TNF-a in both groups.	Decreased
P Lianeza, et al. 2012, Spain (P Llaneza et al., 2012)	Soy isoflavones extract	80 mg	24 months	Post-menopausal women	The level of TNF- α significantly declined in both groups	Decreased
DJA Jenkins et al. 2002, Canada (Jenkins et al., 2002)	Soy protein	50 g and 52g soy protein daily for high-isoflavones phase, and 73 mg and 10 mg isoflavone daily for low-isoflavones phas	Three 1-month phase	Hypercholesterolemic men and postmenopausal women	There was no significant effect on the level of TNF- α in men and women	No effect

Abbreviations: T2DM, type 2 diabetes mellitus; NAFLD, Non-alcoholic fatty liver disease; NC, Nano-curcumin; CHD, Coronary heart diseases;

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