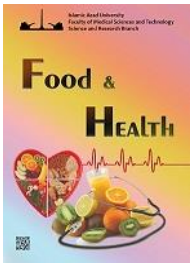

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Nutraceuticals with pleiotropic anti-inflammatory functions for mitigating meta-inflammation

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ABSTRACT

An array of age-related diseases (like diabetes mellitus type 2, cardiovascular disease, Alzheimer's, osteoporosis, cancer, hypertension, atherosclerosis, and arthritis), which are originated from low-grade, chronic, sterile inflammation, called inflammaging have been increased in aged population. In line with this notion, an abundant body of evidence has been demonstrated that quasi-self-stimulations like over-nutrition and gut microbiota could produce metabolic induced inflammation called meta-inflammation. In fact, meta-inflammation which is a result of nutrient excess is a special situation of inflammaging that has a similar molecular mechanism to inflammaging and both inflammaging and meta-inflammation resulted in activating pro-inflammatory pathway. Today it has been revealed that the human diet has significant impacts on preventing meta-inflammation. As a matter of fact, nutrition is one of the most pivotal modulators of low grade- chronic inflammation which can control it. Expanding data showed that phytochemicals especially curcumin and resveratrol, melatonin and vitamin D may exert several anti-inflammatory activities in the context of meta-inflammation. Since these nutrients have pleiotropic functions for inhibiting metabolic inflammation, they could be more efficient in anti-inflammatory based therapy for meta-inflammation in comparison to other nutrients. Here we reviewed the anti-inflammatory and immuno-modulatory effects of some nutrients with pleiotropic effects on inflammation by considering their impacts on the meta-inflammination.

1. Introduction

Increasing incidence of age-related diseases (ARD) which are the consequences of inflammaging caused complications in the health span of the aged population. Inflammaging could interfere with cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal and endocrine systems of the body and could result in functional shortages (1-3). Consequently, inflammaging has crucial roles in progressing the process of aging and also age-related diseases. Both damage-associated molecular patterns (DAMPs) as an internal stressor or self and pathogen-associated molecular patterns (PAMPs) as an external stressor or non-self, could stimulate inflammatory pathways by their sensors (like NOD-like receptors, Toll-like receptors, etc.) which ultimately caused the release of pro-inflammatory mediators. Although this process is essential for survival, the efficiencies of the mechanisms which are essential for neutralizing and removing them are decreased. Although this process is essential for one's survival and eliminates pathogens, as age increases, on the one hand, DAMP and PAMP stimulations increase, on the other hand, the ability of mechanisms to eliminate and neutralize them decrease (4-6). Recent findings demonstrate that in addition to DAMPs (self) and PAMPs (non-self), there are other types of stimulations that are derived from the nutrient and gut microbiota (quasi-self) which can produce systematic pro-inflammatory stimulations. It means that nutrition excess could aberrantly induce innate immunity (7). So, the homeostasis of the body could be disturbed by this quasi-self-chronic excess calorie intake which causes obesity, hyperglycemia, and hypertension. These pathologies are the components of the metabolic syndrome (8).

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In fact, there is a link between inflammaging and metabolic syndrome which is called meta-inflammation. In other words, the chronic low-grade inflammatory state that often goes along with metabolic syndrome and called meta-inflammation is a metabolically triggered inflammation driven by nutrient excess. There are some probabilities for the relation of inflammaging and meta-inflammation. One may be insulin resistance which may account for a higher rate of cytokine productions. Another probability may be that in obese people with the metabolic syndrome increased amount of cytokine in circulation caused higher production of C reactive protein (CRP) which is an inflammatory cytokine (9). As a matter of fact, the ingestion of any meals (especially lipids) could induce inflammatory activation and the adipose tissue is a fundamental site of meta-inflammation. In this regard, nutrition could be considered as a double-edged sword that could affect longevity and innate immunity (10). The latest findings have introduced some nutrients that have anti-inflammatory and immune-modulatory roles which could influence meta-inflammation. Since the inflammation has a multi-factorial mechanism, it is difficult to determine a single reason for its activation. So pleiotropic nutraceuticals that could affect different aspects of inflammation may be more efficient in improving age-related diseases especially meta-inflammation (11). Here we review some nutrients that are involved in reducing inflammation and have immune-modulatory characteristics which improved the meta-inflammation complications.

2. Curcumin

Curcumin (turmeric extract) is a natural compound with a polyphenolic structure that derived from the rhizome of the Curcuma longa which is a member of Zingiberaceae. It has pleiotropic effects because it can target multiple molecules like epidermal growth factor receptor (EGFR) and C-X-C chemokine receptor type-4 (CXCR4) as receptors, mitogen-activated protein kinase (MAPK) and focal adhesion kinase (FAK) as kinases, DNA polymerase and cyclooxygenase-2 (COX2) as enzymes, intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) as adhesion molecules, and particularly nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which is the master regulator of inflammatory pathway. Inhibition of NF-κB may result in the reduction of pro-inflammatory markers and consequently the inflammation. Also, the toll-like receptor4 dependent signaling pathway could be inhibited and peroxisome proliferator-activated receptor-gamma pathway could be activated by curcumin (12). It has been widely applied as an anti-inflammatory remedy for chronic diseases. Although some new data demonstrated the heterogeneous effect of curcumin intake in a patient with chronic inflammatory disease, at the same time most recently reported data have been shown that supplementing with curcumin could decrease the inflammatory biomarkers especially IL-6, IL-8, and C-reactive protein and tumor necrosis factor- α (TNF-α) (13). It could also increase the adiponectin and reduce the leptin. Adiponectin is an important cytokine that is produced by adipose tissue and it is also a master regulator of insulin sensitivity, so the high level of adiponectin is up-regulated by curcumin could have an anti-inflammatory role (14-15). Besides, the level of serum LDL-C, total cholesterol and triglyceride have been decreased by using curcumin which consequently could reduce the inflammation (16-18). One of the most important cytokines with anti-inflammatory characteristics is IL-10. Multiple lines of evidence have been demonstrated that curcumin could induce the expression of IL-10 and augment its function (19). Since curcumin is one of the most potent immune-modulator agents, it could modulate the function of immune cells like neutrophils, T and B cells, natural killer cells, macrophages, and dendritic cells to modulate inflammation (20). There is a large body of evidence suggesting that oral consumption of curcumin could serve to decrease inflammation. Besides, it could improve motor and cognitive functions in aged people. It could also mitigate the symptoms of some age-related diseases like diabetes, cancer, and atherosclerosis (21). Some data have been shown that it's various ranges of curcumin functions are as a result of postponing the cellular senescence, although some data have been demonstrated that its performances are due to sirtuin and AMP-activated protein kinase (AMPK) induction (12).

3. Resveratrol

Resveratrol is another natural polyphenol (phytochemical) that belongs to stilbenoids and it is present in several plants (more than 70 plant species) like some kinds of berries, grapes, peanut, etc. (22). Resveratrol is produced by these plants when they have been stimulated by pathogens and ionizing radiations (23). Again, this molecule has pleiotropic functions such as anti-oxidant, anti-inflammatory, and anti-cancer activities. Like curcumin, it has many molecular targets like adenosine receptors, MAP-kinase, intercellular and vascular adhesion molecules and NF-κB and sirtuin-1 (24). Accumulating data have been indicated their effective properties in age-related diseases which are originated from its anti-inflammatory activity. One of the most important roles that have been being played by resveratrol is calorie mimetic that is due to the increase in the sirtuin-1 which has the main role in the body's reaction to physical activity and diet (25). In this regard, it could also decrease adipocyte propagation and lipogenesis, stimulate adipocyte apoptosis and repress the differentiation of preadipocyte which accounts for reducing the pro-inflammatory state. So, Weight reduction by diminishing the deposit of white adipose tissue is another function of resveratrol according to a meta-analysis study. There is mounting evidence that resveratrol intake could ameliorate the glucose homeostasis and insulin sensitivity in Caucasian men as well (26). Resveratrol also could affect the biogenesis of the mitochondria by increasing the expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) through this, it could improve metabolic rate (27). Although most studies have been claimed that resveratrol usage has been resulted in reducing the inflammatory markers,

a recent meta-analysis study has been shown that using resveratrol in patients with meta-inflammation caused only CRP and TNF-α markers have been considerably reduced (28). Since there is a strong correlation between CRP and meta-inflammation, so utilizing resveratrol could effectively improve the condition of patients with meta-inflammation (29). Besides, supplementation of resveratrol in patients with meta-inflammation has been improved the endothelial functions and also has been increased flow-mediated dilatation among patients with metabolic syndrome (30).

4. Melatonin

Melatonin is a hormone that is secreted by the pineal gland and it regulates the chrono-biological and endocrine function of the body (31). it is produced from L-tryptophan by a four-step process and its secretion is regulated by the circadian clock. The pleiotropic anti-aging characteristics of melatonin are anti-oxidant and immune-modulatory effects which are considered to be performed in a receptor-independent manner (32). It has many roles in metabolism which can affect meta-inflammation. In the growth hormone (GH) signaling pathway, melatonin acts as an augmenter of the GH level (33). GH is involved in glucose uptake which consequently could increase the life span. It could also up-regulate silent mating type information regulation 2 homolog-1 (SIRT-1), which has strong anti-aging effects (34). Accumulating data have been demonstrated that melatonin is the main factor in the health maintenance of metabolic control. In agreement with this finding, supplementation of melatonin could improve the complications which are resulted by meta-inflammation like hypertension, hyperlipidemia, insulin resistance, hyperinsulinemia, dyslipidemia in rats under high fructose diets (35). Consistent with this data, a meta-analysis has been confirmed the effective role of melatonin administration on glycemic control (36). According to a recent meta-analysis, the beneficial effect of melatonin on blood pressure has been supported (37). To counteract the oxidative stress, melatonin increases the anti-oxidant enzymes, the availability of glutathione and the amount of free radical scavengers which resulted in suppression of inflammaging related diseases. Data have been proved that melatonin has anti-aging effects in the nervous system, cardiovascular system, ovary, liver and other tissues (34). A meta-analysis has been revealed that in patients with meta-inflammation, the administration of melatonin could lessen CRP and IL-6 which are the inflammatory markers (38).

5. Vitamin D

Vitamin D is a vitamin that is soluble in fat and it could be synthesized from 7-dehydrocholesterol via UV-B radiation in the skin, besides it could be achieved from the diet (39). Vitamin D deficiency has occurred when the level of serum 25-hydroxyvitamin D (a circulatory form of vitamin D) has been reached below 12ng/ml which is highly prevalent across the world (40). Vitamin D has physiologic roles in calcium and phosphorous homeostasis, and bone mineralization (41). There is accumulating data that vitamin D has a crucial role in modulating the immune system that has led to the research which intended to make a correlation between the level of vitamin D and inflammation (40). In-vitro analysis has been demonstrated that 1, 25(OH) 2D (calcitriol) up-regulates diver's pathways that are involved in anti-inflammation and down-regulates different molecules that are involved in pro-inflammation. Studies have been revealed that there is a direct correlation between obesity and vitamin D deficiency. Since obesity could result in meta-inflammation, so vitamin D could prevent meta-inflammation by anti-adipogenic activity. It may exert its immunomodulatory effects which decrease adipose tissue inflammation by affecting multiple cascades like MAPK pathways, JNK, ERK (extracellular signal-regulated kinase), etc. Toll-like receptor-4 (TLR-4), which is over-expressed via a high level of macrophages and free fatty acids in obese people could be suppressed by vitamin D (42-43). A meta-analysis has been shown that the supplementation of vitamin D could increase the circulatory form of vitamin D which could decrease the level of CRP, triglycerides, low-density lipoprotein (LDL) and parathyroid hormone and increase the level of high-density lipoprotein (HDL) (44).

6. Conclusion

Over-nutrition could stimulate metabolic inflammation which results in meta-inflammation. It means that a high intake of nutrients could lead to increased activation of pro-inflammatory responses that influence many organs. In this regard, some nutrients have multiple anti-inflammatory and immune-modulatory functions. Among them, curcumin, resveratrol, melatonin and vitamin D which all of them have multiple anti-inflammatory roles. Including this nutraceutical in the diet could ameliorate the inflammatory milieu and prevent meta-inflammation.

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