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Proceeding Article

Promotion of Health via Nitrate Containing Foods

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Abstract

The main purpose of presented review is to meet foods include nitrate molecule and to examine how to promote health with daily intake diet. It was declared that nutrition type and it formulation is the most influence factor can be caused acute and chronic diseases. However, at the same time, this can also prevent some of heavy symptoms of those.

Keywords: Health, Nutrition, Functional Foods, Nitrate, Nitrite, Nitric Oxide

Introduction

Current human behaviors in daily nutrition include essential nutrients and bioactive compounds that demonstrate additional benefits to human health (Fardet & Rock, 2014). The presence of phytonutrients such as aminoacids, trace elements, vitamins and minerals protect us against to many diseases (Chomchan et al., 2018). Nothing affects our wellness more than what we choose to consume. Eating a well-balanced, nutritious diet and performing moderate exercise comprise the perfect model of good health. The role of a proper diet in the prevention of disease is well explained by many population-based epidemiological studies (Nunez et al., 2015). Humans are adapted to receive dietary nitrite (Nti) and nitrate (Nta) from birth and throughout life. It was reported that the absence of nitrite and/or nitrate in our foods or daily diets, can be involved in many of the chronic health problems. Improvements in science over the past 30 years have proved both the importance of Nti and Nta in our food supply and how our body makes these molecules naturally.

Today, with over 150,000 scientific papers published on nitric oxide (NO) molecule, a Nobel Prize awarded to the three US scientists responsible for its discovery, and a growing awareness around NO, it can no longer be ignored by medical healthcare practitioners. Surprisingly, there have been no hallmark therapeutic breakthroughs in terms of drug therapy around NO (Bryan, 2018). Perhaps this is due to the fact that NO itself may not be 'drugable' NO, once produced, has a half-life of less than 1 s (Kelm, 1999).

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Importance of consuming dietary nitrate and nitrite

Inorganic Nta and Nti are considered hazardous. There are legal limits to their concentration in food and drinking water. Nta, from fertilizer, accumulates in vegetables and fruit and seeps into groundwater. Therefore, keeping nitrate concentrations below legal limits is a huge struggle for agricultural applications. On the other hand, many of researchers were claimed that Nta and Nti should be considered as nutrients due to theirs health contributions when it consumed at the best ratio. The World Health Organization (WHO), US Food and Drug Administration (FDA), European Food Safety Authority (EFSA) and US Environmental Protection Agency (EPA) were conducted many studies about nitrate and nitrite presence in food, health and environment discipline. The result of those, it was declared that there are some concerns about consuming high ratio of inorganic Nta and Nti such as converting hemoglobin to methemoglobin, causing depression and carcinogenic nitrosamines. These outcomes were collected after animal experiments. However, the results from human experiment, it was expressed that Acceptable Daily Intake of Nti is max. 4.2 ppm (Katan, 2009). It was found too interesting that dietary Nta and Nti intake has shown weak toxicology and it can be harmless instead of taking inorganic Nta and Nti (Hord et al., 2009). This controversy situation was solved many medicinal and food researches over last decades.

The health effects of the dietary consumption of vegetables and fruit have been attributed to their constituents, including vitamins, minerals, fiber, and so-called nonnutritive substances such as polyphenols. One group of antioxidants present in fruits and vegetables is known as ′polyphenols′ or ′polyphenolics′ and is believed to neutralize free radicals formed in the body, thus minimizing or preventing damage to cell membranes and other cell structures (Milkowski et al., 2009). The Nta concentration of green vegetables (lettuce, spinach), cabbages, root vegetables (carrot, mustard leaf), melons (wax gourd, cucumber), eggplant and banana is changed between 12-387, 26-310, 70-195, 1-68, 25-42 and 4.5 mg/100 g fresh weight, repectively. On the other hands, the Nti concentration of cabbages, green vegetables, root vegetables, melons and eggplant is differed between 0-0.5, 0-0.2, 0-0.06, 0-0.01 and 0-0.04 mg/100 g fresh weight, respectively (Wang, 2000). The other rich sources of Nta and Nti are celery, cress, chervil, rocket (rucola), beetroot, radish, banana, pomegranate, acai and green tea (Santamaria, 2006). Several studies correlate healthy dietary patterns with lower plasmatic concentrations of pro-inflammatory markers (Centritto et al., 2009) whilst a meat-based dietary pattern (Western-type) is associated with higher levels of low-grade inflammation (Barbearesko et al, 2013). The current body of evidence shows that healthy dietary patterns have similar sides, such as a high intake of fiber, antioxidants, vitamins, minerals, polyphenols, monounsaturated, and polyunsaturated fatty acids (MUFA and PUFA, respectively); low intake of salt, refined sugar, saturated, and trans fats; and carbohydrates of low glycemic load (Mozaffarian, 2016). This can be generated via a high intake of fruits, vegetables, legumes, fish and seafood, nuts, seeds, whole grains, extra virgin olive oil and dairy foods together with a low intake of pastries,

soft drinks, and red and processed meat (Silveria et al, 2018).

The most recent literature has been heavily focused on beetroot plant and *Morinda officinalis* and *M. citrifolia* (Indian mulberry, noni fruit) (Wan et al., 2019; Yang et al., 2019; Yoshitomi et al., 2020; Kim et al., 2020; Lee at al., 2020a; Lee at al., 2020b). The beetroot is a source of bioactive compounds, including phenolic compounds, saponins, and especially betalains (Mroczek et al., 2012). The antioxidant capacity of the betalains and phenolic compounds suggest a protective role regarding oxidative processes (Georgiev et al., 2010). The beetroot is a Nta-rich food product that is absorbed in the proximal intestine. This plant is a good source of endogenous Nti and nitric oxide (NO) (Lundberg & Weitzber, 2005; Coles & Clifton, 2012). Nti and Nta are vaso-active agents with the ability to increase vasodilatation, decrease blood pressure (BP), and improve cardiovascular function in both healthy individuals (Coles & Clifton, 2012; Miller at al., 2012) and hypertensive patients (Kapil et al., 2014). The dietary administration of Nta caused an acute reduction in systolic and diastolic BP in healthy subjects, after the ingestion of 500 mL of beet juice (Webb et al., 2008). Moreover, beetroot intake has been associated with improved performance and increased tolerance to exhaustion during sportive activity (Lundberg at al., 2009). On the other hands, *M. officinalis* have various biological activities, including protecting against bone loss, osteoporosis, age-induced bone degeneration, and have anti-oxidant, anti-fatigue and anti-inflammatory activities. Some of polysaccharides, flavone glycosides,iridoid,glycosides, anthraquinon, coumarins, and phytosterols, such as rubiadin, rubiadin-1-methyl ether, 2-hydroxy-1-methoxy-anthraquinone, 1,3,8 trihydroxy-2 – methoxy - anthraquinone, morindolide, morofficinaloside, asperuloside, asperulosidic acid, monotropein, scopoletin, stigmasterol, daucosterol, and sitosterol molecules are responsible for those health promotion effects (Lee at al., 2017). Noni was one of the most important medicinal plants for Polynesian people, who used it for multiple reasons, among which was also the treatment of diabetes (Algenstaedt et al., 2018). *M. citrifolia* leaf is consumed raw as vegetable salad called “ulam” and “kerabu” in Traditional Malay Medicine to prevent hypertension and aging and to invigorate the blood (Chong et al., 2018).

Biochemical pathways of NO_x molecules and medical studies

Nitric oxide (NO) and derived molecules, called reactive nitrogen species (R*NS), are novel modulators of diverse physiological processes (Corpas & Palma, 2018). The excellent physiologically redundant mechanisms by which Nti and Nta are produced and reformed by oxidation of NO are illustrated in **Figure 1**. Dietary sources of Nti and Nta may boost the reserve of compounds for optimum function through periods of physiological stress and diseases termed by endothelial dysfunction (Bryan et al. 2007; 2008).

The degradation of Nta to Nti to NO is, by necessity, an inefficient process by which each step yields a 3-log-lower concentration of product than substrate. Therefore, a 10 ppm infusion of Nta given over 5 min yielded a plasma concentration of Nti of ~1 μmol/L and resulted in ostensibly NO–mediated vasodilation after experimentally induced ischemia (Jansson et al., 2008). Notably, the short half-life of NO results from efficient oxidation of NO to Nti and other nitrogen oxides, such as *N*-nitroso compounds by NO oxidases that use transition metals in their active sites, such as copper-containing ceruloplasmin (Shiva et al., 2006), myeloperoxidase, and even endothelial NO synthase (Vanin et al., 2007). Oxidation of NO to nitrite and nitrite to nitrate contributes to the pool of NOx compounds that serve as signaling molecules systemically or as a local substrate for nitric oxide production. Emerging evidence from animal models and human clinical studies indicates that Nti performs unique intracellular signaling properties that mediate physiologic infusion in humans induces rapid local vasodilation, reduces blood pressure acutely, serves as an endocrine reservoir of NO, and, unlike organic nitrates, does not induce tolerance (Dejam et al., 2007; Webb et al., 2008). Nti has also been shown to play a role in mitochondrial respiration (Nohl et al., 2000), cardiac function (Rassaf et al., 2007), activation the α- form of the estrogen receptor (Veselik et al., 2008), and exertion of antiapoptotic effects (Gonzalez et al., 2008). Because Nti is a biologically active compound resulting from Nta reduction in tissues, significant physiologic benefits may be associated with the provision of Nti from dietary sources functions independent of its role as a source of NO in tissues by reduction (Bryan, 2006). The reactive nitrogen species (RNS) are mainly produced through mitochondrial activity and other pathways, such as nitric oxide (NO) synthase, and oxidase enzymes, such as Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (Nox), xanthine oxidase (XO), lipoxygenase, myeloperoxidase, uncoupled endothelial nitric oxide synthase (eNOS), and the mitochondrial respiratory chain via a one-electron reduction of molecular oxygen. Note the role of Nox in oxidative stress, as upregulated and overactive Nox enzymes contribute to oxidative stress and cardiovascular disease (CVD). Increased oxidative stress through production of superoxide can scavenge NO thereby reducing its effective concentrations and signaling actions in. Aging also causes a decrease in NOS enzyme expression. There is also an upregulation of arginase (an enzyme that degrades the natural substrate for NOS, L-arginine) in the blood vessels as we age that causes a reduction in NO production due to a shuttling of L-arginine away from the NOS enzyme. Aging causes a gradual decline in NO production with a greater than 50% loss in endothelial function in some aged populations. Some studies show a more than 75% loss of NO in the coronary circulation in patients in their 70s and 80s compared to young, healthy 20-year olds (Bryan, 2018).

NO is an important mediator of blood pressure homeostasis. It has been reported that pharmacologically reducing the bioavailability of NO can lead to hypertension in NRs (Ribeiro et al., 1992). Furthermore, it is strongly suggested that loss of the vasodilatory action of NO is a main cause to the development of hypertension in some forms of the disease (Naseem, 2005). NO is essential for

maintaining normal blood pressure, preventing adhesion of blood cells to the endothelium, and preventing platelet aggregation; it may, therefore, be argued that this single abnormality, the inability to generate NO, puts us at risk for diseases that plague us later in life, such as atherosclerosis, myocardial infarction, stroke, Alzheimer's disease, and peripheral vascular disease. Therefore, developing strategies and new technologies designed to restore NO availability is essential for inhibiting the progression of certain common chronic diseases. The provision of dietary nitrate and nitrite may allow for such a strategy. NO is also one of the most important molecules produced within the cardiovascular system that maintains normal blood pressure and prevents inflammation, immune dysfunction, and oxidative stress, hallmarks of cardiovascular disease. **Figure 2** shows that the main causes of CVD. Mediterranean and Dietary Approaches to Stop Hypertension (DASH) dietary interventions are well studied for cardiovascular outcomes. Both dietary patterns can reduce the ratio of CVD through the down-regulation of low-grade inflammation and better control of body weight, which also improve other risk factors, and are correlated with lower numbers of clinical events (Mozaffarian, 2016; Silveria et al, 2018).

Dietary intake of Nta is a well-known marker of a health-promoting fruit and vegetable diet. This could be providing via dietary or supplementary nutrition (food supplements) or food additives. The importance of dietary variety, balance and moderation should be stressed along with the importance of protective factors in the total diet, combined with a physically active lifestyle. The risk or benefit balance should be a strong consideration (Milkowski et al., 2009) before there are any suggestions for new regulatory or public health guidelines for dietary nitrite and nitrate exposures. Dietary supplementation of nitrate from food supplements is challenging with regard to daily intake, in order to provide a ready, easy to administer, attractive, nitrate-rich food product with the aim of promoting beneficial effects on the cardiovascular system (Davi Vieira Teixeira da Silva et al., 2016).

Conclusion

Some of the dietary patterns and clinically proven specific foods have significant protective effects for many of human diseases. This review will highlight the biochemical and physiological base for consumers and patients. This study also reveals the beneficial effects of nitrite and nitrate and their metabolism may be affected by lifestyle and diet. Well-balanced nutrition plays a key role in reducing the risks of different chronic diseases. The objective of this review is to summarize the scientific findings and illustrate how diet and lifestyle break NO production down, and, most importantly, illustrate how we can overcome these obstacles to optimize NO generation.

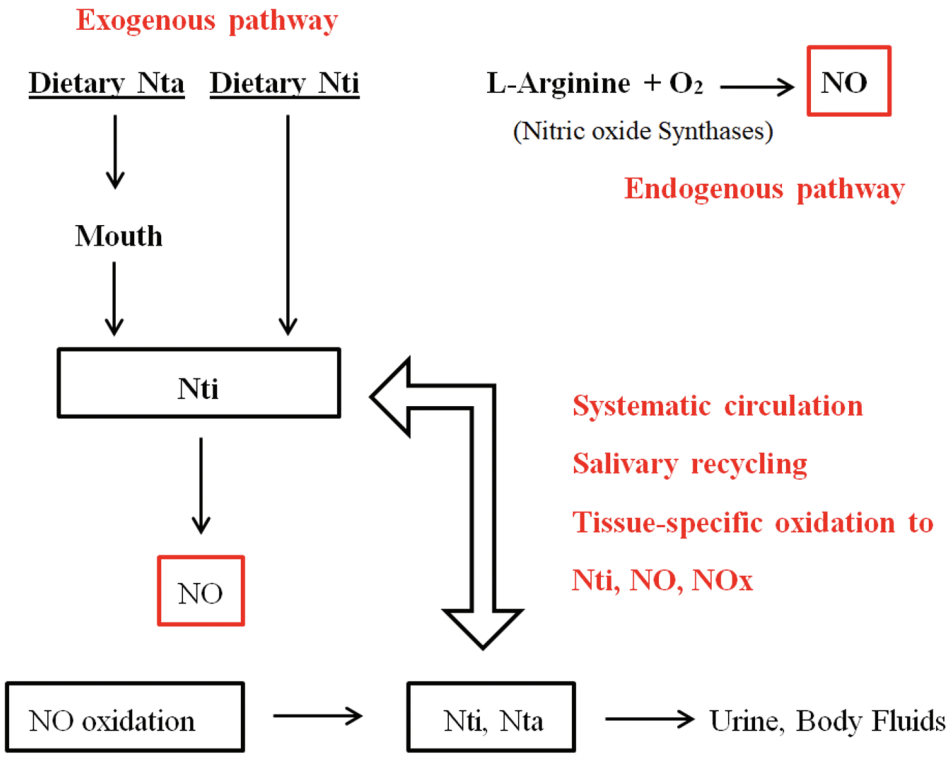

Figure 1. The physiological disposition of nitrate, nitrite, and nitric oxide (Hord, 2009)

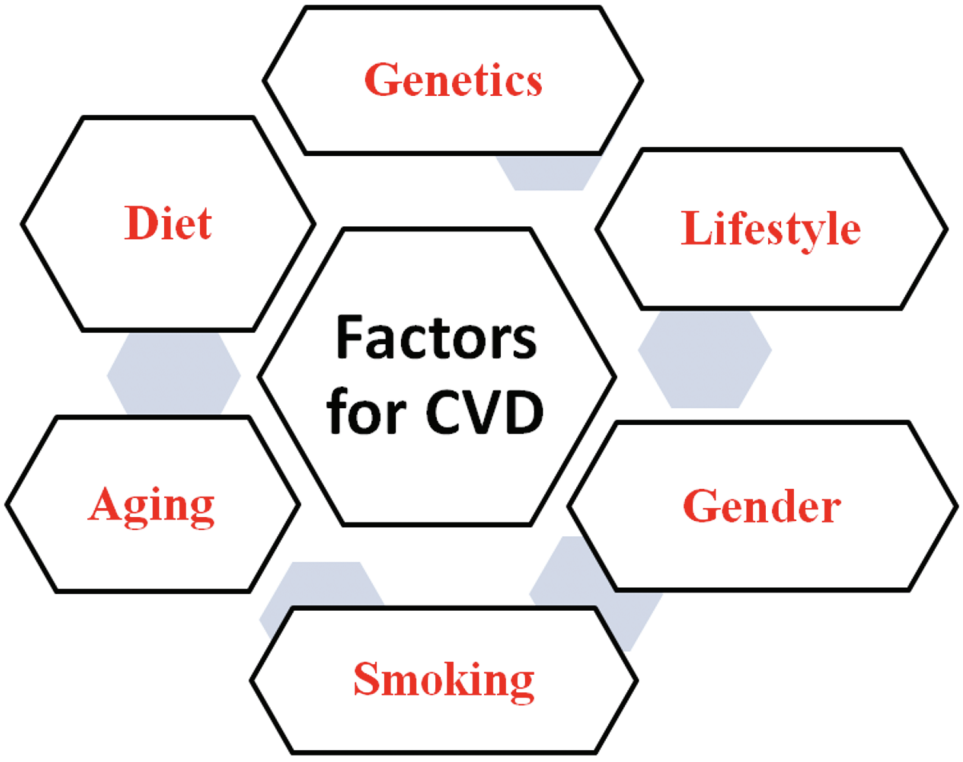

Figure 2. The possible causes lead to the development of cardiovascular disease (CVD) (Casas, 2018).

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