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Risk of Nitrate Residues in Food Products and Drinking Water

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Although nitrate is the essential nutrient of our body, the excess amount of it as residues strongly causes disease. Nitrate comes from plant and animal foods that are vital to our metabolism. The nitrate is absorbed through the soil by plants and becomes an herbal protein that is placed in the food chain. If the nitrate is absorbed more than the plant requirement, it will be accumulated into the plant's organs. Since nitrogen fertilizers increase the weight and yield of the plants, farmers consume large amounts of which. Hence, we investigate the consumption of nitrogen fertilizers in the world and the standard allowable residual nitrate in food and water considering the accumulation of nitrate in water and food. Excess amount of nitrate in the soil enters the drinking water after leaching or directly transported from groundwater to surface water and drinking water. The entry of the excess amount of nitrate from food products and drinking water into our bodies causes dangerous diseases such as different types of cancers, methemoglobinemia, osteoporosis, kidney stones, and some other diseases. The present article, besides indicating the benefits of nitrate for Treatment purposes and demonstrating the state of nitrate accumulation in food and water as well as its standards, deals with diseases caused by it and presents some remedies to reduce the risks.

Introduction

Nitrogen is one of the substances that is commonly used in agriculture and causes several concerns. In particular, it is used in large quantities as fertilizer in agricultural systems [1, 2]. Due to its chemical and physical properties, it can reach fresh water through runoff [3]. The high concentration of nitrogen dispersed in the environment can lead to eutrophication and have adverse effects on aquatic ecosystems [4].

The most common form of anthropogenic nitrogen in water is nitrate (NO^-_3). Nitrate can be found in the natural background at levels ranging from 0 to 2.0 mg L^{-1} [5]. However, in areas with intensive agriculture or a high population, specifically in developing countries, its concentration in water can be more than 100 times higher [6]. The information recorded in some regions where the nitrate concentration can easily reach 100 mg L^{-1} or even up to 500 mg L^{-1} is very alarming [7-9].

Contamination of freshwater by nitrates is a serious risk to human health, especially when it reaches drinking water. In this respect, the World Health Organization (WHO) announced that the permissible nitrate concentration in drinking water should not exceed 50 mg L^{-1} [7]. In fact, the consumption of drinking water by humans with higher concentrations of NO^-_3 can cause various diseases [5].

In particular, Nitrate and nitrite exist in soluble form in the environment or enters the environment by microorganisms through the oxidation of nitrogenous compounds [10-12]. In the natural cycle of nitrogen, bacteria convert it to nitrate. They are absorbed to produce protein in plants. Herbivores consume this nitrate to produce protein in their body. In the return of this cycle, nitrate is excreted from the body of animals or returns to the soil after death from the body of the animal or plant by microbial decomposition and is converted to nitrite and nitrogen afterward [13]. In particular, the risk of certain cancers and birth defects may arise from the consumption of nitrate, and nitrate is reduced to nitrite, which can ultimately form N-nitroso compounds that are known animal carcinogens, and can possibly lead to stomach cancer. Colon cancer, kidney cancer, brain cancer, etc. for humans [14].

Over the last two centuries, with the increase of agricultural and industrial activities, the nitrogen cycle has changed and nitrate has accumulated into vital resources [15, 16]. Improper use of chemical nitrogen fertilizers is the most important cause of nitrate increase [17] that enter the environment by human hands [18, 19]. From the agricultural cycle, excess nitrate is mainly found in fresh vegetables and fruits [20] and processed meat, and partially in dairy products and legumes [19]. Due to the high consumption of fresh products, these foods are the main source of nitrate accumulation and its transfer in the food chain. According to Lian-feng et al. (2011), the highest concentration of nitrate is found in vegetables, especially their leafy forms [21]. Although the total amount of nitrate allowed to enter the body of an adult weighing 70 kg is 51 mg per day, i.e., 0.7 mg per kg of body weight, we absorb large amounts of it due to the consumption of food and water containing excess nitrate [22-24].

In general, besides all therapy purposes of nitrate that we will mention, an excess amount of it entering the soil, water, and human food cycle can cause a lot of damage. Therefore, preventing entry, removal, or reduction of this element is one of the important human concerns.

Meat products contain up more than m <2.7 to 945 mg of nitrate per kilogram and dairy products up to more than <3 to 27 mg of nitrate per kilogram. Also, some vegetables and fruits have 200-2500 mg/kg nitrate due to excessive consumption of nitrogen fertilizers [25]. Among different types of fresh food products, leafy vegetables do have about 80 percentage of the entry of nitrate into our body [26] ; since their juiciness have practically absorbed more nitrate. That is why their feeding is more dangerous compared to other products [27]. Due to the importance of this matter, there are many reports on the state of nitrate accumulatiofertilin in fresh and processed vegetables [28-30].

Consumption of nitrogen fertilizers in the world

Due to the increased activity in agriculture and the use of chemical fertilizers, contamination potential assessment is very critical [31]. Nitrate accumulation has increased dramatically in the world over the past decades due to emissions from sources such as livestock, agricultural waste, and chemical fertilizers [32]. Nitrate accumulation occurs more in plant products as a result of excessive use of chemical nitrogen fertilizers [28-30]. According to FAO statistics, the demand for chemical fertilizers (nitrogen), Phosphate, and potash in 2016 were 185.063 million tons, which in 2016 increased to 186.67 million tons, and this amount with an average annual growth of 1.9 percent at the end of 2022 will reach to 200.919 million tons [33].

It is also expected that from 2016 to 2020, the demand for these fertilizers will increase by 2.4 percent [34]. This is while in developed countries, the standards for the use of chemical fertilizers, especially nitrogen types, have been developed and strongly they seek to reduce their consumption. According to Lenka et al. (2013), the residual soil nitrate (RSN) up to a depth of 100 cm at harvest time should not exceed 150 kg N ha^{-1}, which should be reduced compared to the average consumption of 240 kg N ha^{-1} [35]. Other sources even state that the RSN allowed for the EU is 90-100 kg N ha^{-1} [36].

Nitrate standards

Nitrate limit in the food cycle

The amount of nitrate remaining in food is proportional to the amount of nitrate in the soil and therefore compared to the allowable level of nitrate in the soil [37]. The tolerable standard level of nitrate for our body has been expressed in different sources. According to the European Commission’s Food Science Committee, the permissible daily intake of nitrate (ADI) in 1995 was

3.6 mg/kg of body weight [38] which in 2003 was reported by the Food and Agriculture Organization. Global health for adults with an average weight of 60 kg 3.7 mg/kg [39]. According to a report, the average daily concentration of excess nitrate uptake in an adult is about 75-100 mg, of which 80-90% it is a vegetable and the rest is water. Due to the need to consume healthy vegetables, global standards were set more than 40 years ago for the nitrate limit in a variety of vegetables (Table 1) [40].

Nitrate limit (mg/kg FM)	Type of vegetable
2500<	Racket
2500-1000	Root beet, Cabbage, Radish, Celery, Plain chicory, Lettuce, Leaf beet, Parsley, Spinach
1000-500	Broccoli Raab
500-200	Green onion, carrot, endive, fennel, broccoli, cauliflower, Asparagus Chicory
200>	Carrot, Garlic, Onion, Sweet potato, Potato, Cabbage, Radicchio, Tassel Hyacinth

Table 1. *Standard Limit for Nitrate Residues in Various Vegetables [40]*

Nitrate limit in water

Drinking water contains variable amounts of nitrate. The permitted amount in water is regulated in Europe (50 nitrate ion (mg/l)) and the US (10 nitrate-nitrogen (mg/l), equivalent to 44 nitrate ion (mg/l)) due to the concerns about methemoglobinemia disease. Nitrate in drinking water derives from bacterial nitrogen fixation and from the decomposition of organic material in the soil. Excessive use of nitrogen-containing fertilizers may also be critical, although there is a complex relationship between nitrate application, nitrate uptake by plants, and nitrate leachingw which has been extensively reviewed [41].

Accumulation of nitrate in water and food

Excess amount of nitrate accumulates in soil and water in several ways and finally reaches our body. First and foremost, it is absorbed directly from the soil and after accumulation reaches our body through livestock products. Moreover, it enters groundwater or surface water from washed soil and afterwards reaches the sources of drinking water. On the other hand, it enters directly into surface or groundwater through agricultural runoff and then it reaches the sources of drinking water. However, feeding on plants, livestock products, and nitrate-contaminated water means an increase in nitrate in the food chain and eventually in our bodies [42].

Nitrate concentrations in surface water are usually low. However, it can Reach higher levels through agricultural runoff. Nitrate concentration rise up when the river is fed by nitrate-rich aquifers. In the last 20 years, the concentration of nitrate in the water of many European countries has doubled [39]. In the United States, its concentration in groundwater is about 4-9 mg/l [43], while in developing countries such as India, due to agricultural activities, the concentration of nitrate in groundwater in agricultural areas has been reported to be more than 1500 mg/l [39]. Denmark and the Netherlands with an annual increase of 0.3-1.2 mg/l nitrate are encountered in agricultural waters. In 15 European countries, the amount of nitrate above 50 mg/l in drinking water has been reported, while its standard in drinking water of surface water origin should be less than 10 mg/l [44, 45].

Diseases caused by nitrate residues in water and food

Higher concentrations of nitrate occur where fertilizers are applied to the land. A regulatory restriction for nitrate in public drinking water supplies was established to protect against infant Methemoglobinemia. In addition, the risk of certain cancers and birth defects may increase with nitrate consumption, and nitrate is reduced to nitrite, which can react with amines and amides to form N-nitroso compounds known to be carcinogenic [14]. Finally, excess nitrates are easily accumulated in human bodies by eating vegetables, fruits, red and white meat, dairy products, grains, and their products [46].

Extra amount of nitrate is absorbed by the salivary glands, which are converted to nitrite by symbiotic bacteria in the oral cavity. This nitrite is converted to NO and other bioactive nitrogen oxides [47]. Some of the excess amounts of nitrate are also rapidly absorbed into the bloodstream through the proximal intestine. Nitrate residues cause perilous, diseases such as cancer, diabetes, osteoporosis, kidney stones, and some other new diseases [10]. High nitrate uptake in gastric cancer in the UK, Chile, Japan, Hungary, and Italy has also been proven because Nitrite in the stomach reacts with amines and amides, so the stomach is at risk of synthesizing an internal carcinogenic compound [48].

There are two views on the relationship between nitrate and cancer. One is that after nitrate enters the body, gastrointestinal bacteria convert it to nitrite, which combines with secondary amines to form carcinogens such as (NAD) and (NOC) [49] and Second, nitrite provides the nutrient raw material for tumor cells and provides the NO signaling molecule necessary for tumor cell growth, in which nitrite indirectly accelerates disease by proliferating and stimulating malignant cancer cells [50].

An increased nitrate concentration in drinking water supplies causes methemoglobinemia in infants and cancer of the alimentary canal; no other group of carcinogens produces such an extensive variety of tumors [51, 52]. The residual carcinogenic potential of nitrate in drinking water is an important issue of the day and many studies have shown the prevalence of various cancers Such as stomach, esophagus, thyroid, and bladder are associated with nitrate levels of drinking water [53]. Methemoglobin is one of the most well-known effects of excess nitrate uptake. In this complication, the enzyme “nitrate reductase” (in saliva or stomach) converts nitrate to nitrite. Combining nitrite with hemoglobin makes methemoglobin, which is unable to carry oxygen. Infants up to 6 months of age are most sensitive because they have higher levels of the enzyme nitrate reductase and therefore more nitrate is converted to nitrite in their body [54]. In severe cases, the disease causes brain damage and eventually death due to suffocation due to lack of oxygen [53, 55]. Infants and children have been reported to be more vulnerable to nitrate than women and the elderly [56, 57]. If even small amounts of nitrate are present in the food of children and infants, they are very vulnerable because their stomach acidity is lower than that of adults [55]. High plasma nitrate concentrations also cause kidney problems and are a major cause of some deaths [58]. Combines it with calcium to form excretable calcium nitrate from the kidneys. There are two serious problems with this condition: first, calcium must be taken from the bones, which in turn causes osteoporosis [59, 60], and second, calcium nitrate must be excreted by the kidneys. This is due to high amounts in them and causes kidney stones and kidney failure [61]. The relationship between excessive nitrate intake and thyroid malfunction has also been reported in different countries [25]. The range of the effects and damage of nitrate in our body correlated to the amount of absorption, duration, and how we are exposed to nitrate. Other factors such as age, sex, diet, family traits, lifestyle, and health status should also be considered [62]. Excess amount of nitrate, less than dangerous level for adults, cause childhood diabetes and acute respiratory infections in children [63].

Based on the study of Lowe (2021), more than 30 epidemiological studies have demonstrated a link between nitrates in drinking water and detrimental health effects since 2005 [64]. Conditions that lead to nitrate contamination in water, such as open defecation, the proximity of septic tanks to water sources, and the use of mineral fertilizers, are common in Indonesia, which has done little research on the assessment of nitrate in drinking water. Estimates of daily nitrate intake, calculated at 50% and 95% exposure to the maximum drinking water nitrate concentration in the two villages, were higher than levels pertinent to birth defects, thyroid conditions, and colorectal cancer observed in other research. There was a large difference in nitrate concentration level between and in the villages at different water sources. Table 2 reports some studies on Nitrate-related disease from contaminated water.

Disease	Description	References
Different cancers	There is an association between the intake of nitrate from drinking water and a type of cancer in humans (brain cancer & glioma, colon cancer, stomach cancer)	[14]
Congenital anomalies	Nitrate exposure was associated with a significantly increased risk of limb deficiencies in models without well restriction. Nitrate was also weakly associated with an increased risk of congenital heart defects and neural tube defects in models with well restriction (< 10%). The positive associations found between nitrate exposure via drinking water and congenital abnormalities are largely consistent with some previous epidemiologic studies.	[65]
Pancreas cancer	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence; nitrate and TTHM estimates for PWS (20,945 women; 189 pancreas cases); no measurements for private wells Adjusted for TTHM (1955–1988), measured levels in 1980s, prior year levels estimated by expert)	[66] (USA)
Preterm birth Low birth weight	Counties had one or more water utility in EPA’s atrazine monitoring program; excluded counties with> 20% of population on private wells and > 300,000 population. Computed county-specific monthly weighted averages of NO^-_3N in finished drinking water; exposure metric was average 93 months prior to birth.	[67] (USA)
Kidney cancer	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence. PWS measurements for nitrate and TTHM; no measurements for private wells (20,945 women; 163 kidney cases)	[68] (USA)
Colorectal cancer	· nitrate levels at residence (presumed to be private wells) estimated by kriging using data from a 1994 representative sample of 289 private wells	[69] (USA),
	· Analyses include those with nitrate estimates for ≥70% of period 30 years before interview	[70] (Spain, Italy),
	· Analyses included participants who reported drinking well water	[71] (Indonesia), [72] (Denmark)
	· Nitrate levels in PWS and private wells	

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	among 1,742,321 who met exposure assessment criteria (5944 colorectal cancer cases, including 3700 with colon and 2308 with rectal cancer)	
Bladder Cancer	· 1986 nitrate level in 364 pumping stations, exposure data available for 871 cases, 4359 members of the subcohort	[73] (Netherlands),
	· Nitrate levels in PWS (1979–2010) and bottled water (measurements of brands with highest consumption based on a Spanish survey); analyses limited to those with ≥70% of residential history with nitrate estimate (531 cases, 556 controls)	[74] (Spain),
	· Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence with nitrate and trihalomethane estimates (20,945 women; 170 bladder cases); no measurements for private wells Adjusted for total trihalomethanes (TTHM)	[75] (USA)
Different cancers	Excess nitrate in drinking water increases the risk of kidney, rectal, bladder, ovarian and uterine cancers for women, which are more dangerous for the bladder and ovaries.	[53], [76]
Preterm birth	Measurements of atrazine metabolites and NO_3 in community water systems (263 municipalities) were linked to birth addresses.	[77] (France)
Breast cancer	· Nitrate levels in public water supplies (PWS) since 1972 was used as an indicator of wastewater contamination and potential mammary carcinogens and endocrine disrupting compounds; excluded women on private wells	[24] (USA),
	· Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollmentresidence (20,147 women; 1751 breast cases); no measurements for private wells	[78] (USA),[79] (Spain), [80], [81],
	· Nitrate levels in PWS (2004–2010), bottled water measurements and private wells and springs (2013 measurements in 21 municipalities in León, Spain, the area with highest non-PWS use) Analyses include women with ≥70% of period from age 18 to 2 years before interview	[82], [83], [84]
Ovary	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence; PWS measurements for nitrate and TTHM; no measurements for private wells (17,216 women; 190 ovarian cases)	[85] (USA)
Congenital malformations	Maternal addresses at delivery linked to municipal water supply median nitrate (NO^{-}_3)3 concentrations; nitrate in rural private wells estimated from historic sampling and kriging.	[86] (Canada)
Congenital heart defects Limb deficiencies Neural tube defects Oral cleft defects	Maternal addresses during the first trimester linked to public water utility nitrate measurements; nitrate intake from bottled water estimated with survey and laboratory testing; nitrate	[87][88] (USA)

	from private wells predicted through modeling; nitrate ingestion (NO_3) estimated from reported water consumption.	
Colon cancer	Increased incidence of nitrate-associated colon cancer in drinking water has also been shown in Iowa	[47]
Small-for-gestational age (SGA) births	Measurements of atrazine metabolites and NO3 in community water systems (263 municipalities) were linked to birth addresses.	[89] (France)
Thyroid cancer	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollmentresidence (21,977 women; 40 thyroid cases); no measurements for private wells	[90] (USA)
Stomach and esophagus (adenocarcinomas)	Nitrate levels (1965–1985) in PWS for ≥70% of person-years (79 distal stomach, 84, esophagus, 321 controls); Private well users sampling at interview (15 stomach, 22 esophagus, 44 controls)	[91] (USA)
Premature rupture of membranes at term (PROM) (37 weeks' gestation or later)	Linked birth residences to 24 water distribution zones; computed average NO3mg/L from historical measurements; independent sampling conducted for 6 zones as part of exposurevalidation; also evaluated trihalomethanes (THM).	[92] (Australia)
Birth defects categorized into 22 groups	Rates of combined and specific birth defects (computed by month of last menstrual period) linked to monthly surface water nitrate concentrations (USGS-NAWQA data); also evaluated atrazine and other pesticides (combined)	[93]
Gastroschisis	Calculated distance between maternal residence and closest stream monitoring site with concentrations >MCL for NO^-_3N, NO^-_2N, or atrazine in surface water (USGS-NAWQA data).	[94] (USA)
Gastric cancer	Epidemiological studies have shown a direct link between gastric cancer and excess nitrate indrinking water.	[95], [96]
Thyroid condition	Nitrate uptake from drinking water has more detrimental effect on thyroid function than uptakefrom food	[97]
Abdominal wall birth defects	Monthly abdominal wall defect rates linked to monthly surface water nitrate and atrazine concentrations (USGS-NAWQA monitoring data).	[98] (USA)
adverse reproductive outcomes, diabetes, and thyroid	In addition to methemoglobinemia, a range of other health effects have been associated with ingesting nitrate-contaminated drinking water, including various cancers, adverse reproductive outcomes (especially neural tube defects), diabetes, and thyroid conditions.	[37]
non-cancer healtheffects	Type 1 childhood diabetes (T1D), blood pressure, and acute respiratory tract infections in children.	[37]
Non-Hodgkin lymphoma	Nitrate levels in PWS among those with nitrate estimates for ≥70% of person-years ≥1960 (181 case, 142 controls); nitrate measurements for private well users at time of interviews (1998–2000; 54 cases, 44 controls)	[99] (USA)

Kidney (renal cell carcinomas)	Nitrate levels in PWS among those with nitrate estimates for ≥70% of person-years ≥1960 (201 cases, 1244 controls)	[100] (USA)
Brain, childhood	Water source during pregnancy and first year of child's life (836 cases, 1485 controls); nitrate test strip measurements of nitrate and nitrite for pregnancy home (except Italy) (283 cases, 537 controls; excluding bottled water users: 207 cases, 400 controls)	[101](USA, Canada, France, Italy, Spain)

Table 2. Nitrate-related Disease from Contaminated Water.

Nitrate removal

Increased use of artificial fertilizers, the disposal of animals and farming wastes, and land-use changes are the main causes responsible for the gradual increase in nitrate levels in groundwater supplies [44, 102]. Because nitrate is highly soluble and mobile, an excess amount of nitrate can be released to surface and groundwater, therewith decreasing the water quality [103-105].

Bioremediation and biodegradation are one of the most environmentally-friendly, cost effective, and practical method for removal of the pollutants out of soil or water [106]. Biological denitrification is one of the main approaches of biological nitrate removal in the dissimilatory pathway, has been shown to be economic and environmentally friendly, due to its selective removal ability to the complete elimination of nitrate and formation of harmless final products [107]. See different technologies for nitrate removal in Table 3.

Technology	Description	Reference
Brine treatment	Removal of dissolved salt ions from the waste stream.Brine treatment removes all of the ions in the medium and meanwhile cannot selectively remove nitrate.	[107]
Reverse osmosis	Reverse osmosis can be very effectively applied for water desalination.	[108]
Ion exchange	A bench-scale ion exchange process with batch biological denitrification of the spent regenerant brine can be developed to remove nitrate from drinking water.	[109]
Electrochemical reduction	Using reactors	[110]
Electrodialysis (ED)	Using membranes- electrodialysis shows several advantages such as highly selective desalination, high water recovery, practically no addition of chemicals and the possibility of stop and go operation (covering of peak demands).	[111]
Catalytic denitrification	Using different types of reactors	[112]
Sorbents	Using carbon-based adsorbents (activated carbon adsorption), clay adsorbents, layered-double hydroxides/hydrotalcite-like compounds/hydroxyapatite, zeolite, chitosan, agricultural wastes, industrial wastes, miscellaneous adsorbents and, etc.	[113]
Chemical denitrification	using zero-valent iron (Fe0), zero-valent magnesium (Mg0)	[113]

Electro-bioremediation	Using bioreactors	[114]
Bioremediation	Using heterotrophic or autotrophic microorganisms in denitrification processes	[115]
Phytoremediation	Using different plants, microalgae and cyanobacteria	[116]
Vermiremediation	Using earthworms	[117]

Table 3. Different Technologies for Nitrate Removal from Water and Soil.

Nitrate benefits

Inorganic nitrate is synthesized by humans and is consumed in large amounts in a healthy vegetable-rich diet. Recently, it has been demonstrated that supplementation of the diet with nitrate has many effects that may be useful in future studies in the prevention and treatment of a wide range of diseases. The next few years should shed light that we can guide whether we should be taking more or less of this substance in our diet. In particular, it is hoped that we can identify individuals (such as those with high blood pressure and atherosclerosis) who are definitely benefit from increased nitrate and conversely individuals (such as those with esophageal dysplasia) who should avoid foods containing a high concentration of nitrate [13]. Much has been reported about inorganic nitrate in scientific journals and popular press. Articles in the 1970s warned us that inorganic nitrate could theoretically be metabolized in the human body to the compounds which are carcinogenic. Recently, There is a record that nitrate can be metabolically converted to nitrite and nitric oxide, providing a beneficial protective function to improve exercise performance and prevent vascular disease, prevent infection, and protect the stomach [13].

Dietary amounts of nitrate obviously have strong effects in humans, including blood pressure reduction, inhibition of platelet aggregation, and vasoreactivity. In animal models, nitrate protects against ischemic-reperfusion injuries and a wide range of cardiovascular disorders. Furthermore, nitrate unexpectedly decreases whole body oxygen cost during exercise with preserved or even improved maximal performance. Oxidative stress and reduced NO bioavailability are significantly associated with the development of hypertension and other forms of cardiovascular diseases. A major goal for the effects of nitrate and its reaction products can be the mitochondrion and modulation of oxidative stress. All in vivo effects of nitrate can be achieved with high intake of vegetables. A theory is emerging suggesting nitrate as an active component in vegetables plays an important role in the beneficial health effects of this food group, including protection against cardiovascular disease and diabetes [95].

Although Injectable gallium nitrate which is a treatment for hypercalcemia of malignancy due to its immunosuppressive properties, has few adverse effects at therapeutic doses, high-dose infusions may result in severe nephrotoxicity, exclusively in patients who are not adequately hydrated, and severe anemia [118].

Organic nitrates are extensively used in the management of coronary artery disease. These drugs are given to patients with stable angina pectoris and also to patients with unstable angina pectoris, heart failure, and acute myocardial infarction. Although they are advantageous for the treatment of these disorders, their therapeutic value is compromised by the rapid development of tolerance during ongoing therapy [119].

A double-blind randomized crossover eight-week pre-experiment included 16 patients with severe congestive heart failure who received isosorbide dinitrate or placebo followed by the opposite treatment for another eight weeks. This initial trial suggests that long-term vasodilator therapy may be clinically beneficial in congestive heart failure [120].

Long-acting nitrates could reverse CHF-induced changes in drenoceptors (AR) and angiotensin II receptor (ATR) subtypes in the kidney, and restore heart function to protect kidney function. In Comparision with monotherapy, the combination of olmesartan and nitrates indicates significant advantages in regulating AR and ATR subtypes [121].

The findings of a systematic review demonstrate that silver nitrate may be effective in managing the clinical symptoms of recurrent aphthous stomatitis (RAS), and no side effects have been reported so far. To confirm these findings, more high-quality RCTs is needed [122].

Nitrate intake from vegetables is inversely linked with atherosclerotic vascular disease (ASVD) mortality independent of lifestyle and cardiovascular risk factors in this population of elderly women without widspread ASVD or diabetes. These results support the idea that nitrate-rich vegetables may reduce the risk of age-related mortality from ASVD. Independent of other risk factors, higher plant nitrate was correlated to reduced CCA-IMT and a lower risk of an ischemic cerebrovascular disease event [123].

Webb et al (2008) showed a significant reduction in systolic and diastolic blood pressure within 3 h of ingestion of 500 ml of beetroot juice (a rich source of nitrate) [124]. This is consistent with previous results from Lundberg and Weitzberg's group (2006) showing a significant blood pressure-lowering effect from 3 days of supplementation with sodium nitrate [125].

In 1867, the organic nitrate, Amyl of nitrite firstly used as a therapeutic agent in the treatment of angina pectoris but was replaced later by the organic nitrate, nitroglycerin (NTG), owing to the ease of administration and longer duration of action. The administration of NTG, continues to be used in the treatment of angina pectoris and heart failure during the birth of modern pharmacology [126]. The nitrates/nitrites are classified as agents that directly relax vascular smooth muscle and relax other smooth muscles including ureteral, bronchial, and uterine smooth muscle [127-130].

Nitric oxide (NO), produced from L-arginine and oxygen by NO synthases, is a pleiotropic signaling molecule involved in the regulation of cardiovascular and metabolic systems. The inorganic anions nitrate and nitrite, originating from dietary and endogenous sources, generate NO bioactivity in a process involving symbiotic oral bacteria and host enzymes in blood and tissues. The cardio-metabolic effects of dietary nitrate from experimental and clinical studies include improved endothelial function, increased exercise performance, lowering of blood pressure, and reversal of metabolic syndrome, as well as antidiabetic effects.

The underlying mechanisms of nitrate's metabolic health effects are being revealed, including reduction of oxidative stress, interaction with mitochondrial respiration, and activation of key metabolic regulatory pathways (Lundberg et al. 2018). Besides, a couple of researches provided evidence on the Potential Benefit of inorganic Nitrate in Acute Kidney Injury and Renal Cell Cancer [131, 132].

In conclusion, an effective way to control the concentration of nitrate in food and drinking water is to prevent contamination of which. This means that forms of proper management of agricultural practices, septic tanks, sewer leakage control, as well as management of fertilizer and manure application and storage of animal manures, as well as Educate consumers and farmers and increase organic production should be encouraged. Despite the effectiveness of nitrate in the treatment of diseases, in the case of soil and water contamination with the excess amount of nitrate, the most cost-effective and efficient approach is the use of the biological method.

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