IJPSR (2018), Volume 9, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 August, 2017; received in revised form, 15 October, 2017; accepted, 20 October, 2017; published 01 May, 2018

A JOURNEY OF DIETARY NITRATE AS A HEALTH PROMOTER

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Keywords:

Nitrite, Nitrate, Nitric oxide, Therapeutic effects, Blood Pressure, Ischaemia-reoxygenation injury, Cancer, Bone marrow, Angiogenesis, Vasodilator, Hypoxia

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ABSTRACT: Dietary nitrate has been demonstrated to have a range of beneficial vascular effects, including reducing blood pressure, reduction in pulse wave velocity, regulation of cerebral blood flow, enhancing exercise performance in healthy individuals, stimulating angiogenesis and vasculogenesis *etc*. Earlier studies with nitrate or nitrite also demonstrate the synergistic effects against ischaemia-reperfusion injury and reduce arterial stiffness, inflammation and intimal thickness. However, there is a need for scientific evidences for hard endpoints beyond epidemiological studies. Although studies have suggested reduction in cardiovascular risk and cancer with diets high in nitrate-rich vegetables but still a lot remains to be elucidated. Moreover various therapeutic effects have reported that the nitrate and nitrite have more affluent biological actions till now, and numerous attempts are currently ongoing for the consideration of potential useful effects in the clinical uses. Here we corroborated a brief data regarding clinical uses of nitrite and nitrate that may serve as potential therapeutic regimes.

INTRODUCTION: Nitrate is an inorganic polyatomic anion present in the environment. Nitrate content of vegetables is its key characteristic and usually found in them in the maximum amount. Approximately 80% of dietary nitrates are derived from vegetables, fruits, meats and processed meats. It also plays a crucial role in the nitrogen cycle of the environment [1, 2]. It is usually a non-toxic element but its metabolites may have adverse health effects on human health. Although inorganic nitrate is considered as an undesirable food component and pollutant in drinking water [3], yet dietary nitrogen which is commonly found in beetroot and spinach is linked with various physiological health benefits [4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(5).1737-44

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(5).1737-44

Nitrates are usually found in soil, air, water and food and are produced naturally within the human body [1]. It can also be used as food additives [5]. Nitrate is converted into nitrite with the help of bacterial (Nitrosococus) enzyme. The dietary nitrites and nitrates which are produced from vegetables and fruits may cause blood pressure lowering effects due to intake of a Dietary approach to stop hypertension (DASH) diet. Nitrites are produced endogenously by the oxidation of nitric oxide in gastrointestinal tract [6].

Over the last 5 years, an increasing evidence of physiological effects of nitrate, particularly on human system and the 'nitrate-nitrite-NO pathway' has been observed. This review provides an update on the human diseases related to the potential effects of introducing nitrate as a therapeutic regime and thus guides patients and health professionals about the uses of nitrate.

2. Nitrate Sources: Approximate 85% nitrate (NO_3^-) is derived from vegetables [7, 8] rest comes from drinking water and other food sources [9]. The common sources of nitrate are lettuce, celery, beetroot and spinach [7]. It has been seen that nitrate content in organic vegetables may be lesser than that of the vegetables which are grown in the presence of nitrogen containing fertilizers. Dietary nitrite (NO_2^-) has been derived from processed meat, where it is added to prevent the development of botulinum toxin [10]. Inorganic nitrate obtained from food and vegetables is a major component of gun powder [11] and can be used as a food preservative [12 - 14] **Table 1**.

TABLE 1: THE NITRATE AND NITRITE CONTENT OF EDIBLE VEGETABLES, FRUITS AND PROCESSED MEAT

Types of vegetables and the varieties	Nitrate (mg/100 gm fresh weight)	Nitrite (mg/100 gm fresh weight)
Green vegetable:		
Spinach	23.9–387.2	0–0.073
Lettuce	12.3–267.8	0.008–0.215
Mustard leaf	70-95	0.012–0.064
Root vegetables:		
Carrot	92–195	0.002–0.023
Melon:		
Cucumber	1.2–14.3	0–0.011
Wax gourd	35.8–68.0	0.001–0.006
Nightshade:		
Eggplant	25.0–42.4	0.007–0.049
Cabbage:		
Cabbage	25.9–125.0	0–0.041
Chinese cabbage	42.9–161.0	0–0.065
Cole	76.6–136.5	0.364–0.535
Bok choy	102.3–309.8	0.009–0.242
Fruit:		
Banana		
Apple sauce	4.5	0.009
Orange	0.3	0.008
Fruit mix	0.8	0.02
Meats/Processed meats:	0.9	0.08
Bacon	5.5	0.38
Hot dog	9.0	0.05
Bacon, nitrite free	3.0	0.68
Pork tender loin	3.3	0.00
Ham	0.90	0.89

Norman G H *et al*., 2009 [14]

3. Modulation of Nitric Oxide Production by Dietary Nitrate: The gastrointestinal and vascular nitric oxide production can be increased through various ways based upon human food choices and lifestyle habits. Various dietary factors, commensal bacteria and physical activity may influence nitric oxide generation. The normal plasma concentration of nitrite, nitrate and nitric oxide is found to be 100 to 500 nmol/L, 20 - 50000 nmol/L and < 1 nmol/L respectively. Physical activity enhances the production of nitric oxide in vascular endothelium [15] and post exercise plasma nitrite concentrations is considered as an index of exercise capacity [16]. Dietary nitrate supplementation at the concentrations achievable by vegetable consumption has resulted in more efficient energy production without increasing lactate concentrations during sub maximal exercise [17]. Consumption of polyphenol rich diets provides significant increase in nitric oxide production in gastrointestinal tract [18, 19]. The metabolic activity of common bacteria in gastrointestinal tract and probiotic bacteria produce nitric oxide from nitrite and to a small amount from the nitrate [20, 21].

The physiological redistribution of nitrate, nitrite, and nitric oxide from exogenous (dietary) and endogenous sources is depicted in **Fig. 1**. The bacterial nitrate reductases and certain mammalian enzymes having nitrate reductase activity in tissues play a role in nitric oxide generation from dietary nitrate **Fig. 1**.

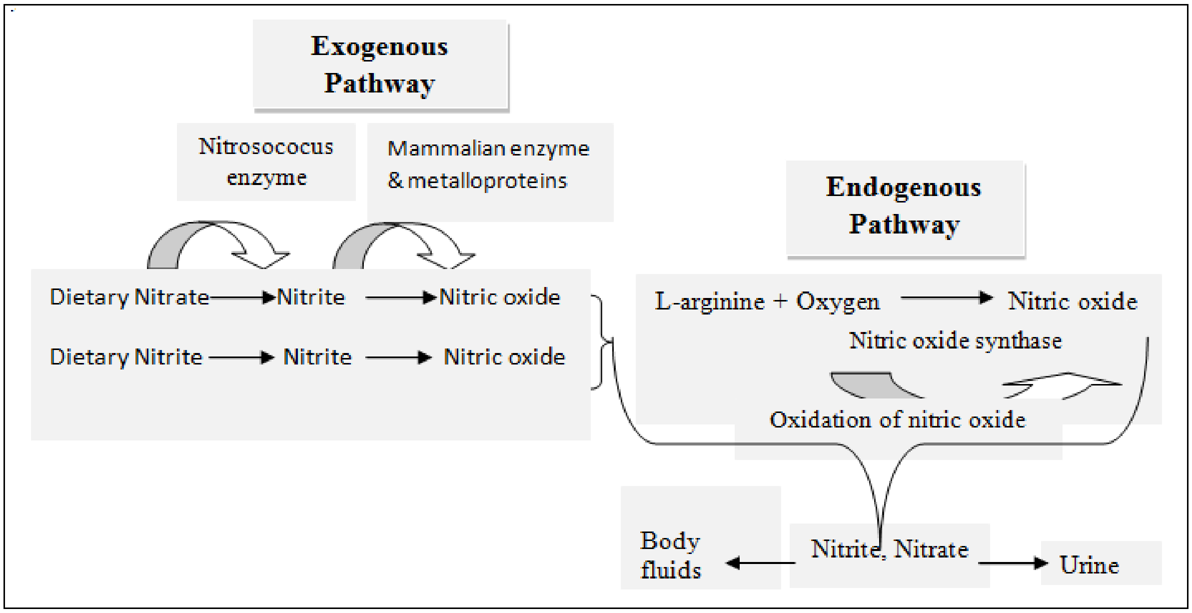

FIG. 1: MECHANISM OF NITRATE, NITRITE AND NITRIC OXIDE PRODUCTION FROM EXOGENOUS (DIETARY) AND ENDOGENOUS SOURCES (L-ARGININE)

The exogenous dietary consumption of nitrate leads to the formation of nitrite through nitrosococcus enzyme and then it is further converted to nitric oxide with the help of mammalian enzyme and metalloproteins. L-arginine (endogenous) combines with oxygen and forms nitric oxide with the help of nitric oxide synthase enzyme. The oxidation of nitric oxide yields nitrite and nitrate which are redistributed in the body fluids and excreted by urine.

4. Acceptable Daily Intake: The World Health Organization (WHO) has set an acceptable daily intake (ADI) of nitrate and nitrite, respectively at 3.67 mg/kg body weight and 0.13 mg/kg body weight (expressed as nitrate and nitrite ion) [22]. European food safety authority has recommended the ADI for nitrate as 3.7 mg kg^{-1} (0.06 mmol kg^{-1}) this equals to ~260 mg day^{-1} for a 70 kg adult (~4.2 mmol) [6]. Acceptable daily intake of dietary intake of nitrate at global level based on body weight is depicted in **Table 2** [23].

TABLE 2: ACCEPTABLE DAILY INTAKE (ADI) OF NO 3 FROM SOURCES OTHER THAN FOOD ADDITIVES AT THE GLOBAL LEVEL (BASED ON 60 kg BODY WEIGHT)

Regional diet	Intake ($mgday^{-1}$)	ADI (μgmg^{-1})
Latin American	55	250
Far Eastern	28	100
African	20	100
Middle Eastern	40	200
European	155	700

Hambridge T: 2003 [23]

5. Effects of Dietary Nitrate on Human Health: Earlier reported dietary nitrate intervention studies on human health are summarized in **Table 3**. The nitrate-nitrite-NO pathway is considered as a back-up system (mostly during hypoxia and low pH) to the classical L-arginine-NO synthase pathway [24]. Recent reports have given evidences that nitrate and nitrite may include various therapeutic inferences [25] such as lowering blood pressure in humans [26, 27], protection against ischemia-reperfusion injury [28], decreasing oxidative stress, and reduced oxygen consumption during exercise which may improve physical capacity in individuals with restricted pulmonary functions [24] as well as increasing mitochondrial efficiency [26]. Nitric oxide availability is a central event in the pathogenesis of metabolic syndrome and other diseases [29]. A 10-week inorganic nitrate therapy decreased levels of serum triglycerides, lowered visceral fat accumulation, and controlled disturbed glucose tolerance [30]. The therapeutic effects of dietary nitrate in the body are shown in **Fig. 2**.

5.1 Lowering Blood Pressure: In a randomized, double-blind, crossover study, Larsen *et al.*, [26] found that diastolic BP was brought down to 3.7 mmHg following 3 day dietary supplementation with sodium nitrate compared to placebo sodium chloride in 17 healthy volunteers [26, 31]. Similar studies of Webb *et al.*, and Vanhatalo *et al.*, [27, 32] have shown that a single ingestion of 500 ml beetroot juice, leads to an acute fall in blood pressure. Kapil *et al.,* [33] used potassium nitrate capsules and revealed a dose dependent reduction in BP (with 4, 12 and 24 mmol nitrate) with zero effect seen with potassium chloride as control. The post hoc analysis estimated that there is a significant reduction in BP in males than in females. A study carried out on physically active healthy Japanese volunteers (10 men and 15 women; mean age 36 ± 10 years, BMI < 18.5) has shown a sustained reduction in diastolic BP (4.5 mmHg over 10 days), where the subjects took a nitrate rich diet in comparison to a low nitrate diet taken by other subjects [34].

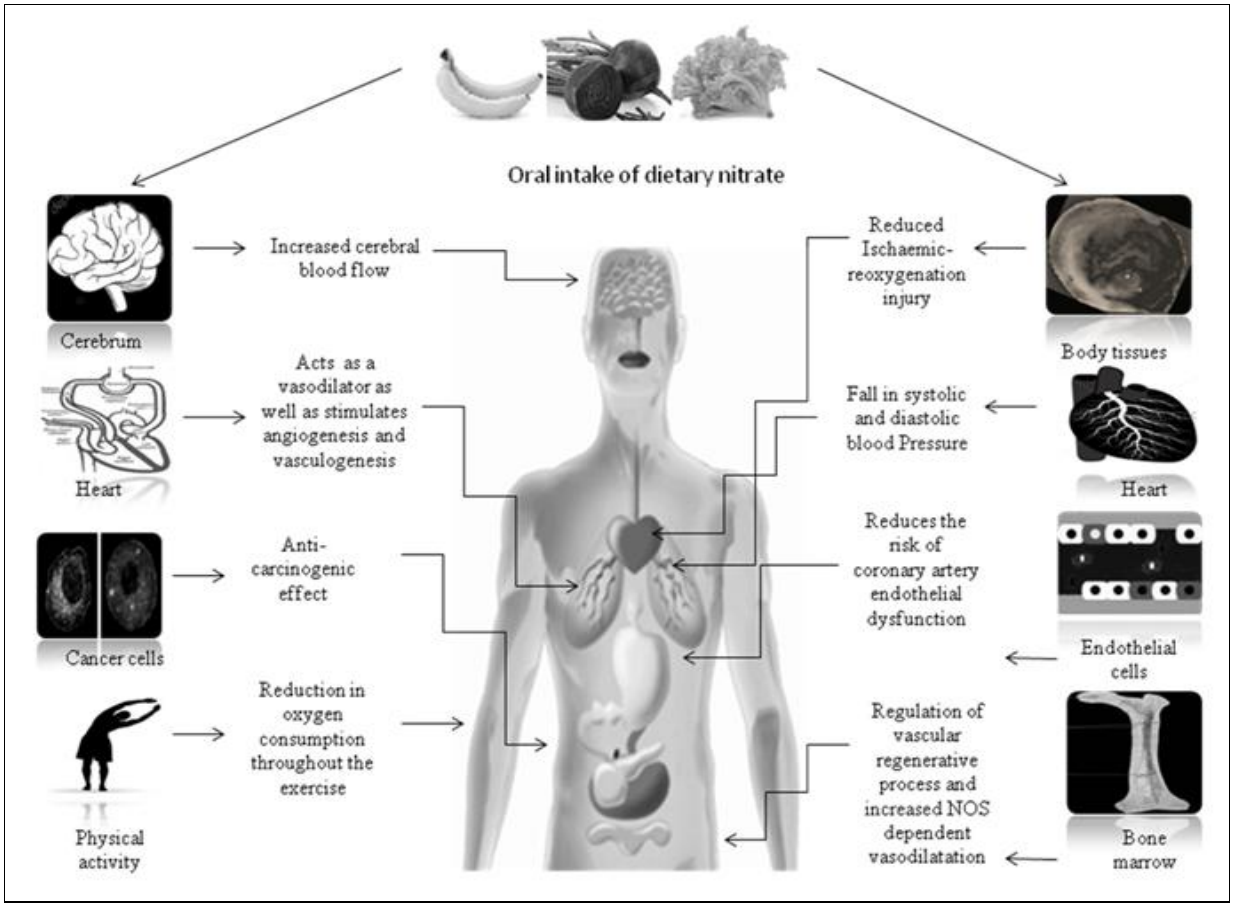

FIG. 2: BENEFITS OF DIETARY NITRATE ON HUMAN HEALTH

5.2 Coronary Artery Endothelial Dysfunction (CAED): The endothelial dysfunction is a result of imbalance between vasodilatation and vaso-constriction substances formed by the endothelium. The plasma nitrate concentration indicates inherent NOS activity which is inversely related to various cardiovascular risk factors and directly correlated with endothelial functions as estimated by flow mediated dilation (FMD) *i.e.* flow mediated dilation in humans [35]. Previously documented study has shown that there is a reduction in pulse wave velocity accompanied by lowering in systolic blood pressure (SBP) with intake of nitrate [36]. Another study has estimated a small increase in mean FMD of ~0.5% for duration of 4 min in 30 healthy volunteers following ingestion of 200 mg of spinach for a period of one week [37].

5.3 Ischaemia-reoxygenation Injury: Ischemia-reoxygenation injury is a damage of the tissue when blood supply returns back to the tissue after a period of ischemia or anoxia or hypoxia. One of the study reported that nitrate supplementation in the form of beetroot juice reduced endothelial function impairment after ischemia-reperfusion injury during flow mediated dilation of the brachial artery in healthy human subjects [27].

5.4 Nitrate in Cancer Prevention: Epidemiological studies found that fruits and vegetables play a protective role in preventing various types of cancer [38]. The National Institutes of Health (NIH)-Diet and Health Study has shown a beneficial role of nitrate in ovarian and thyroid cancer in Retired Persons [39, 40].

Also, some other studies have shown potential associations between dietary intakes of nitrate with gastric cancer [41]. The betalain extracts obtained from beetroot may suppress the effect of malignant tumours. The beetroot extracts noticeably repressed angiogenesis and tumorgenesis in oesophageal lesions, cell proliferation.

These effects were largely attributed to its radical scavenging and anti-inflammatory activity. The chemo-preventive role of *betacyanin* extracts have also been seen in human prostate, skin, breast and pancreatic tumour cells [42, 43, 44]. Human cell line studies suggested that beetroot supplementation can be considered as a future strategy to handle symptoms of inflammation in cancer.

5.5 Nitrate in Bone Marrow – Acquired Disseminating Angiogenesis: Endothelial nitric oxide is implicated in regulating vascular homeostasis. Nitric oxide (NO) was also found to regulate mobilization and function of circulating angiogenic cells (CACs). The supposedly inert anion nitrate, abundant in vegetables, can be stepwise reduced *in vivo* to form nitrite, and consecutively NO, representing an alternative to endogenous NO formation by NO Synthase. Dietary inorganic nitrate acutely mobilizes CACs via serial reduction to nitrite and NO.

Heiss and colleagues hypothesized that sodium nitrate intake (0.15 mmol/kg) led to an acute increase in $CD34^+/KDR^+$ (Kinase Insert Domain Receptor) and $CD133^+/KDR^+$ cells with simultaneous increase in NOS-dependent vasodilatation [45, 46, 47]. The nitrate-nitrite - NO pathway could offer a novel nutritional approach for regulation of vascular regenerative processes.

5.6 Nitrate in Oxygen Consumption during Exercise in Hypoxic Condition: High intensity vigorous exercise leads to hypoxia in muscles which is linked to decreased muscle oxidative function and lowered exercise tolerance. Larsen *et al*., have shown the effects of 3 days intake of sodium nitrate on exercise performance resulting in lowering of oxygen consumption during sub maximal exercise [26]. Previously reported studies have shown that nitrate may have therapeutic applications in improving muscle energetic and functional capacity during hypoxia [17, 48 - 50].

5.7 Effect of Nitrate on Cerebral Blood Flow: Nitric oxide (NO) plays an important role in regulating cerebral blood flow during stroke, neural activity and brain blood flow. A study has established that high-nitrate diet selectively increased regional cerebral perfusion in frontal lobe white matter in the brain, especially between the dorsolateral prefrontal cortex and anterior cingulated cortex, which are the regions concerned with the executive functioning of the brain [51]. Further studies are needed to confirm that dietary nitrate affect cerebral functions in the elderly subjects.

5.8 Nitrate in High-altitude Pulmonary Edema (HAPE): High altitude pulmonary edema (HAPE) is a non-cardiogenic pulmonary edema, which occurs in non-acclimatized individuals at altitudes above 3,000 m usually on rapid ascent within the first 2 - 5 days after arrival. An extreme increase in pulmonary artery pressure (PAP) leads to the formation of edema. This is considered as a critical pathophysiological condition associated with HAPE. Many of the previously reported studies have indicated that the involvement of reduced NO availability in hypoxia is a major cause of excessive hypoxic PAP rise in HAPE-susceptible individuals [52 - 56].

6. Synergistic Role of Nitrate and Nitrite with Various Nutrients: The end effect of dietary nitrate can be improved or altered by correlating with other nutrients. They have established that polyphenols present in fruits, vegetables and red wine is effective in transforming nitrite to nitric oxide both *in vitro* and in human [19]. Hawthorn berry extract containing polyphenols was developed to have abundant potent nitrite reductase activity which converted nitrite to nitric oxide. A placebo-controlled study has shown that 30 days intake of sodium nitrite, beetroot, Vitamin C, L-citrulline, Vitamin B12 and Hawthorn berry extract in patients with three or more cardiovascular risk factors, decreased triglyceride levels. However, no reduction was seen in the blood pressure [57].

Future Prospective: The therapeutic benefits of nitrite and nitrate are beginning to be translated in humans by the use of increasing number of clinical trials based on nitrite and nitrate. The collective body of evidence suggests that food enriched in nitrite and nitrate provide significant health benefits with very little risk. Future studies should assess exposure for individuals (*e.g.*, case-control, cohort studies) in a time frame relevant to disease development, and evaluate factors which are beneficial for human health. Studies should account for the potential effects of dietary nitrate and should include human population.

TABLE 3: EFFECTS OF DIETARY NITRATE IN HEALTHY INDIVIDUALS STUDIES, SHOWING DURATION, ACTIVITY, FINDING OF NITRATE AND SUMMARY OF EFFECT

Activity Reported	Study Population	Findings	Reference
Effect in lowering of BP	• 10 males and 10 females aged between 47 – 57 with a high risk of CVD	After a single ingestion of 500 ml beet root juice, an acute falls in BP	Larsen *et al.*, (2006) [26]
	• 6 Healthy Human subjects	A dose dependent reduction in BP with the utilization of potassium nitrate capsules (with 4, 12 and 24mmol nitrate)	Kapil *et al.*, (2010) [33]
	• 25 Healthy volunteers	Sustained reduction in the diastolic BP of ~ 4.5mmHg over 10 days	Sobko *et al.*, (2010) [34]
	• 25 Healthy human subjects participants, 10 men and 15 women	Reduction in BP near 7/5 mmHg following 15 days supplementation with 500ml beetroot juice	Vanhatalo *et al.*, (2010) [32]
	• 69 Healthy human subjects	Reduction in pulse wave velocity accompanying the reduction in systolic blood pressure	Bondonno *et al.*, (2012) [37]
Role in Ischaemia-reoxygenation injury	• 14 Healthy randomized subjects	Nitrate supplementation in the form of beetroot juice reduced endothelial function impairment subsequent to ischemia-reperfusion	Webb *et al.*, (2008) [27]
Chemo protective role	• Healthy human subjects	Potential links between high nitrate intake and epithelial ovarian cancer and thyroid cancer	Ward *et al.*, (2010) [39] Aschebrook-Kifoy *et al.*, (2012) [40]
Anti-cancer effects of beetroot	• Human prostate (PC-3) and breast (MCF-7) cancer cell lines	Betacyanin extracts shown a chemo-preventive role in human prostate, skin, breast and pancreatic tumour cells	Das *et al*., (2013) [41] Kapadia *et al*., (2011) [42] Kapadia *et al*., (2003) [43] Kapadia *et al*., (2013) [44]
Bone marrow–acquired disseminating angiogenic cells	• Healthy Volunteers	Sodium nitrate intake (0.15 mmol/kg) leads to acute increase in CD34+/KDR+ and CD133+/KDR+ cells, raised NOS-dependent vasodilatation and increased flow-mediated vasodilatation	Heiss *et al*., (2012) [45]
Oxygen consumption throughout the exercise	• Low fit and high fit participants at five different exercise intensities	Reduction in oxygen consumption during sub maximal exercise between 45–80% of peak exercise	Larsen *et al*., (2007) [17] Bailey *et al*., (2010) [48] Lansley *et al*., (2011) [49]
Response to hypoxia	• Nine healthy subjects	Nitrate supplementation debilitated muscle metabolic agita during hypoxic exercise	Vanhatalo *et al*., (2011) [50]
Outcome of nitrate on cerebral blood flow	• Healthy old adults	High nitrate intake selectively increased regional cerebral perfusion in frontal lobe in the brain	Presley *et al*., (2011) [51]
Role in High-altitude pulmonary oedema (HAPE)	• HAPE mountain Japanese patients	Acts as a vasodilator, and directly stimulates angiogenesis and vasculogenesis	Bartsch (1999) [52] Hackett *et al*., (2001) [53] Schoene (2004) [54] Schoene *et al*., (2001) [55] Swenson *et al*., (2002) [56]

CONCLUSION: Synergistic effects of dietary (inorganic) nitrate originate from the ‘nitrate-nitrite-nitric oxide (NO) mechanism’. Nitrate has potential therapeutic role on human health. Dietary nitrate can be of immense medical use in conditions like: hypoxia, HAPE, cardiovascular, cancer, brain functions and angiogenesis. The data provided in this review highlights the importance of nitrate in human health which can help medical professionals and scientific community to guide individuals on the therapeutic benefits of dietary nitrate. However, in spite of its enormous role as therapeutic regimes, it finds very little use in the field of medicine.

ACKNOWLEDGEMENT: Support received from DRDO is gratefully acknowledged. The authors are thankful to Director DIPAS, DRDO in providing all the necessary support.

CONFLICT OF INTEREST: The authors have no conflict of interest.

REFERENCES:

1. Walker R: Nitrates, nitrites and N-nitrosocompounds: A review of the occurrence in food and diet and the toxicological implications. Food Addit Contam. 1990; 7: 717–768.
2. Speijers GJA and Vanden Brandt PA: Nitrate and potential endogenous formation of N-nitroso compounds. WHO Food Additives Series 2003; 50.
3. Magee PN and Barnes JM: The production of malignant primary hepatic tumours in the rat by feeding dimethyl nitrosamine. Br J Cancer 1956; 10: 114-122.
4. Gilchrist M, Winyard PG, Aizawa K, Anning C, Shore A and Benjamin N: Effect of dietary nitrate on blood pressure, endothelial function, and insulin sensitivity in type 2 diabetes. Free Radic Biol Med. 2013; 60: 89–97.
5. Speijers GJA: Nitrite (and potential endogenous formation of N-nitroso compounds), in Toxicological evaluation of certain food additives and contaminants in food. Ed by World Health Organization, Food Additives Series 35, Geneva 1996; 269: 323.
6. Katan MB: Nitrate in foods: harmful or healthy? Am J Clin Nutr. 2009; 90: 1-10.
7. Gangolli SD, Van den Brandt PA, Feron VJ, Janzowsky C, Koeman JH, Speijers GJ *et al.*: Nitrate, nitrite and N-nitroso compounds. Eur J Pharmacol 1994; 292: 1-38.
8. Van Loon AIM and Van Klaveren JD: Nitraatinname van de Nederiandse bevolking. Voeding 1991; 52: 96-100.
9. Knight TM, Forman D, Al-Dabbagh SA and Doll R: Estimation of dietary intake of nitrate and nitrite in Great Britain. Food and Chemical Toxicology 1987; 25: 277-285.
10. Brender J, Olive JM, Felkner M, Suarez L, Marckwardt W and Hendricks KA: Dietary nitrites and nitrates, nitrosatable drugs, and neural tube defects. Epidemiology 2004; 15: 330-336.
11. Lundberg JO and Govoni M: Inorganic nitrate is a possible source for systemic generation of nitric oxide. Free Radic Biol Med. 2004; 37: 395-400.
12. Cassens R: Use of sodium nitrite in cured meats today. Food Technol. 1995; 49: 72-81.
13. Wang R, Tischner R, Gutiérrez RA, Hoffman M, Xing X, Chen M *et al.:* Genomic Analysis of the Nitrate Response Using a Nitrate Reductase-Null Mutant of Arabidopsis. Plant Physiol 2004; 136: 2512-2522.
14. Norman GH, Yaoping T and Nathan SB: Food sources of nitrates and nitrites: The physiologic context for potential health benefits. Am J Clin Nutr. 2009; 90: 1-10.
15. Allen JD, Cobb FR, Gow AJ: Regional and whole-body markers of nitric oxide production following hyperemic stimuli. Free Radic Biol Med. 2005; 38: 1164-1169.
16. Rassaf T, Lauer T, Heiss C, Balzer J, Mangold S, Leyendecker T *et al.*: Nitric oxide synthase-derived plasma nitrite predicts exercise capacity. Br J Sports Med. 2007; 41: 669-673.
17. Larsen FJ, Weitzberg E, Lundberg JO and Ekblom B: Effects of dietary nitrate on oxygen cost during exercise. Acta Physiol. 2007; 191: 59-66.
18. Peri L, Pietraforte D, Scorza G, Napolitano A, Fogliano V, Minetti M *et al.*: Apples increase nitric oxide production by human saliva at the acidic pH of the stomach: a new biological function for polyphenols with a catechol group? Free Radic Biol Med. 2005; 39: 668-81.
19. Gago B, Lundberg JO, Barbosa RM and Laranjinha J: Red wine-dependent reduction of nitrite to nitric oxide in the stomach. Free Radic Biol Med. 2007; 43: 1233-42.
20. Sobko T, Huang L, Midtvedt T, Norin E , Gustafsson LE , Norman M *et al.*: Generation of NO by probiotic bacteria in the gastrointestinal tract. Free Radic Biol Med. 2006; 41: 985-91.
21. Panesar NS: Downsides to the nitrate-nitrite-nitric oxide pathway in physiology and therapeutics? Nat Rev Drug Discov. 2008; 7: 156-167.
22. Lundberg JO and Govoni M: Inorganic nitrate is a possible source for systemic generation of nitric oxide. Free Radic Biol Med. 2004; 37: 395-400.
23. Hambridge T: Nitrate and nitrite: intake assessment. WHO Food Additives Series 50 2003.
24. Weitzberg E and Lundberg JO: Dietary nitrate-a slow train coming. J Physiol. 2011; 589: 5333-5334.
25. Ghasemi A and Zahediasl S: Is nitric oxide a hormone? Iran Biomed J. 2011; 15: 59-65.
26. Larsen FJ, Ekblom B, Sahlin K, Lundberg JO and Weitzberg E: Effects of dietary nitrate on blood pressure in healthy volunteers. N Engl J Med. 2006; 355: 2792-2793.
27. Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S *et al.*: Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. Hypertension 2008; 51: 784-790.
28. Bryan NS, Calvert JW, Elrod JW, Gundewar S, Ji SY and Lefer DJ: Dietary nitrite supplementation protects against myocardial ischemia-reperfusion injury. Proc Natl Acad Sci USA 2007; 104: 19144-19149.
29. Lundberg JO, Carlstrom M, Larsen FJ and Weitzberg E: Roles of dietary inorganic nitrate in cardiovascular health and disease. Cardiovasc Res. 2011; 89: 525-532.
30. Carlstrom M, Larsen FJ, Nystrom T, Hezel M, Borniquel S, Weitzberg E *et al.*: Dietary inorganic nitrate reverses features of metabolic syndrome in endothelial nitric oxide synthase-deficient mice. Proc Natl Acad Sci USA 2010; 107: 17716-20.
31. Lundberg JO and Govoni M: Inorganic nitrate is a possible source for systemic generation of nitric oxide. Free Radic Biol Med. 2004; 37: 395-400.
32. Vanhatalo A, Bailey SJ, Blackwell JR, DiMenna FJ, Pavey TG, Wilkerson DP *et al.*: Acute and chronic effects of dietary nitrate supplementation on blood pressure and the physiological responses to moderate-intensity and incremental exercise. Am J Physiol Regul Integr Comp Physiol. 2010; 299: 1121-1131.
33. Kapil V, Milsom AB, Okorie M, Maleki-Toyserkani S, Akram F, Rehman F *et al.*: Inorganic nitrate supplementation lowers blood pressure in humans: role for nitrite-derived NO. Hypertension 2010; 56: 274-281.
34. Sobko T, Marcus C, Govoni M and Kamiya S: Dietary nitrate in Japanese traditional foods lowers diastolic blood pressure in healthy volunteers. Nitric Oxide 2010; 22: 136-140.
   Kleinbongard P, Dejam A, Lauer T, Rassaf T, Schindler A, Picker O *et al.*: Plasma nitrite reflects constitutive nitric oxide synthase activity in mammals. Free Radic Biol Med. 2003; 35: 790-796.
35. Bahra M, Kapil V, Pearl V, Ghosh S and Ahluwalia A: Inorganic nitrate ingestion improves vascular compliance but does not alter flow-mediated dilatation in healthy volunteers. Nitric Oxide 2012; 26: 197-202.
36. Bondonno CP, Yang X, Croft KD, Considine MJ, Ward NC, Rich L *et al.*: Flavonoid-rich apples and nitrate-rich spinach augment nitric oxide status and improve endothelial function in healthy men and women: A randomized controlled trial. Free Radic Biol Med. 2012; 52: 95-102.

37. Steinmetz KA and Potter JD: Vegetables, fruit, and cancer prevention: a review. J Am Diet Ass 1996; 96: 1027-1039.
38. Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR *et al.*: Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology 2010; 21: 389-95.
39. Aschebrook-Kilfoy B, Ward MH, Gierach GL, Schatzkin A, Hollenbeck AR, Sinha R *et al.*: Epithelial ovarian cancer and exposure to dietary nitrate and nitrite in the NIH-AARP Diet and Health Study. Eur J Cancer Prev. 2012; 21: 65-72.
40. Das S, Filippone SM, Williams DS, Das A and Kukreja RC: Beet root juice promotes apoptosis in oncogenic MDA-MB-231 cells while protecting cardiomyocytes under doxorubicin treatment. J Exp Second Sci. 2013; 2-6.
41. Kapadia GJ, Azuine MA, Rao GS, Arai T, Iida A and Tokuda H: Cytotoxic effect of the red beetroot (*Beta vulgaris* L.) extract compared to doxorubicin (Adriamycin) in the human prostate (PC-3) and breast (MCF-7) cancer cell lines. Anti-Cancer Agent Med Che 2011; 11: 280-84.
42. Kapadia GJ, Azuine MA, Sridhar R, Okuda Y, Tsuruta A, Ichiishi E *et al.*: Chemoprevention of DMBA-induced UV-B promoted, NOR-1-induced TPA promoted skin carcinogenesis, and DEN-induced phenobarbital promoted liver tumors in mice by extract of beetroot. Pharmacol. Res. 2003; 47: 141-148.
43. Kapadia GJ, Rao GS, Ramachandran C, Iida A, Suzuki N, Tokuda H *et al.*: Synergistic cytotoxicity of red beetroot (*Beta vulgaris* L.) extract with doxorubicin in human pancreatic, breast and prostate cancer cell lines. J. Complement. Med. 2013; 10: 113-122.
44. Heiss C, Meyer C, Totzeck M, Hendgen-Cotta UB, Heinen Y, Luedike P *et al.*: Dietary inorganic nitrate mobilizes circulating angiogenic cells. Free Radic Biol Med. 2012; 52: 1767-1772.
45. Dezfulian C, Shiva S, Alekseyenko A, Pendyal A, Beiser DG, Munasinghe JP *et al*.: Nitrite therapy after cardiac arrest reduces reactive oxygen species generation, improves cardiac and neurological function, and enhances survival *via* reversible inhibition of mitochondrial complex I. Circulation 2009; 120: 897-905.
46. Lundberg JO and Weitzberg E: Biology of nitrogen oxides in the gastrointestinal tract. Gut 2013; 62: 616-629.
47. Bailey SJ, Winyard P, Vanhatalo A, Blackwell JR, Dimenna FJ, Wilkerson DP *et al.*: Dietary nitrate supplementation reduces the O2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. J Appl Physiol. 2009; 107: 1144-1155.
48. Lansley KE, Winyard PG, Fulford J, Vanhatalo A, Bailey SJ, Blackwell JR *et al.*: Dietary nitrate supplementation reduces the O_2 cost of walking and running: a placebo-controlled study. J Appl Physiol. 2011; 110: 591-600.
49. Vanhatalo A, Fulford J, Bailey SJ, Blackwell JR, Winyard PG and Jones AM: Dietary nitrate reduces muscle metabolic perturbation and improves exercise tolerance in hypoxia. J Physiol. 2011; 589: 5517-5528.
50. Presley TD, Morgan AR, Bechtold E, Clodfelter W, Dove RW, Jennings JM *et al*.: Acute effect of a high nitrate diet on brain perfusion in older adults. Nitric Oxide 2011; 24: 34-42.
51. Bartsch P: High altitude pulmonary edema. Med Sci Sports Exerc. 1999; 31: 23-27.
52. Hackett PH and Roach RC: High-altitude illness. N Engl J Med. 2001; 345: 107-114.
53. Schoene RB: Unraveling the mechanism of high altitude pulmonary edema. High Alt Med Biol. 2004; 5: 125-135.
54. Schoene RB, Swenson ER and Hultgren HN: High-altitude pulmonary edema. In: High Altitude-An Exploration of Human Adaptation, edited by Hornbein TF and Schoene R. New York: Dekker 2001; 777-814.
55. Swenson ER and Maggiorini M: Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med. 2002; 347-1284.
56. Zand J, Lanza F, Garg HK and Bryan NS: All-natural nitrite and nitrate containing dietary supplement promotes nitric oxide production and reduces triglycerides in humans. Nutr Res. 2011; 31: 262-269.

How to cite this article:
Rana RT, Chopra S, Rakhra G and Singh SN: A journey of dietary nitrate as a health promoter. Int J Pharm Sci Res 2018; 9(5): 1737-44. doi: 10.13040/IJPSR.0975-8232.9(5).1737-44.