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A JOURNEY OF DIETARY NITRATE AS A HEALTH PROMOTER

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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 water³, yet dietary nitrogen which is commonly found in beetroot and spinach is linked with various physiological health benefits⁴.

Nitrates are usually found in soil, air, water and food and are produced naturally within the human body¹. It can also be used as food additives⁵. Nitrate is converted into nitrite with the help of bacterial (Nitrosococcus) 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 tract⁶.

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 (NO₃⁻) is derived from vegetables^{7, 8} rest comes

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from drinking water and other food sources⁹. The common sources of nitrate are lettuce, celery, beetroot and spinach⁷. 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 toxin¹⁰. Inorganic nitrate obtained from food and vegetables is a major component of gun powder¹¹ and can be used as a food preservative¹²⁻¹⁴ **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: | | |
| 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., 2009¹⁴

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 endothelium¹⁵ and post exercise plasma nitrite concentrations is considered as an index of exercise capacity¹⁶. Dietary nitrate supplementation at the concentrations achievable by vegetable consumption has resulted in more efficient energy

production without increasing lactate concentrations during sub maximal exercise¹⁷. 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**.

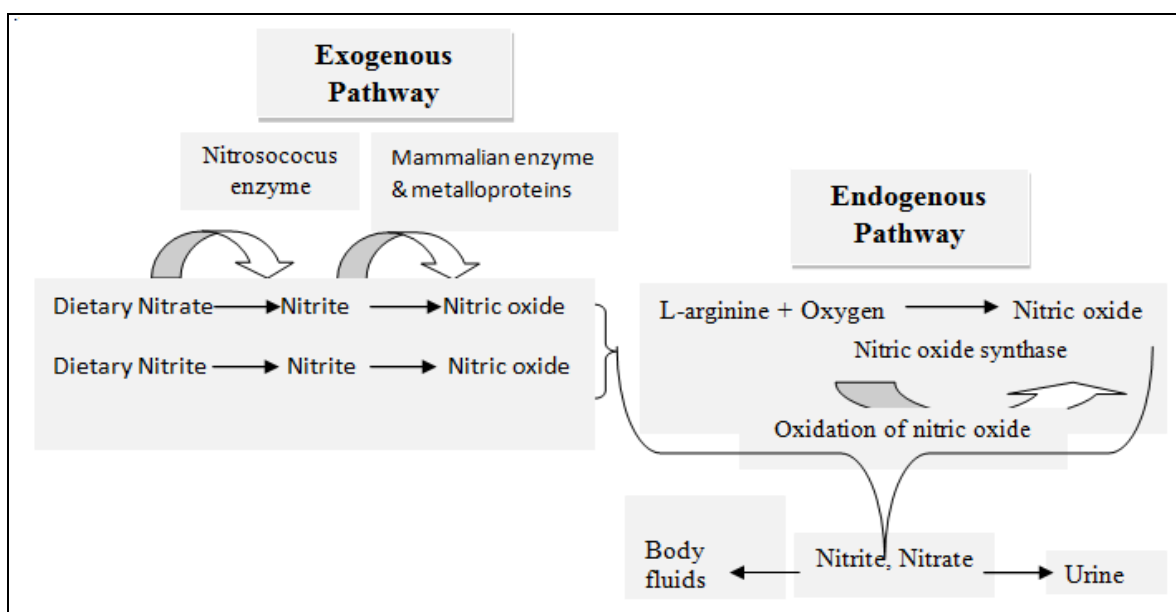


FIG. 1: MECHANISM OF NITRATE, NITRITE AND NITRIC OXIDE PRODUCTION FROM EXOGENOUS (DIETARY) AND ENDOGENOUS SOURCES (L-ARGININE)

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 NO₃ 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: 2003²³

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 pathway²⁴. Recent reports have given evidences that nitrate and nitrite may include various therapeutic inferences²⁵ such as lowering blood pressure in humans^{26, 27}, protection against ischemia-reperfusion injury²⁸, decreasing oxidative stress, and reduced oxygen consumption during exercise which may improve physical capacity in individuals with restricted pulmonary functions²⁴ as well as increasing mitochondrial efficiency²⁶. Nitric oxide availability is a central event in the pathogenesis of metabolic syndrome and other diseases²⁹. A 10-week inorganic nitrate therapy decreased levels of serum triglycerides, lowered visceral fat accumulation, and controlled disturbed glucose tolerance³⁰. 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 subjects³⁴.

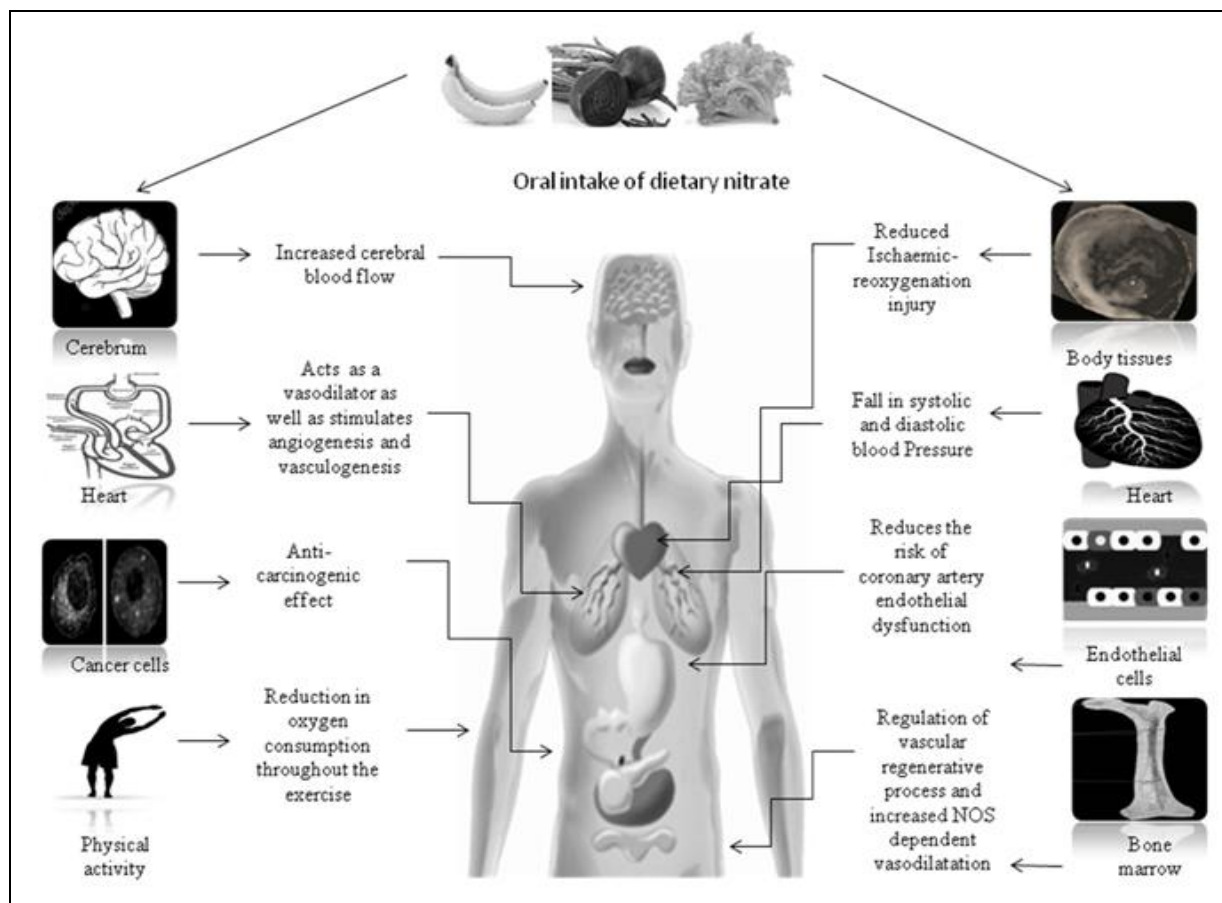


FIG. 2: BENEFITS OF DIETARY NITRATE ON HUMAN HEALTH

5.2 Coronary Artery Endothelial Dysfunction (CAED): The endothelial dysfunction is a result of imbalance between vasodilatation and vasoconstriction 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 humans³⁵. 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 nitrate³⁶. 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 week³⁷.

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 subjects²⁷.

5.4 Nitrate in Cancer Prevention: Epidemiological studies found that fruits and vegetables play a protective role in preventing various types of cancer³⁸. 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 cancer⁴¹. The betalain extracts obtained from beetroot may suppress the effect of malignant tumours. The beetroot extracts noticeably repressed angiogenesis and tumorigenesis 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 exercise²⁶. 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 cingulate cortex, which are the regions concerned with the executive functioning of the brain⁵¹. 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 individuals⁵²⁻⁵⁶.

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 human¹⁹. 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 pressure⁵⁷.

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 <i>et al.</i> , (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 <i>et al.</i> , (2010) ³³ |
| | • 25 Healthy volunteers | Sustained reduction in the diastolic BP of ~ 4.5mmHg over 10 days | Sobko <i>et al.</i> , (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 <i>et al.</i> , (2010) ³² |
| | • 69 Healthy human subjects | Reduction in pulse wave velocity accompanying the reduction in systolic blood pressure | Bondonno <i>et al.</i> , (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 <i>et al.</i> , (2008) ²⁷ |
| Chemo protective role | • Healthy human subjects | Potential links between high nitrate intake and epithelial ovarian cancer and thyroid cancer | Ward <i>et al.</i> , (2010) ³⁹ Aschebrook-Kifoy <i>et al.</i> , (2012) ⁴⁰ |
| Anti-cancer effects of beetroot | • Human prostate (PC-3) and breast (MCF-7) cancer cell lines | Betacyanin extracts shown a chemopreventive role in human prostate, skin, breast and pancreatic tumour cells | Das <i>et al.</i> , (2013) ⁴¹ Kapadia <i>et al.</i> , (2011) ⁴² Kapadia <i>et al.</i> , (2003) ⁴³ Kapadia <i>et al.</i> , (2013) ⁴⁴ Heiss <i>et al.</i> , (2012) ⁴⁵ |
| 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 | |
| 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 <i>et al.</i> , (2007) ¹⁷ Bailey <i>et al.</i> , (2010) ⁴⁸ Lansley <i>et al.</i> , (2011) ⁴⁹ |
| Response to hypoxia | • Nine healthy subjects | Nitrate supplementation debilitated muscle metabolic agita during hypoxic exercise | Vanhatalo <i>et al.</i> , (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 <i>et al.</i> , (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 <i>et al.</i> , (2001) ⁵³ Schoene (2004) ⁵⁴ Schoene <i>et al.</i> , (2001) ⁵⁵ Swenson <i>et al.</i> , (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.

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