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A nutritional intervention against Covid-19: Possibilities on the use of an alkaline diet to boost physiological resistance and immunity

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Novel Coronavirus (2019-nCoV) is a causative agent of COVID-19. The perilous pandemic caused by 2019-nCoV erupted in late 2019 in China has blanketed the whole world and continues to do so. The incidence of the disease, its morbidity, and mortality is high. Strategic planning to contain a virus, fast track research for prophylactics and therapeutics are underway. Food is one of the components of complementary and alternative medicine of the cultures all over the world. Routine diet and its management which is an easily manageable affair will also play crucial to improve an individual's resistance to infection. In recent years alkaline diet has secured a large number of proponents and gained popularity among the scientific community as well. Its significance for the treatment of many non-communicable diseases has been recognized. The diet or food component whose net potential renal acid load (PRAL) is low is defined as an alkaline diet. We hypothesize that the alkaline diet could significantly boost an individual's physiological resistance and immunity against 2019-nCoV by targeting endosomal pH which plays an important role in viral pathogenesis. Hydroxychloroquine, a therapeutic drug that is being used at present for COVID-19 treatment also targets endosomal pH to viral prevent infection. In the present article, we have discussed the significance of diet in traditional medicine, pH homeostasis, the role of pH in 2019-nCoV pathogenesis and the possibilities of how the alkaline diet could interfere with the initial stages of infection. Clinical evidences of the use of the alkaline diet for the treatment of infectious and non-infectious diseases have been reviewed. Further, technical details of the alkaline diet, its correlation to Ayurvedic dietetics have been discussed. Though the current article emphasizes the management of the COVID-19 in the light of pandemic, the approach holds grounds for the other respiratory tract viral pathogens too whose pathogenesis is similar to 2019-nCoV. Future experimental studies to establish such correlation are warranted. Adopting the food which has low dietary acid load (alkaline diet) will aid in boosting the physiological resistance resulting in improved health conditions to fight against 2019-nCoV.

Key words: 2019-nCoV, Alkaline diet, COVID-19, Endosomal pH, Physiological resistance

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Coronaviruses (CoV) is a group of pathogenic viruses responsible for causing respiratory tract or intestinal infections in humans and other mammals and belongs to the family Coronaviridae of order Nidovirales[1]. The pandemic that emerged in Wuhan city of Hubei province of China in late 2019 caused by a novel Coronavirus (2019-nCoV) is an example of zoonosis (infectious disease transmitted from a vertebrate animal to humans)[2]. On 11th February 2020 World health organization (WHO) announced a name for the new coronavirus disease (also called severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) as COVID-19[3, 4]. The pandemic affected a major part of the world with high morbidity and mortality rate. The symptoms and consequences of the COVID-19 range from the common cold to severe pneumonia and respiratory failure which can be fatal[5].

Within four months of its outbreak, the pandemic affected around 215 countries with ~2.9% fatality rate which varies by location and transmission intensity[6]. Governments all over the globe, under tremendous pressure, are trying to contain the spread of the virus. Large numbers of strategies have been formulated to prevent the virus from spreading including personal hygiene, personal safety, social distancing, and draconian lockdowns. Treatment of clinical cases, isolation, and quarantine of suspected individuals is also a part of this strategy. Besides these, numbers of research institutes, pharmaceutical industries all over the world are engaged to design the vaccine for prophylaxis of COVID-19. In some countries, anti-malarial drug-like hydroxychloroquine has been

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approved for the treatment of the COVID-19 while numbers of drugs are under the different phases of clinical trials[7]. Strategies that have been adopted to prevent viruses may not prove ideal to deal with the situation 2019-nCoV has caused. Draconian lockdowns cannot be continued for a long period. Possibility of the resurgence of the cases and the waves of the outbreaks cannot be ruled out. Further, it may take time for vaccines and therapeutic approaches to come in the market and reach the last susceptible person of society. Therefore, along with personal hygiene, social distancing and others, the diet will play an important role to boost physiological resistance and immunity against the spread of 2019-nCoV.

In recent years alkaline diet has secured a large number of proponents and gained popularity among the scientific community as well. The availability of myriads of scientific, non-scientific and technical literature points out this fact. We hypothesize that; adoption of an alkaline diet in day to day routine life could help to boost the physiological resistance and immunity of an individual and thus prevent the spread of the 2019-nCoV infection in the initial stages. In the present article, the importance of the diet in the traditional medicine, significance of pH homeostasis in metabolism, some aspects of the alkaline diet, pH and its correlation to the 2019-nCoV life cycle in the target cells have been reviewed. Further, the clinical evidence to support the hypothesis has been discussed. Books written in lay literature, the articles from the internet (research articles and reviews, blogs of reputed Ayurveda practitioners) were evaluated to represent the work.

Let your food be thy medicine: Importance of food in traditional medicine

Almost all the cultures in the world in their traditional medicine believe primarily at food habits for good health indicating the significant relationship between diet and health of an individual. "Ahara", the nutrition or diet has been one of the central pillars of the ayurvedic system. Balance or homeostasis plays a key role in normal body and mind health, the fact which also holds when it comes to the pH of the body. Diet, a foremost pillar in the Ayurveda is considered in "pathya vyavastha" which deals with in-depth information food and diseases[8].

Chinese traditional medicine believes the presence of the Ying-Yang elements in the human body, the balanced state of which signifies the health while imbalance results in disease. The "food therapy" or "medical diet therapy" in Chinese traditional medicine aims at maintaining health, prevent diseases, and improve the longevity of the individual by harmonizing the Ying-yang[9].

The pH, diet and Acid-Base homeostasis

The pH of the body fluid is determined by the concentration of the protons (H^+ ions) that are generated from organic acids in metabolically active cell[10]. Maintenance of the pH of the blood, the cytoplasm of the cells and other body fluids is critically important to ensure the normal functioning of the physiological and metabolic processes in the body[11]. Lungs, kidneys and complex buffer systems in the body are responsible for regulating pH in the body and pH homeostasis[11, 12].

Diet plays a crucial role in the maintenance of the pH homeostasis. Once the ingested food mixes with gastric and pancreatic juices, the food is digested in the gastrointestinal tract. The acid-base state is maintained by the gastrointestinal tract by absorbing sulfur amino acids and alkaline salts. These substances are transported to the liver and metabolically active tissues where they are further metabolized. Sulfur-containing amino acids and organic acids release H^+ and alkali respectively affecting the acid-base reserve which then is excreted in the kidney to achieve equilibrium. The gastrointestinal tract is not responsible for generating any acids or bases in this process but the composition and the characteristic of the diet determine the formation of acids and bases upon their metabolism in the liver. Thus, the composition of the diet can critically affect the acid-base balance of the body[13].

Life cycle of Coronavirus: role of pH in the pathogenesis

The life cycle of the 2019-nCoV is similar to those of other Coronaviruses. Briefly, it begins with the entry of the virion from the atmosphere to the upper respiratory tract of humans. It binds to the host cell in the tract through receptors specific to the virus and then internalized by receptor-mediated endocytosis forming early endosome containing virus. At acidic pH, the lipid envelope of virus fuses with the endosomal membrane (late endosome) and viral nucleic acid (RNA) enters the cytoplasm by crossing is followed by replication of the virus[14].

At present, the drug which has been used at large for treatment of COVID-19 is chloroquine and it's

less toxic form hydroxychloroquine[15] which being a weak base diffuses into the endosome and becomes protonated thereby increasing the pH and the ionic strength of the endosome. The viruses that require acidic pH to fuse with the endosomal membrane fail to do so in the presence of the hydroxychloroquine and host cells are protected from infection[16]. Thus, achieving the slightly alkaline pH in endosome to prevent the fusion of the viral envelope and thereby preventing the infection is an underlying mechanism for the action of hydroxychloroquine.

Alkaline diet, endosomal pH and 2019-nCoV: Targeting endosomal pH?

In the lay as well as technical literature, the pH has been correlated to the stability of the Coronavirus. According to Mousa 2017, alkaline diet induces slight alkalosis in the blood that causes denaturation of the virus and thus helps to curb the infection[17]. Here, we emphasize the possibility of an alkaline diet increasing the cellular pH (especially in the respiratory cells) and thus endosome to prevent the viral nucleic acid entering into the cytoplasm and prevent its multiplication and further spread. Intracellular pH is slightly acidic and lies between 6.0 and 7.2 due to the production of acid due to metabolic reactions[18]. An alkaline diet may induce low-grade alkalosis in the cells and slightly increase the cytoplasmic pH and further the pH of the endosome. If the endosomal pH is slightly enhanced through this mechanism, it could disrupt the viral life cycle in the initial stages and improve the resistance towards infection. Alkaline forming diet or drinks could induce low-grade metabolic alkalosis in the cytoplasmic pH of the respiratory tract cells, which is a slight increase then what is considered normal. The pH of the cell and thus endosome could equilibrate near the higher end of the normal. Sustained maintenance of such low-grade alkalosis in the target cells could partially aid to build up the physiological resistance to the viral infection.

Clinical evidences

There is no substantial evidence to show the relationship between the person's diet, its acid load, and susceptibility to the COVID-19 as well as other respiratory tract viral infections. Nevertheless, reports are available in the literature on respiratory viral pathogens like the influenza virus, a causative agent of flu. The Spanish Influenza pandemic that erupted during 1918-1919 is aptly named as "Mother of all Pandemics" caused the death of approximately ≈ 50 million people all over the world[19]. During this pandemic, it was brought to the notice of United States public health services that those people who were thoroughly alkalinized resisted the contraction of flu and those who still contracted showed mild symptoms[17]. Evidence is available where flu during this pandemic was treated by administering the generous doses of bicarbonates of soda[20].

It has been reported that the cytoplasmic pH can lead to the alteration in the pH of the endosomes. A study on alternation in the pH change carried out by Desai *et al.*[21] found that acidic pH mediated fusion of endocytosed avian sarcoma and leukosis virus (ASLV) was delayed in the human alveolar epithelial cell line (A549) derived cells bathed in the mildly alkaline medium (pH =7.8). This points out to the fact that it may be possible to alter the endosomal pH through an alkaline diet. Khan et al., 2010 showed that chloroquine was efficient *in vitro* prophylactic and therapeutic approach against Chikungunya virus in Vero cells. The addition of the chloroquine to the Vero cells leads to alkalization of the endosome and subsequently leads to viral abrogation[22]. The chloroquine mediated interference of pH-dependent endosome fusion was shown to be effective in the treatment of dengue virus and chikungunya virus infection[14,23]. Use of alkaline diet for management of non-communicable diseases such as chronic kidney disease (CKD)[24], hypertensive nephropathy[25], Osteoporosis[26,27], hormone deficiency[28], back pain[29] has been reported. Probiotics such as yogurt, buttermilk, yeast-based products have been implicated for the prevention of acute respiratory tract infections are components of alkaline diet[30, 31].

Alkaline diet- beyond lay literature

The alkaline nature of the diet is the function of the net concentration of acid produced upon the metabolism of food component[32]. Several parameters are used to measure the acid production which in turn decides the alkaline nature of the food component. Kidneys are responsible for excreting the metabolic products that may include organic acids anions or cations. During this process, the mechanism of hydrogen ion i.e. acid excretion is stimulated if the concentration anions exceed the concentration of the cations[33]. The net concentration of the acid produced is called net acid production (NEAP). Two methods have been reported to determine the net acid content produced. Measurement of NEAP (direct NEAP) is

carried out in the urine by finding of titrable ammonium (NH_4^+) and subtracting it from the concentration of bicarbonate ions (HCO_3^-). NEAP can be estimated based upon the composition of the diet. The net concentration of the acid and alkali according to the nutrient profile is termed as potential renal acid load (PRAL)[34]. Technical details of the method are not dealt with in the present article.

Since the present article deals with the alkaline diet and its role, we use the diet based aspect to define the alkaline food. In the lay literature, the alkaline diet has been described rather than technical terms. The diet whose net potential renal acid load (PRAL) is low is defined as an alkaline diet[35]. The negative value of the PRAL indicates the low PRAL and low potential of the diet to generate metabolic acid and vice versa. In other words, the diet to be called an alkaline, its net PRAL value should be negative or low. In the following table, the food items and their PRAL (per 100 g) values have been summarized which is based on preliminary nutrient intake[36].

Ayurvedic and traditional Indian food: Is it an alkaline diet?

Since ancient time Indian traditional diet and Ayurveda has emphasized the vegetarian type of food for improved health conditions. Fruits, vegetables and some milk products have been given special importance in Ayurveda[37]. From the values of the PRAL (see Table 1), it is clear that these items have very low PRAL values and thus contribute to low dietary acid load. Raisins are highly alkaline in nature (PRAL = -21.0) has been mentioned in Ayurveda as one of the important food and medicine. *Charak Samhita Sutrasthana*-27 mentions the use of raisins to treat the respiratory disorders involving difficulty in breathing[38]. Milk products like curd, buttermilk are indigenous to Indian and intricate part of the Indian traditional food. These products contribute a very low PRAL value (see Table 1) and have been reported to be useful as an anti-influenza agent[39]. On the other hand, non-vegetarian food like fish and meat products and highly processed dairy products such as cheeses do not find a significant place in Indian traditional food. These products contain a high amount of amino acids like methionine and cysteine that are the main contributors to the dietary acid load[40, 41].

Prospects

Looking at the reports on the implications of the alkaline diet for the management and the treatment of

Table 1 — Some food items and their PRAL values[36]

Nutrient group or food item	Energy (Kcal)	PRAL (mEq of Cl + PO_4 +SO_4 - Na-K-Ca-Mg)
Vegetables		
Spinach	25	-14.0
Carrots (young)	30	-4.9
Cauliflower	34	-4.0
Cucumber	10	-0.8
Radish (red)	12	-3.7
Green capsicum	15	-1.4
Tomatoes	17	-3.1
Tomato juice	14	-2.8
Sugar and sweets		
Honey	288	-0.3
Milk Chocolate	529	2.4
Cane sugar (white)	409	-0.1
Milk and dairy products		
Parmesan cheese	452	34.2
Camembert cheese	297	14.6
Butter milk	39	0.5
Plain processed cheese	330	28.7
Yoghurt (from whole milk, plain)	79	1.5
Milk (Whole and evaporated)	151	1.1
Milk (Whole and pasteurized)	66	0.7
Ice cream (vanilla, dairy)	194	0.6
Egg and egg products		
Egg (whole from chicken)	147	8.2
Egg white	36	1.1
Egg yolk	339	23.4
Fruits, juices and nuts		
Raisins	272	-21.0
Bananas	95	5.5
Apple juice	38	-2.2
Peanuts (plain)	564	8.3
Lemon juice	7	-2.5
Oranges	37	-2.7
Strawberries	27	-2.2
Watermelons	31	-1.9
Grape juice (Unsweetened)	46	-1.0
Beverages		
Stout beer	37	-0.1
Pale beer	45	0.9
Red wine	68	-2.4
White wine	66	-1.2
Tea (Indian infusion)	0	-0.3
Coffee (5 minute infusion)	2	-1.4
Oils and fats		
Sunflower seed oil	899	0
Olive oil	899	0
Butter	737	0.6
Grain products		
Wheat flour (whole meal)	198	1.8
Brown rice	357	12.5
White rice	138	1.7
Oats	355	10.7
Corn flakes	360	6.0
Meat and fish		
Chicken (meat)	121	8.7
Beef (lean)	123	7.8
Turkey (meat)	107	9.9
Cod fish	76	7.1

non-infectious disorders, its significance cannot be overlooked. Since there is no substantial evidence to clinically correlate the role of an alkaline diet for the prevention of the COVID-19 as well as other respiratory tract pathogens, where pH plays important role in the pathogenesis of the disease, the future studies are warranted. Research towards prevention of the SARS-CoV-2 infection by targeting endosomal pH in the target host cells through the alkaline diet is necessary. Influenza virus (H1N1), Semliki forest virus, Vesicular stomatitis virus, etc. cause the respiratory tract infection that may lead to acute respiratory disease. The initial phase for the entry of these viruses is similar to that of Coronaviruses. Future research studies could help to establish the correlation between the prevention of these infections by targeting endosomal pH and alkaline diets.

Ayurveda, traditional Indian medicine is very different from modern nutrition concepts and modern medicine systems because of its own unique universally applicable principles, practices, and methods[42]. This fact is pointed by the way Ayurveda looks at the diet as one of the therapy for diseases. Experimental studies about the alkaline diet and viral respiratory tract diseases and its Ayurvedic basis need to be undertaken.

Conclusion

Alkaline diet can possibly play important interventional role against COVID-19. By concentrating on diet consumed daily, which is an easily manageable affair we can enhance physiological resistance as well as immunity against novel 2019-nCoV. Existing evidence, point out the potential of the alkaline diet as a mean to improve resistance against COVID-19. Adopting the alkaline diet will not kill the 2019-nCoV nor is it a treatment for COVID-19 infection but will aid in boosting the physiological resistance and immunity resulting in improved health conditions to fight against 2019-nCoV, other respiratory tract viral pathogens (that may represent the co-morbidity in COVID-19 patient) and other metabolic disorders. In 1903, Thomas Edison concerned about healthcare said, *"The doctor of the future will give no medicine, but will interest his patient in the care of the human frame, in diet and in the cause and prevention of disease."* In the current scenario, where modern medicine just addresses chemical processes with other chemicals, nutrition and diet could provide an approach for improved health conditions of the individual.

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Conflict of Interest

Authors declare they have no conflict of interest.

Authors Contribution Statement

AEG and SRB conceived the hypothesis and prepared the manuscript.

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