Antioxidant Molecules and Minerals in Prevention of HIV and AIDS: A Review

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Abstract
AIDS is a chronic, potentially life-threatening condition, caused by human immunodeficiency virus (HIV) that devastates the human immune function by destroying a type of white blood cells and thus obstruct human capacity to fight various infections. AIDS is known to be the final stage of HIV infection and AIDS happens when the human immune system is completely damaged by the infection caused by the virus leading to various types of infections and fatal diseases like cancer. Till date, there is no exact and final cure for HIV/AIDS, however, not every HIV positive individual develops AIDS. It was established by various research works that proper use of certain therapeutic agents can prevent the growth of HIV infection and completely avert its progression to AIDS and certain well acknowledged antiviral medications for HIV have reduced AIDS related global mortality. Thus, the recent research community is very much concerned with the preventive measures of the viral infection and numerous research works have been going on to amplify the accessibility of therapeutic agents that can provide prevention measures and proper cure in resource-poor countries. Many reports revealed the prospective benefits of antioxidant supplementation in diminution of HIV related infection via augmentation of human immune function and thus can prevent the development of AIDS. This review is aimed to explore the contribution of some well recognised antioxidants in HIV prevention and hindrance of AIDS progression along with their prospective applications in the treatment of the viral infection.

Keywords: HIV, AIDS, Antioxidant Molecules, Antioxidant Minerals, Vitamins, Phytochemicals.

INTRODUCTION

The earliest reports on five cases of fungus infection, *Pneumocystis carinii* pneumonia amongst formerly healthy young homosexual men in Los Angeles were reported on June 5, 1981 with subsequent lesions of Kaposi's sarcoma [1]. These initial cases accounted for the deadly ailment that was consequently recognized as Acquired Immune Deficiency Syndrome (AIDS), followed by the detection of human immunodeficiency virus (HIV) to be the cause of this illness in 1983 [2, 3]. During 1990s, both or any of the parents of greater than 10 million children were died from AIDS or HIV. Through the end of 1991, this disease turned out to be the second principal reason of fatality in case of men among 25-44 years of age and also it happened to be one of the five primary sources of casualty in case of women among 15-44 years of age in the United States. The

World Health Organization assessed that, in the entire world, around 8-10 million people were infected by HIV including 1 million children, which became more than 40 million in 2000 [4, 5]. Thus, within few years from its discovery, it became an epidemic of international concern, and in 21st century also, it still signifies as a major undefeatable public health problems being a substantial cause of global mortality and has thus led to universal socioeconomic damage [6, 7]. HIV deteriorates the protective power of the immune system among human beings. When a person is infected by this virus, the human body tries to surmount the virus via antibody generation to fight with the virus. Nevertheless, in a rate-limiting process, the subsequent development of the ailment declines the capacity of the immune system to combat the virus and thus the infection increases. While the immune system of the body gets compromised, quite a lot of diseases get the opportunity to build up in the body that ultimately causes AIDS [8].

In case of biological systems, oxidative stress is a phenomenon originated by a relative surplus of oxidants or a discrepancy in production and accumulation of free radicals (i.e., reactive oxygen species) in cells and tissues or an insufficient antioxidant defence mechanism [9]. Continuous or uncontrolled oxidative stress causes damage to DNA, fatty tissue and proteins in human body and thus damage cellular functions and structures, which are usually controlled by critical oxidation-reduction pathways and thereby, may lead to the development of a vast numbers of health conditions. Quite a lot of research evidences suggested that individuals infected by HIV have been suffered from persistent oxidative stress that can additionally be augmented by HIV, thereby dwindle the human immunity to an uncontrollable extent and also oxidative stress lead to augmentation of HIV replication, or increment of apoptosis [9-10]. Thus, many in vitro and in vivo studies confirmed oxidative stress to be a principal contributor of development of AIDS [11, 12]. The prospective implications of reducing agents were analyzedby many researchers and it was also predicted that the progression pathways of AIDS might possibly be overturned via introduction of antioxidant reducing agents [13-15].

Molecules endowed with antioxidant activities are capable of protecting cells, tissues and DNAs from various infections and inflammatory diseases and restrain lipid peroxidation. Numerous research works on oxidative stress related health problems, conducted in a diverse range of conditions have established that antioxidants have the potential to boost immune system in human beings. Insufficiency in antioxidant intake, like vitamins and minerals, causes immune function decline and amplification of lipid peroxidation, prompting various infections in humans [16, 17] and intake of dietary antioxidants can retard the development of HIV. Along with antioxidant nutrients, various enzymatic antioxidants like superoxide dismutase, glutathione peroxidase, catalases etc., also have essential functions in reduction of free radicals and thus provide shielding effect against oxidative stress [18]. Another well recognised way for treatment of HIV is by fortification of the infected person's immune function. A range of experimental evidences have suggested that certain immune modulator compounds such as immunitin, resveratrol [19], setarud [20–22], murabutide [23-25], interleukin-7, tucaresol, reticulose, cytolin, etc., participate in the prevention or cure of AIDS and subsequently augments the anti-HIV potential [26].

Considering the fact that, in comparison to the costly treatment procedures, nutritional supplements are cost effective, non-toxic and efficient for prevention of free radical initiated diseases, the author aims to analyse the involvement of some antioxidant compound minerals in the prevention of HIV by improving the immune response of the body against the virus, as well as their involvement in the progression and treatment of AIDS, through this review article.

METHODOLOGY

Various research articles, review articles and necessary literature required for writing this

review were obtained thorough scientific literature databases counting various research sites like Google Scholar, Scopus, PubMed, Web of Science, ScopeMed and Science direct by using keywords like – HIV, AIDS, antioxidant molecules, phytochemicals, antioxidant minerals, anti-viral activity, vitamins, natural products, phenolic compounds, etc.

RESULTS AND DISCUSSIONS

AIDS represents a chronic, potentially life-threatening and tremendously intricate health condition. HIV-induced oxidative stress causes depletion of $CD4^+$ T-cell levels via apoptosis, additionally augmenting virus replication and transcription. These processes are predicted to be dependent on the activation of NF-κB throughout redox impairment. A study reported a noteworthy reduction in the quantity of antioxidants vitamins A, C and E in HIV-infected kids [27]. Additionally, various investigations revealed that insufficiency in antioxidant levels can cause enhancement and progression of HIV-originated diseases. Thus, majority of researchers proposed that supplementation of antioxidants may have a significant role in reduction of HIV viral loads leading to improvement of immune response and thus may prospectively impede the development of AIDS [28].

A. Gluthathione

Gluthathione is an extremely important substance that our body makes. It is one of the strongest essential natural antioxidants that provide protection against ROS and RNS, present in every cell of body and detoxify endogenous and exogenous toxins. It is also available in various food sources like grapes, strawberries, watermelon, asparagus, peach, avocado, potato, squash, broccoli, spinach, cantaloupe, zucchini, meat, fish, whey proteins, etc. [29]. It assists nutrients transportation to lymphocytes and phagocytes and helps in the shielding of cell membranes. HIV positive individuals exhibited higher oxidized gluthathione levels and reduced concentrations of gluthathione as well as amino acids. A number of experiments indicated that gluthathione impedes with the entry of HIV into CD4 cells and hampers the virus survival. Many experiments revealed that intracellular glutathione reduction and generation of reactive oxygen species can control the infection of HIV and its insufficiency is linked to damage of T-cell (T-lymphocyte) function and continued existence in case of infection of the virus [30-32].

B. *N*-Acetyl-Cysteine

N-acetyl-cysteine is an instant precursor of glutathione and is admired because of its cysteine residues and its function on glutathione maintenance and metabolism. It controls the levels intracellular thiol in case of oxidative stress and repairs the depletion of glutathione during infections. Affirmative outcomes were observed on oral administration of *N*-acetyl-cysteine supplement in case of life quality advancements of individuals suffering from a variety of genetic and metabolic ailments, counting HIV infection [33, 34]. De Rosa and his co-workers investigated the conditions of 81 HIV-infected patients continuously for a period of eight weeks by providing oral supplementation of *N*-acetyl-cysteine on efficient glutathione replacement in case of damaged T-cell functions [35]. The observations disclosed a noteworthy amplification of entire blood glutathione levels as well as T-cell glutathione levels for *N*-acetyl-cysteine introduced patients. Thus, the observations of these experiments indicated the medical function of *N*-acetyl-cysteine treatment in defending the body against oxidative stress and immune system recovery in case of HIV-infected people. Another experiment investigated the impact of *N*-acetyl-cysteine on envelope glycoprotein gp120, which plays a major function in attachment of virus to definite cell surface receptors and thus indispensable for the entrance of the virus into cells [36]. The gp120 is discharged throughout the infection of macrophages and produces oxidative stress that is the cause of the development and further progression of the ailment. The observations of the tests revealed that gp120 induced lipid peroxidation was contradicted by *N*-acetyl-cysteine. Another study also concluded that *N*-acetyl-cysteine overturned both gp120 and

transregulatory protein (Tat) caused oxidative stress. As both gp120 glycoprotein and transregulatory protein are known to cause oxidative stress that has an imperative role in the transcription and replication of the virus, supplementation of *N*-acetyl-cysteine may restrain pro-oxidants and diminish detrimental impact of reduced glutathione levels [37].

C. Vitamin A

Vitamin A is a fat-soluble group of compounds including retinol, retinal, retinoic acid and various provitamin A carotenoids that has a significant role in bone development, cell division, cell differentiation, embryo development and growth, vision, maintenance of immune system etc. It controls the generation of white blood cells that prevent and completely wipe out infecting bacteria and viruses. Vitamin A accumulates in the human liver and basically consists of two types- preformed vitamin A and provitamin A carotenoid. First one is obtained in milk, liver, and animal foods, absorbed as retinol and instantly used in the body. On the other hand, provitamin A carotenoids are found in various coloured fruits and vegetables and can be transformed into vitamin A. β-carotene demonstrated a provitamin function in case of vitamin A shortage, attributable to its efficiency in conversion into retinol. Investigations have reported the antioxidant potential of β-carotene in free radical scavenging [38] and dearth of vitamin A has been observed to cause oxidative stress [39]. It was observed in a variety of cases that, a majority of HIV-infected patients have vitamin A deficiency, particularly in case of kids and pregnant females [40, 41]. Vitamin A deficit was linked to a huge number of mortality in AIDS as well as in HIV caused faltering growth of children [41]. Treatment using vitamin A administration demonstrated reduction in infections of respiratory tract and severe diarrhea for HIV positive kids and thus depicted shielding effects against morbidity and mortality in AIDS [42, 43]. Vitamin A deficiency was also linked to the amplified danger of transmission of HIV from mother to child [44, 45]. In a study including 7528 women, it was observed that supplementation of vitamin A in prenatal condition considerably enhances birth weight. As vitamin A is indispensable for immune function of macrophages that are one of the first cells to be attacked by the virus during infection of HIV, in a direct or indirect manner, it can be considered to be very much accountable for the reduction of a huge quantity of $CD4^+$ T-cells as well as for the growth of the ailment [46].

D. Vitamin E

Vitamin E is known to be an assemblage of eight lipid-soluble compounds comprising four tocopherols and four tocotrienols. It is available in an assortment of foods such as-fruits, nuts, meat, seeds, eggs, cereals, poultry, different plant oils including vegetable oil, soya, sunflower, corn and olive oil, etc. Among the group of compounds that makes vitamin E, α-tocopherol is the one compound that is utilized by the human body, which is available in blood and tissues in huge amounts, particularly in the cell membranes. It is an imperative vitamin obligatory for appropriate functioning of several human body organs. The primary role of vitamin E is as an antioxidant, by which it protects vitamin A and vital fatty acids from oxidative damages and thus it averts tissue breakdown [47, 48]. Vitamin E is also responsible for immune system improvement and it protects heart arteries from the formation of blood clotting. In general, shortage of vitamin E is uncommon, but on its shortage severe nerve problems may arise. Studies have revealed that regular consumption of foods, rich in vitamin E, or intake of vitamin E supplements reduce the occurrences of cancer, tumour, cardiovascular disease, dementia and many other diseases. Human body cannot generate vitamin E on its own, so it must be included in the regular diet from food sources or should be taken as a supplement. It was observed in various reports that lack of vitamin E, along with oxidative stress is related to HIV-infection [49, 50]. A considerable reduction in the jeopardy of AIDS development was observed by B Abrams *et al.* in an experiment including 296 HIV positive male persons when the vitamin

E supplementation was regularly doubled [51]. Additionally, although azidothymidine or AZT (also known as zidovudine) is used as a major drug to lessen HIV infection and to hinder the development of AIDS, yet it is recognised to have lethal effects on bone marrows. It was reported by R G Geissler and his co-workers that on increase in concentration of azidothymidine from 1 to100 μM, there is drastic augmentation of bone cell quantities in culture [52]. So, it was recommended that inclusion of vitamin E with azidothymidine might provide analogous anti-viral activity, with reduction of toxic effects against bone marrows. Incorporation of vitamin E supplements in the diet was also reported to decrease the activated B cell or NF-κB cell levels in HIV-1 positive individuals' lymphocyte cells in culture and it also decreased the generation of oxidant in the lymphocyte cells, preventing the replication of the virus and cell death [15, 53]. Vitamin E is also acknowledged to participate in cell membrane defence via inhibition of lipid peroxidation attributable to its lipophilicty, and in boosting up the potential of other antioxidant molecules by increasing their free radical scavenging activity [54]. Another experiment indicated that intake of vitamin E acetate entirely stopped activation of NF-κB in case of HIV-1-infection, whereas vitamin E depicted a negligible influence [55].

E. Vitamin C

Ascorbic acid or vitamin C is a hydrophilic antioxidant molecule, indispensable for regular development and restoration of tissues in human body. It is usually available in a range of fruits and vegetables, like citrus fruits, strawberries, tomatoes, green peppers, raw cabbage, broccoli, sweet potatoes and green leafy vegetables, etc. As human body is incompetent to produce vitamin C by itself, so it is ought to be included in the regular diet. It is a fundamental antioxidant molecule that can augment the scavenging process of hydroxyl radicals and superoxide anion radicals and can enhance immune function of the body [56, 57]. J. Huang *et al.* reported that vitamin C demonstrated the capacity to inhibit the oxidative stress related cellular damages caused by lipid peroxidation [58]. E. Eylar *et al.* suggested that continuous intake of high quantity of ascorbic acid might be lethal and immuno oppressive to the T-cells and biologically favourable amounts might be helpful in preventing the harmful impacts of reactive oxygen species and thus can augment human immunity during infection [59].

F. Vitamin D

Vitamin D is a fat-soluble vitamin and a collection of secosteroids accountable for escalating absorption of magnesium, calcium and phosphate in the intestine and loads of important physiological functions. In human body, the most significant vitamin D compounds are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D is extensively found in fish, eggs and fortified milk and it can also be prepared in the skin on exposure to sunlight [60, 61]. Deficiency in vitamin D can reduce the absorption of dietary calcium to a greater extent. Severe vitamin D dearth in children can lead to dysfunction in bone mineralization causing softening and weakening of bones, a condition known as rickets in children and osteomalacia in adults [62, 63]. Various studies have illustrated significantly higher rates of reduced vitamin D levels or hypovitaminosis D in HIV-positive patients that leads to immunity dysfunction and various contagious ailments [64]. It is a key regulator that activates genes and regulates multiple cellular pathways to improve innate and adaptive resistance against viral attack by binding to the vitamin D receptor. Higher amounts of vitamin D and vitamin D receptor (VDR) expression also improve the usual resistance to HIV-1 attack. Conversely, its shortage caused inflammation and immunity decline, reduced blood $CD4^+$ T-cell counts, rapid growth of HIV infection and shorter lifetime of patients. It was established that intake of vitamin D by HIV-positive individuals may enhance immunologic recovery throughout antiretroviral therapy, decrease inflammation and augments immunity against pathogen attack. Furthermore, it was also reported to provide protection against the expansion of immune reconstitution inflammatory syndrome, pulmonary

tuberculosis and mortality in case of HIV-positive patients [65-68].

G. Vitamin B_{12}

Vitamin B_{12} or cobalamin is one of the eight B vitamins and is one of the most chemically complex of all vitamins. This water soluble vitamin have antioxidant ability and is involved in metabolism and is the only vitamin that has to be obtained from various animal-derived foods like meat, fish, eggs, poultry, liver, clams, dairy products or from supplements. It is necessary as a cofactor in DNA synthesis for fatty acid and also important in amino acid metabolism and cellular energy production. It is very crucial for development of human brain and nervous system functioning as it plays a significant role in myelin synthesis as well as in the circulatory system of the bone marrow related red blood cells. Owing to limited animal food intake in regular diet, deficiency of vitamin B_{12} is very common, particularly in case of vegetarians. Also, its malabsorption is frequently observed in old people or in case of people suffering from gastric achlorhydria. Deficiency of vitamin B_{12} can lead to severe and irreversible damages, particularly in brain and nervous system, like mania, psychosis, Alzheimer's disease, etc., and potential adverse impacts on immune response, fertility, pregnancy outcomes, cognitive, vascular, eye, bone health and blood circulation in women. Its deficiency may also lead to pericious anemia, megaloblastic anemia due to the inhibition of DNA syntheses. Even its slight deficiency can be determined by various symptoms like weakness, breathlessness, tiredness, muscle weakness, dizziness, headaches, upset stomach, mouth ulcers, reduced appetite, difficulty in walking, depression, confusion, poor memory, poor reflexes, abnormal sensations, pale skin, diarrhea, constipation, etc., particularly in case of people over age 60 [69-73]. Prabha M. R. Adhikari *et al.* reported low blood levels of vitamin B_{12}, along with folic acid in HIV-positive people. Deficiency of vitamin B_{12} was observed to be greater in case of HIV infected patients with tuberculosis. In HIV-positive people, sufficient vitamin B_{12} levels appear to delay progression of HIV to AIDS and also death from AIDS [74, 75]. Kavitha Kasipandy *et al.* also reported considerably lower vitamin B_{12} levels in HIV positive people than healthy people, which were observed to be directly proportional to their CD4 counts. Along with CD4 counts, their CD8 counts were also observed to be associated to serum B_{12} levels. Throughout the initial stage of the infection, fast dividing immune cells led to enhanced utilization of micronutrients causing scarcity of vitamin B_{12}. It causes malfunctions in methylation disturbing the immune response and ability of NK Cell that augments the quantity of CD8 counts. Therefore, they reported that vitamin B_{12} can act as an advantageous immuno modulator in HIV related diseases and can work like a prospective game changer in HIV and AIDS [76]. It was also reported that HIV infected patients may have a greater probability of nervous system or neurological disorders attributable to vitamin B_{12} shortage [77]. A study by J. S. James *et al.* including 300 men revealed that people with unusually lower vitamin B_{12} blood levels develop AIDS around two times faster than people with normal vitamin B_{12} levels. This also indicated that vitamin B_{12} levels are an initial and independent indicator of HIV-1 infection growth [78]. Similar observations were also reported by A. M. Tang and his co-workers [79].

H. Phytochemicals

a) Carotenoids

Carotenoids are colourful lipid-soluble pigments, generally available in various coloured plants, algae, and photosynthetic bacteria. They are the cause of red, orange or bright yellow colours in different vegetables, fruits and plants and are extensively found in various plant sourced foods like carrots, pumpkins, sweet potatoes, tomatoes, red peppers, oranges, spinach or other dark green leafy vegetables, etc. There exists higher than 600 different types of carotenoids and they exhibit antioxidant behaviour following various antioxidative pathways like free radical quenching, mitigation of damage caused by reactive oxidant species and inhibition of lipid peroxidation etc. In human body, carotenoids can be converted into

vitamin A, which is indispensable for human growth, proper vision and immune response. Thus carotenoids are important for improvement of immune system function. Various research works have revealed that higher intake of carotenoids in regular diet is related to reduction in cardiovascular diseases, eye infections as well as cervical, breast, vaginal and colorectal cancers [80, 81]. Along with the decrease in oxidative stress in human cells, carotenoids were reported to inhibit thymic atrophy, lymphoid tissues atrophy by maintenance of epithelial cells present in skin and mucous membranes. Thymic atrophy or atrophy of thymus gland causes loss of thymocytes and damage of the thymic architecture and ultimately provides a way to reduction in naive T-cell numbers and restricted T-cell receptor variety. Thus carotenoids are essential for proper working of immune system response in order to resist the infection caused by HIV. A study conducted by O. Gregg *et al.* on patients with all stages of HIV infection revealed that HIV positive individuals have considerably lower concentration of β- carotene, α-carotene and β-cryptoxanthin in comparison to seronegative controls. Carotenoid levels were observed to be minimum in infected persons with CD4 < 200 cells/mm^3 [82]. They also reported that intake of 180 mg β-carotene per day amplified the quantity of T-helper lymphocytes, white blood cell numbers as well as the ratio of helper/suppressor cells in HIV positive patients [82-84]. It was also suggested by various other reports that intake of β-carotene can maintain CD4 counts in HIV-positive people. In addition, numerous reports established the importance of β-carotene in prevention of HIV-infection and therefore β- carotene supplements are usually recommended for people existing with HIV-1 infection [85- 88].

b) Flavonoids

Flavonoids are an assemblage of natural phenolic compounds available in various vegetables, fruits and foods like lemons, oranges, berries, grapefruits, beets, tea, black grapes, red grapes, cranberries, chocolates, wine as well as in grains, roots, bark, stems, and flowers of various plants. There are six dissimilar classes of flavonoids that can be obtained from foods and every class is broken down in human body in a dissimilar manner. They are very strong antioxidants and are very much helpful for protection of the human body against daily toxins [89]. Also, flavonoids improve health of human body cells and tissue growth and thus participate in renewal of cells in entire human body. Thus, now-a-days, they are well recognised for their beneficial effects on health and increase in the supplementation of flavonoids in the regular diet is known to be a widely appreciated technique in order to decrease the jeopardy of chronic pathologic ailments and for maintaining a healthy body. In addition, flavonoids are considered as an essential constituent in a wide range of pharmaceutical, nutraceutical, medicinal and cosmetic products. All flavonoids were reported to exhibit anti-HIV potential. According to some of the reports, myricetin was observed to be efficient than quercetin or pinocembrin. Silvana Pasetto *et al.* reported that, in TZM-bl cells, myricetin prevented more than 90% of type-1 HIV Bronchoalveolar lavage (BaL) infection. The HeLa cell-derived TZM-bl reporter cell line is highly sensitive to infection by diverse strains of HIV and extensively used for the estimation of neutralizing antibodies against HIV. In H9 cells and human peripheral blood mono-nuclear cells (or PBMC cells), myricetin demonstrated greater than 80% anti-viral activity in case of infection caused by HIV-1 MN as well as by HIV-1 89.6, whereas quercetin and pinocembrin exhibited modest potential against HIV. Myricetin was also successful in 49% inhibition of the HIV-reverse transcriptase (HIV-RT) enzyme, which is used by the virus in the process of its reverse transcription, to convert its RNA into DNA [90]. Bao Qun Li and his co-workers studied the anti-HIV-1 potential of another flavonoid baicalin [91, 92] that can be obtained from medicinal plant *Scutellaria baicalensis* Georgi and found that non-cytotoxic concentrations of the flavonoid inhibited HIV-1 X4-tropic virus (or T-tropic virus) as well as R5 virus (or M tropic virus) envelope glycoprotein related cell fusion

expressing CD4/CXCR4 or CD4/CCR5. Existence of baicalin at early stage of HIV-1 stopped the replication of the virus [93]. Rajeev Mehla *et al.* examined the influence of another flavonoid luteolin on HIV-1 and reported that it intensely diminished the virus infection in primary lymphocytes and reporter cells. It effectively removed both HIV-1 clade-B protein and clade-C protein Tat (the trans-activator of HIV) mediated long terminal repeat (LTR) trans-activation but depicted no influence over the expression of trans-activator along with its localization at sub-cellular level [94]. Again, various experimental analyses revealed that quercetin can reduce TNF-α led IL-8 as well as MCP-1 expression in cultured human synovial cells and can appreciably downregulate the expression of pro-inflammatory cytokines in cultured cells. Various other reported studies have shown that quercetin suppresses TNF-α induced IL-8 and MCP-1 expression in synovial cells of human [95, 96]. Madhavan P. N. Nair and his co-workers reported that, in case of HIV infected patients, quercetin, in a dose dependent manner, appreciably decreased viral infection, LTR gene expression and p24 antigen generation. Also, it drastically reduced the pro-inflammatory cytokine expression, TNF-α expression with associated upregulation of anti-inflammatory cytokine IL-13. A superior level of IL-13 has been identified to restrain TNF-α generation as well as growth of HIV-1 infection [97].

c) Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a polyphenol and a pleiotropic phytochemical of stilbene family and is found in a range of foods, basically in dark blue and purple coloured fruits, like grapes, peanuts, raspberries, blueberries, mulberries, etc. [98, 99]. It is a phytoalexin produced by a wide variety of plants when the plants are under attack by various pathogens like fungi or bacteria, as a response to the wound caused by the attack [99, 100]. It is also a well acknowledged antioxidant as it helps free radical scavenging and known for its anti-tumour, anti-cancer, antiviral activity, etc. It is reported to limit HIV replications and reduce inflammations. Zeming Feng and his co-workers reported that resveratrol could induce promotion of HIV-1 Tat protein level that is reliant on the AKT/FOXO1 signalling axis. It could moderately detach Positive Transcription Elongation Factor b (P-TEFb) from 7SK small nuclear Ribonucleoprotein and can enhance Tat-Super Elongation Complex or Tat-SEC interaction. Preclinical observations depicted that resveratrol increases the power of the HIV therapeutic drug, Vorinostat to induce latency in HIV-1 infection [101]. Again, Xiaoyun Zeng *et al.* reported that resveratrol could reactivate latent HIV, devoid of in vitro T-cell activation, via amplification in acetylation of histone and activation of heat-shock factor-1. In addition, co-treatment of resveratrol with commonly used latency-reversing agents demonstrated synergistic activation of latent HIV reservoir [102]. Again, studies by Chi N. Chan *et al.* revealed that introduction of resveratrol, synergistically with nucleoside reverse transcriptase inhibitors can prevent reverse transcription in activated T-cells.They also revealed that resveratrol and pterostilbene can absolutely stop HIV-1 growth at a small micro-molar concentration in latent CD4 T-cells, mostly during the reverse transcription phase [103].

I. Antioxidant Minerals

a) Selenium

Selenium is a crucial trace mineral and a vital component of a range of enzymes and proteins, known as selenoproteins. It is available in various sources like milk, chicken, red meat, fish, egg, shellfish, beef, pork, etc. Plantation of various food derived plants like nuts, garlic, grains, etc., in selenium-rich soils can also provide plant sources of selenium. It is also known for its antioxidant ability that facilitates peroxide break down and thus protects various ailments related to the damage of DNA and tissues, caused by peroxides. Its scarcity in human body may lead to enhanced jeopardy of diverse illnesses, like cancer and heart disease. It is important for reproduction and thyroid hormone metabolism [104, 105]. It helps in reduction of the impact of inflammatory cytokines, thereby decreasing the peril of growing neurological dysfunc-

tions, wasting syndrome and Kaposi's sarcoma. Several experimental observations have confirmed that selenium can inhibit in vitro HIV growth via antioxidative pathways of glutathione peroxidase and various selenoproteins. Low selenium quantities were observed in HIV-positive people in abundant cases and reduction in serum selenium levels were also observed along with the continuous growth of infection. Other investigations revealed the link of selenium insufficiency with development of AIDS from HIV as well as with AIDS caused death rates. In a number of trials, intake of selenium decreased hospitalization of infected people along with diarrheal morbidity, in addition to augmentation of $CD4^+$ cell counts [106-110].

b) Zinc

Zinc is available in various food sources like meats, oysters, shellfish, fortified beans, pea nuts, soya beans, spinach, mushroom, wheat gram and squash seeds, etc. It acts as an immune modulator and depicts anti-viral ability. It is known to assists in the inhibition of wasting syndrome, cell death and cellular apoptosis. Zn is also important for Cu, Zn superoxide dismutase, the enzyme vital for antioxidant mechanism of body and also for thymulin, the hormone obligatory for T-lymphocyte formation [111, 112]. It was observed in various studies that sufficient zinc is crucial for a strong immune response and zinc scarcity has been observed in more than 50% HIV-positive people. Research work by Marianna K. Baum *et al*. suggested that supplementation of zinc for a long-period of around 18-months, was successful in causing a 4-fold decrease in the probability of immunological malfunction and reduction in rate of diarrhea by greater than half, in case of HIV-infected patients. Zinc intake lessens the peril of CD4 cell counts declining lower than the vital 200 cells/mm^3 level [113]. Macarena Silva and his co-workers conducted a study on 80 patients to find out whether intake of zinc for 12 months by people having immunovirological discordance (IVD), can reduce their immune breakdown and it was observed that zinc intake by IVD patients helps in maintaining their CD4 levels [114]. It was also revealed that zinc scarcity leads to swift and distinct thymus atrophy, lymphopenia and damaged cell-induced cutaneous sensitivity. Zinc deficiency also reduces the response of primary and secondary antibodies, predominantly for the antigens in which T-cell help is necessary, like the heterologous RBCs. Inadequate zinc levels also lower the production of splenic cytotoxic T-cells subsequent to immunization. Zinc can prohibit the generation of tumor necrosis factor that is linked to the increase in mortality rate from AIDS [115].

c) Magnesium

Magnesium can be extensively found in foods like beans, nuts, sweet potatoes, pineapple, brown rice, wheat germ, whole grains, green leafy vegetables and fish. Magnesium has abundant functions in human body, counting that fact that it acts as a cofactor in 300 plus enzymatic reactions. It is crucial for energy production, muscle relaxation, active transmembrane transportation of other ions, neuromuscular transmission, glycemic control, myocardial contraction, calcium absorption, blood pressure maintenance, bone growth etc. [116, 117]. It has many preventive and therapeutic functions in numerous health issues like osteoporosis, diabetes, migraine, preeclampsia, bronchial asthma and cardiovascular diseases etc., and its deficiency has been reported in many chronic diseases. A number of analyses revealed that hypomagnesemia is observed in patients in critical condition requiring intensive care and it is related to amplification of mortality rates [118]. Various reports on HIV-positive people also confirmed the relation of the serum magnesium level with CD4 lymphocyte counts and it was established that hypomagnesemia is interrelated to the growth of AIDS [119]. E. C. Okwara *et al.* also reported depletion of magnesium, selenium and zinc levels in HIV positive patients, predominantly in malescompared to females [120].

d) Chromium

Chromium is a micronutrient, crucial for carbohydrate, protein and lipid metabolism in human body. It can be found in various foods, like vegetables, fruits, meats, grain products,

spices etc. Chromium is biologically active as a component of chromoduli, that helps in the impact of insulin via assisting the binding of insulin to receptors at cell surface and thus its deficiency causes insulin resistance, hyperglycemia and hyperlipidemia [121, 122]. It was observed that chromium concentrations were reduced in HIV-infected people in comparison to normal people, regardless of the same dietary intake [123]. It was also reported by Elaheh Aghdassi *et al.* that chromium supplementation augmented the resistive potential of insulin, metabolic irregularities and body composition of HIV infected people [123, 124]. Keneil K. Shah *et al.* also reported about the influence of chromium, selenium, iron and zinc against HIVgrowth and its treatment [125].

CONCLUSION

Advancement in the research related to diagnosis, prevention and cure of infections and diseases caused by HIV and AIDS brought rays of hope to the medical and clinical field. It was largely accepted by the research community that if the infection can be caught at an initial phase and the agents or factors leading to the grave consequences can be determined at proper time, then curing processes might change the mechanism of action of these detrimental factors or agents and can save lives of many infected people. Although, it was established by numerous reported research experiments that supplementation of antioxidants or their therapeutic implications in HIV infection can repress the injurious impacts of oxidative stress and can retard the development of HIV to AIDS; yet, further in-depth research experiments and analyses are necessary to authenticate many of the outcomes, to understand their proper mechanism of actions and to have confirmed understanding of their probable side effects in different health conditions. Also, proper analyses are necessary to assess the appropriate antioxidant dosages for various ages of patients with diverse health conditions, requirement of antioxidant levels at different stages of infection and the probability of their resistance against the treatment methods etc. However, the author believes that, this review will help towards the understanding of novel therapeutic potentials of some known antioxidant molecules and minerals against HIV and AIDS that have been recognised as potential threats to the human welfare in the entire world.

ACKNOWLEDGEMENT

The author, G. Bora sincerely acknowledges DST for providing analytical and technical assistance, via DST-FIST programme and UGC, New Delhi for granting UGC- SAP to the Department of Chemistry, Dibrugarh University.

REFERENCES

1. Hymes KB, Cheung T, Greene JB, et al. Kaposi's Sarcoma in homosexual men – a report of eight cases. Lancet, 1981; **2(8247):** 598-600.
2. Date AA, Destache CJ. A review of nanotechnological approaches for the prophylaxis of HIV/AIDS. Biomaterials, 2013; **34(26):** 6202–28.
3. Buckheit Jr RW, Watson KM, Morrow KM, Ham AS. Development of topical microbicides to prevent the sexual transmission of HIV. Antiviral Res, 2010; **85(1):**142–58
4. Centers for Disease Control (CDC). Mortality attributable to HIV infection/AIDS--United States, 1981-1990. MMWR Morb Mortal Wkly Rep. 1991 Jan 25; **40(3):** 41-4.
5. World Health Organization. In point of fact. Geneva: World Health Organization, May 1991 (no. 74).
6. Ramana LN, Anand AR, Sethuraman S, Krishnan U. Targeting strategies for delivery of anti-HIV drugs. J Control Release, 2014; **192:** 271–83.
7. Hankins CA, Dybul MR. The promise of pre-exposure prophylaxis with antiretroviral drugs to prevent HIV transmission: a review. Curr Opin HIV AIDS, 2013; **8(1):** 50–8.
8. Kashou AH and Agarwal A. Oxidants and antioxidants in the pathogenesis of

HIV/AIDS. The Open Reproductive Science Journal, 2011; **3:** 154-161
9. Pace GW and Leaf CD. The role of oxidative stress in HIV disease. Free Radic Biol Med, 1995; **19(4):** 523-528.
10. Garland M, Fawzi WW. Antioxidants and progression of human immunodeficiency virus (HIV) disease. Nutr Res, 1999; **19(8):** 1259–76.
11. Papadopulos-Eleopulos E. Reappraisal of AIDS – is the oxidation induced by the risk factors the primary cause? Med Hypotheses, 1988; **25(3):** 151-62.
12. Papadopulos-Eleopulos E, Hedland-Thomas B, Causer DA, Dufty AP. An alternative explanation for the radiosensitization of AIDS patients. Int J Radiat Oncol Biol Phys, 1989; **17(3):** 695-7
13. Scheib RG, Parenti DM, Simon GL, et al. Prolonged antiviral activity of D-penicillamine in human immunodeficiency virus-infected homosexual men. Am J Med, 1987; **83(3):** 608.
14. Bitterlich G, Larcher C, Solder B, et al. Effect of D-penicillamine on the expression and propagation of the human immunodeficiency virus by H9 T-lymphoblastoid cells. Arzneimittelforschung, 1989; **39(8):** 825-8.
15. Kalebic T, Kinter A, Poli G, Anderson ME, Meister A, Fauci AS. Suppression of human immunodeficiency virus expression in chronically infected monocytic cells by glutathione, glutathione ester, and N-acetylcysteine. Proc Natl Acad Sci USA, 1991; **88(3):** 986-90.
16. Maggini S, Wintergerst ES, Beveridge S, Hornig DH. Selected vitamins and trace elements support immune function by strengthening epithelial barriers and cellular and humoralimmune responses. Br J Nutr, 2007; **98:** 29–35.
17. Bendich A. Role of antioxidants in the maintenance of immune functions. In: Frei B, editor. Natural antioxidants in human health and disease. San Diego, CA: Academic Press, 1994; 447–67.
18. Catania AS, Barros CR, Ferreira SRG. Vitamins and mineralswith antioxidant properties and cardiometabolic risk: controversies and perspectives. Arq Bras Endocrinol Metab, 2009**; 53:** 550–9.
19. Singh G, Pai RS. Recent advances of resveratrol in nanostructured based delivery systems and in the management of HIV/AIDS. J Control Release, 2014; **194:** 178–88.
20. Alinaghi SAS, Paydary K, Emamzadeh-Fard S, Mohraz M. Treatment with IMODTM as a novel immune modulator in HIV positive patients. J AIDS Clinic Res, 2012; **3:** 180.
21. Kheirandish P, Mohraz M, Farzamnfar B, Abdollahi M, Shahhosseiny MH, Madani H, et al. Preclinical and phase 1 clinical safety of Setarud (IMOD), a novel immunomodulator. DARU J Pharm Sci, 2009; **17(3):** 148–56
22. Mohraz M, Kheirandish P, Kazerooni PA, Davarpanah MA, Shahhosseiny MH, Mahdavian B, et al. A clinical trial on the efficacy of IMOD in AIDS patients. DARU J Pharm Sci, 2009; **17(4):** 277–84.
23. Jakopin Z. Murabutide revisited: a review of its pleiotropic biological effects. Curr Med Chem, 2013; **20(16):** 2068–79
24. Jackson EM, Herbst-Kralovetz MM. Intranasal vaccination with murabutide enhances humoral and mucosal immune responses to a virus-like particle vaccine. PLoS ONE, 2012; **7(7):** e41529.
25. Darcissac EC, Truong MJ, Dewulf J, Mouton Y, Capron A, Bahr GM. The synthetic immunomodulator murabutide controls human immunodeficiency virus type 1 replication at multiple levels in macrophages and dendritic cells. J Virol, 2000; **74(17):** 7794–802.
26. Singh G, Pai RS. Dawn of antioxidants and immune modulators to stop HIV-progression and boost the immune system in HIV/AIDS patients: An updated comprehensive and critical review. Pharmacol Rep, 2015; **67:** 600–605
27. Srinivas A, Dias BF. Antioxidants in HIV positive children. Indian J Pediatr, 2008; **75(4):** 347-50.
28. Hurwitz BE, Klaus JR, Llabre MM, et al. Suppression of human immunodeficiency virus type 1 viral load with selenium

supplementation. Arch Intern Med, 2007; **167(2):** 148-54.
29. Pizzorno J. Glutathione!. Integr Med (Encinitas), 2014; **13(1):** 8-12.
30. Herzenberg LA, De Rosa SC, Dubs JG, et al. Glutathione deficiency is associated with impaired survival in HIV disease. Proc Natl Acad Sci USA, 1997; **94(5):** 1967-72.
31. Morris K. Glutathione may have major role in HIV-1 disease. Lancet, 1997; **349(9054):** 781.
32. Borges-Santos MD, Moreto F, Pereira PC, Ming-Yu Y, Burini RC. Plasma glutathione of HIV$^+$ patients responded positively and differently to dietary supplementation with cysteine or glutamine. Nutrition, 2012; **28(7-8):** 753-6.
33. Atkuri KR, Mantovani JJ, Herzenberg LA, Herzenberg LA. N-Acetylcysteine—a safe antidote for cysteine/glutathione deficiency. Curr Opin Pharmacol, 2007; **7(4):** 355-9.
34. Millea PJ. N-acetylcysteine: multiple clinical applications. Am Fam Physician, 2009; **80(3):** 265-9.
35. De Rosa SC, Zaretsky MD, Dubs JG, Roederer M, Anderson M, Green A, et al. N-acetylcysteine replenishes glutathione in HIV infection. Eur J Clin Invest, 2000; **30(10):** 915-29.
36. Visali V, Muscoli C, Sacco I, et al. N-acetylcysteine prevents HIV gp 120-related damage of human cultured astrocytes: correlation with glutamine synthase dysfunction. BMC Neurosci, 2007; **8:** 106.
37. Price TO, Uras F, Banks WA, Ercal N. A novel antioxidant N-acetylcysteine amide prevents gp120- and Tat-induced oxidative stress in brain endothelial cells. Exp Neurol, 2006; **201(1):** 193-202.
38. Niki E, Noguchi N, Tsuchihashi H, Gotoh N. Interaction among vitamin C, vitamin E, and beta-carotene. Am J Clin Nutr, 1995; **62 (Suppl 6):** 1322-6.
39. Chiu, HJ, Fischman DA, Hammerling U. Vitamin A depletion causes oxidative stress, mitochondrial dysfunction, and PARP-1 dependent energy deprivation. FASEB J. 2008; **22(11):** 3878-87.
40. Semba RD, Miotti PG, Chiphangwi JD, et al. Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. Lancet, 1994; **343(8913):** 1593-7.
41. Semba RD, Miotti P, Chiphangwi JD, et al. Maternal vitamin A deficiency and child growth failure during human immunodeficiency virus infection. J Acquir Immune Defic Syndr Hum Retrovirol, 1997; **14(3):** 219-22.
42. Mehta S, Fawzi W. Effects of vitamins, including vitamin A, on HIV/AIDS Patients. Vitam Horm, 2007; **75:** 355-83.
43. Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai WY, Stein ZA. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. Am J Public Health, 1995; **85(8 Pt 1):** 1076-81.
44. Wiysonge CS, Shey M, Kongnyuy EJ, Sterne JA, Brocklehurst P. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev, 2011; **(1):** CD003648..
45. Kongnyuy EJ, Wiysonge CS, Shey MS. A systematic review of randomized trails of prenatal and postnatal vitamin A supplementation of HIV-infected women. Int J Gynecol Obstet, 2009; **104(1):** 5-8.
46. Siems W, Sommerburg O, Schild L, Augustin W, Langhans CD, Wiswedel I. Beta-carotene cleavage products induce oxidative stress in vitro by impairing mitochondrial respiration. FASEB J, 2002; **16(10):** 1289-91
47. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The role of vitamin E in human health and some diseases. Sultan Qaboos Univ Med J, 2014; **14(2):** e157-65.
48. Traber MG. Vitamin E. Adv Nutr, 2021; **12(3):** 1047–1048.
49. Mehta S, Spiegelman D, Aboud S, et al. Lipid-soluble vitamins A, D, and E in HIV-infected pregnant women in Tanzania. Eur J Clin Nutr, 2010; **64(8):** 808-17.
50. Pacht ER, Diaz P, Clanton T, Hart J, Gadek JE. Serum vitamin E decreases in HIV-seropositive subjects over time. J Lab Clin Med, 1997; **130(3):** 293-6.

51. Abrams B, Duncan D, Hertz-Picciotto I. A prospective study of dietary intake and acquired immune deficiency syndrome in HIV seropositive homosexual men. J Acquir Immune Defic Syndr, 1993; **6(8):** 949-58.
52. Geissler RG, Ganser A, Ottmann OG, et al. In vitro improvement of bone marrow-derived hematopoietic colony formation in HIV positive patients by alpha-D-tocopherol and erythropoietin. Eur J Haematol, 1994; **53(4):** 201-6.
53. Suzuki YJ, Packer L. Inactivation of NF-kappa B activation by vitamin E derivatives. Biochem Biophys Res Commu, 1993; **193(1):** 277-83.
54. Packer L. Protective role of vitamin E in biological systems. Am J Clin Nutr, 1991; **53(4 Suppl):** 1050-5.
55. Packer L, Suzuki Y. Vitamin E and alpha lipoate: role in antioxidant recycling and activation of the NF-kB transcription factor. Mol Aspects Med, 1993; **14(3):** 229-39
56. Li Y, Schellhorn HE. New developments and novel therapeutic perspectives for vitamin C. J Nutr, 2007; **137:** 2171-84.
57. Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci USA, 1989; **86:** 6377-81.
58. Huang J, May JM. Ascorbic acid spares alpha-tocopherol and prevents lipid peroxidation in cultured H4IIE liver cells. Mol Cell Biochem, 2003; **247(1-2):** 171-6.
59. Eylar E, Baez I, Nevas J, Mercado C. Sustained levels of ascorbic acid are toxic and immunosuppressive for human T cells. P R Health Sci J, 1996; **15(1):** 21-6.
60. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr, 2008; **88 (2):** 491S–499S.
61. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol, 2014; **21 (3):** 319–29.
62. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global consensus recommendations on prevention and management of nutritional Rickets. J Clin Endocrinol Metab, 2016; **101 (2):** 394–415.
63. Eriksen EF, Glerup H. Vitamin D deficiency and aging: implications for general health and osteoporosis. Biogerontology, 2002; **3 (1–2):** 73–7.
64. Lake JE, Adams JS. Vitamin D in HIV-Infected Patients. Curr HIV/AIDS Rep, 2011; **8(3):** 133-41.
65. Jiménez-Sousa MÁ, Martínez I, Medrano LM, Fernández-Rodríguez A, Resino S. Vitamin D in Human Immunodeficiency Virus Infection: Influence on Immunity and Disease. Front Immunol, 2018: **12(9):** 458.
66. Qurban R, Saeed S, Kanwal W, Junaid K, Rehman A. Potential immune modulatory effect of vitamin D in HIV infection: A review. Clin Nutr ESPEN, 2022; **47:** 1-8.
67. Janbakhsh A, Afsharian M , Ramezani M, Mozaffari HR , Sadeghi M. Serum levels of vitamin D, magnesium, calcium, iron, and total iron binding capacity in HIV-infected patients. HIV AIDS Rev, 2019; **18(2):** 148-152.
68. Wang Y, Huang X, Wu Y, Li A, Tian Y, Ren M, Li Z, Zhang T, Wu H, Wang W. Increased Risk of Vitamin D Deficiency Among HIV-Infected Individuals: A Systematic Review and Meta-Analysis. Front Nutr, 2021; **8:** 722032.
69. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010; **2(3):** 299-316.
70. Vitamin $_{B12}$. Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis. 2015.
71. Baik HW, Russell RM. Vitamin B12 deficiency in the elderly. Annual Review of Nutrition, 202; **19**: 357–377
72. Skerrett PJ. Vitamin B12 deficiency can be sneaky, harmful. Harvard Health Blog. February 2019.
73. MJ, Thachil J. Vitamin B12 deficiency - A 21st century perspective. Clin Med (Lond). 2015; **15(2):** 145-50.
74. Adhikari PM, Chowta MN, Ramapuram JT, Rao S, Udupa K, Acharya SD. Prevalence of Vitamin B_{12} and folic acid deficiency in HIV-positive patients and

its association with neuropsychiatric symptoms and immunological response. Indian J Sex Transm Dis AIDS, 2016; **37(2):** 178-184.
75. Adhikari PM, Chowta MN, Ramapuram JT, Rao SB, Udupa K, Acharya SD. Effect of Vitamin B12 and folic acid supplementation on neuropsychiatric symptoms and immune response in HIV-positive patients. J Neurosci Rural Pract, 2016; **7(3):** 362-7.
76. Kavitha K, Saharia GK, Singh AK, Mangaraj M. Association of serum vitamin B_{12} with immuno-hematological parameters in treatment-naive HIV positive cases. J Family Med Prim Care, 2022; **11(7):** 3784–3789.
77. Robertson KR, Stern RA, Hall CD, Perkins DO, Wilkins JW, Gortner DT, Donovan MK, Messenheimer JA, Whaley R, Evans DL. Vitamin B12 deficiency and nervous system disease in HIV infection. Arch Neurol, 1993; **50(8):** 807-11.
78. James JS. Low vitamin B-12 blood levels associated with faster progression to AIDS. AIDS Treat News. 1997; **(No 264):** 3-4.
79. Tang AM, Graham NM, Chandra RK, Saah AJ. Low serum vitamin B-12 concentrations are associated with faster human immunodeficiency virus type 1 (HIV-1) disease progression. J Nutr. 1997; **127(2):** 345-51
80. Maoka T. Carotenoids as natural functional pigments. J Nat Med, 2020; **74(1):** 1-16.
81. Johnson EJ. The role of carotenoids in human health. Nutr Clin Care, 2002; **5(2):** 56-65.
82. Gregg O, Coodley MD, Marcia K, Coodley MD. Serum Carotenoids, Vitamin A and Vitamin E in HIV Infected Patients. Journal of Nutritional Immunology. 1996: **4:** 3.
83. Coodley GO, Nelson HD, Loveless MO, Folk C. Beta-carotene in HIV infection. J Acquir Immune Defic Syndr (1988). 1993; **6(3):** 272-6.
84. Sheehan NL, van Heeswijk RP, Foster BC, et al. The effect of β-carotene supplementation on the pharmacokinetics of nelfinavir and its active metabolite M8 in HIV-1-infected patients. Molecules, 2012; **17(1):** 688-702.
85. Kaio DJ, Rondó PH, Souza JM, Firmino AV, Luzia LA, Segurado AA. Vitamin A and beta-carotene concentrations in adults with HIV/AIDS on highly active antiretroviral therapy. J Nutr Sci Vitaminol (Tokyo), 2013; **59(6):** 496-502.
86. Patrick L, Nutrients and HIV: Part One — Beta Carotene and Selenium. Altern Med Rev, 1999; **4:** 6
87. Phuapradit W, Chaturachinda K, Taneepanichskul S, Sirivarasry J, Khupulsup K, Lerdvuthisopon N. Serum vitamin A and beta-carotene levels in pregnant women infected with human immunodeficiency virus-1. Obstet Gynecol, 1996; **87(4):** 564-7.
88. J Austin, N Singhal, R Voigt, F Smaill et al. A community randomized controlled clinical trial of mixed carotenoids and micronutrient supplementation of patients with acquired immuno deficiency syndrome. Eur J Clin Nutr, 2006**; 60:** 1266–1276
89. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016; **5:** e47.
90. Pasetto S, Pardi V, Murata RM. Anti-HIV-1 activity of flavonoid myricetin on HIV-1 infection in a dual-chamber in vitro model. PLoS One, 2014; **9(12):** e115323.
91. Li BQ, Fu T, Yan YD, Baylor NW, Ruscetti FW, Kung HF. Inhibition of HIV infection by baicalin--a flavonoid compound purified from Chinese herbal medicine. Cell Mol Biol Res, 1993; **39(2):** 119-24.
92. Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun, 2000; **276(2):** 534-8.
93. Mehla R, Bivalkar-Mehla S, Chauhan A. A Flavonoid, Luteolin, Cripples HIV-1 by Abrogation of Tat Function. PLoS ONE, 2011; **6(11):** e27915.
94. Sato M, Miyazaki T, Kambe F, Maeda K, Seo H. Quercetin, a bioflavonoid inhibits

the induction of interleukin 8 and monocytes chemoattractant protein-1 expression by tumor necrosis factor-α in cultured human synovial cells. J Rheum, 1997; **24:** 1680-1684.
95. Cho SY, Park SJ, Kwon MJ, Jeong TS, et al. Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF-κB pathway in lipopolysacchride-stimulated macrophage. Mol. Cell. Biochem, 2003; **243:** 153-160.
96. Wadsworth TL, Dennis RK. Effects of the wine polyphenolics quercetin and resveratrol on pro-inflammatory cytokine expression in Raw 264.7 macrophages. Biochem. Pharmacol, 1999; **57:** 941-949.
97. Nair M, Saiyed ZM, Gandhi NH, Ramchand CN. The Flavonoid, Quercetin, Inhibits HIV-1 Infection in Normal Peripheral Blood Mononuclear Cells. Am. J. Infect. Dis, 2009; **5(2):** 135-141.
98. Resveratrol, Micronutrient Information Center, Linus Pauling Institute, Oregon State University, Corvallis, OR. 11 June 2015. Retrieved 26 August 2019
99. Jasiński M, Jasińska L, Ogrodowczyk M. Resveratrol in prostate diseases - a short review. Cent European J Urol, 2013; **66(2):** 144-9.
100. Frémont L. Biological effects of resveratrol. Life Sci, 2000; **66(8):** 663-673
101. Feng Z, Yang Z, Gao X, Xue Y, Wang X. Resveratrol Promotes HIV-1 Tat Accumulation via AKT/FOXO1 Signaling Axis and Potentiates Vorinostat to Antagonize HIV-1 Latency. Curr HIV Res, 2021; **19(3):** 238-247.
102. Zeng X, Pan X, Xu X, Lin J, Que F, Tian Y, Li L, Shuwen Liu. Resveratrol Reactivates Latent HIV through Increasing Histone Acetylation and Activating Heat Shock Factor 1. J. Agric. Food Chem, 2017; **65 (22):** 4384-4394,
103. Chan CN, Trinité B, Levy DN. Potent Inhibition of HIV-1 Replication in Resting CD4 T Cells by Resveratrol and Pterostilbene. Antimicrob Agents Chemother, 2017; **61(9):** e00408-17.
104. Tinggi U. Selenium: its role as antioxidant in human health. Environ Health Prev Med, 2008; **13(2):** 102-8.
105. Zoidis E, Seremelis I, Kontopoulos N, Danezis GP. Selenium-Dependent Antioxidant Enzymes: Actions and Properties of Selenoproteins. Antioxidants, 2018; **7(5):** 66.
106. Stone CA, Kawai K, Kupka R, Fawzi WW. Role of selenium in HIV infection. Nutr Rev. 2010; **68(11):** 671-81.
107. Hadadi A, Ostovar A, Edalat Noor B, Rasoolinejad M, et al. The effect of selenium and zinc on CD4(+) count and opportunistic infections in HIV/AIDS patients: a randomized double blind trial. Acta Clin Belg, 2020; **75(3):** 170-176..
108. Pitney CL, Royal M, Klebert MJ. Selenium supplementation in HIV-infected patients: is there any potential clinical benefit? Assoc Nurses AIDS Care, 2009; **20(4):** 326-33
109. Shor-Posner GS, Miguez MJ, Pineda LM, Rodriguez A, et al. Impact of selenium status on the pathogenesis of mycobacterial disease in HIV-1-infected drug users during the era of highly active antiretroviral therapy. Acquir Immune Defic Syndr, 2002; **29(2):** 169-73.
110. Muzembo BA, Ngatu NR, Januka K, Huang HL, Nattadech C, Suzuki T, Wada K, Ikeda S. Selenium supplementation in HIV-infected individuals: A systematic review of randomized controlled trials. Clin Nutr ESPEN, 2019; **34:** 1-7.
111. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci, 2013; **18(2):** 144-57.
112. Ripa S and Ripa R. Zinc and immune function. Minerva Med, 1995; **86:** 315–318
113. Baum MK, Lai S, Sales S, Page JB, Campa A. Randomized, controlled clinical trial of zinc supplementation to prevent immunological failure in HIV-infected adults. Clin Infect Dis, 2010; **50(12):** 1653-60.
114. Silva M, Montes CG, Canals A, Mackenna MJ, Wolff M. Role and effects of zinc supplementation in HIV-infected patients with immunovirological discor-

dance: A randomized, double blind, case control study. PLoS One, 2021; **16(1):** e0244823.
115. Baum MK, Posner GS, Campa A. Zinc Status in Human Immunodeficiency Virus Infection. J Nutr, 2000; **130(5):** 1421S–1423S,
116. Bertinato J, Wu Xiao C, Ratnayake WM, et al. Lower serum magnesium concentration is associated with diabetes, insulin resistance, and obesity in South Asian and white Canadian women but not men. Food Nutr Res**,** 2015; **59(1):** 25974
117. Grober U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients, 2015; **7(9):** 8199–8226.
118. Al Alawi AM, Majoni SW, Falhammar H. Magnesium and Human Health: Perspectives and Research Directions. Int J Endocrinol, 2018; **2018:** 9041694.
119. Moreno Díaz MT, Ruiz López MD, Navarro Alarcón M, et al. Deficiencia de magnesio en pacientes VIH-SIDA [Magnesium deficiency in patients with HIV-AIDS]. Nutr Hosp. 1997; **12(6):** 304-8.
120. Okwara EC, Meludu SC, Okwara JE, Enwere OO, Diwe KC, Amah UK, Ubajaka CF, Chukwulebe AE, Ezeugwunne IP. Selenium, zinc and magnesium status of HIV positive adults presenting at a university teaching hospital in Orlu-Eastern Nigeria. Niger J Med. 2012; **21(2):** 165-8.
121. Krejpcio Z. Essentiality of chromium for human nutrition and health. Pol. J. Environ. Stud, 2001;**10(6):** 399–404
122. Pechova A, Pavlata L. Chromium as an essential nutrient: a review. Vet Med (Praha), 2007; **52(1):** 1–18
123. Aghdassi E, Salit IE, Fung L, Sreetharan L, Walmsley S, Allard JP. Is chromium an important element in HIV-positive patients with metabolic abnormalities? An hypothesis generating pilot study. J Am Coll Nutr, 2006; **25(1):** 56-63.
124. Aghdassi E, Arendt BM, Salit IE, Mohammed SS, Jalali P, Bondar H, Allard JP. In patients with HIV-infection, chromium supplementation improves insulin resistance and other metabolic abnormalities: a randomized, double-blind, placebo controlled trial. Curr HIV Res, 2010; **8(2):** 113-20.
125. Shah KK, Verma R, Oleske JM, Scolpino A, Bogden JD. Essential trace elements and progression and management of HIV infection. Nutr Res, 2019; **71:** 21-29.