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Review article

Role of micronutrients and natural antioxidants in fighting against HIV; a quick mini-review

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Abstract

Oxidative stress has been implicated in the progression of HIV to AIDS, since HIV usually replicates in a highly oxidized condition and $CD4^+$ T lymphocytes can be activated via a cascade of internal oxidative pathways, which enhances the formation of proteins and enzymes. Thus, antioxidants should potentially be useful for the treatment and prevention of HIV infection as a new alternative strategy. Regarding the point that there are various approaches for treating the HIV-positive patients, antioxidant supplementation therapy alongside with other medications possesses many benefits. In fact, antioxidants and micronutrient supplements have been considered as a costly and short-term strategy to improve antioxidant deficiency. If diets come with sufficient education and scientific recommendations, they can provide a low-cost and long-term strategy to reduce oxidative stress, prevent micronutrient deficiency, and slow down HIV progression. This strategy may be applicable and beneficial particularly in countries around coast of Africa, where HIV is most common. Meantime these countries are rich of natural food resources. It seems that a healthy diet is the best way to insure proper nutrient intake, since it contains many nutrients not available in pills.

Keywords: antioxidants, HIV, mechanism of action, phytochemicals

Introduction

Human immunodeficiency virus or HIV (a lentivirus) can cause acquired immunodeficiency syndrome (AIDS), in which progressive failure of the immune system puts the subject to the risk of opportunistic infections and cancers. This risky infection is able to transfer via blood, semen, vaginal fluid, pre-ejaculate, and breast milk due to presence of HIV particles and virus within the infected immune cells within body fluids [1].

It is well documented that oxidative stress has been implicated in the progression of HIV to AIDS. In fact, HIV usually replicates in a highly oxidized condition and the $CD4^+$ T lymphocytes are activated via a cascade of internal oxidative pathways involving inflammatory cytokines and enzymes. Therefore, not only such activation signaling can stimulate the HIV genes to reproduce in infected cells, but also the elevated

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metabolism in those mentioned cells helps to provide required cellular factors for generation of new viral particles. As a result, activated but uninfected $CD4^+$ T lymphocytes are susceptible targets to be infected by HIV. Literature reveals that cells infected with HIV might produce a large number of inflammatory molecules, such as superoxide anions, peroxynitrite and nitric oxides. In this scenario, the antioxidant enzymes such as superoxide dismutase and catalase are stimulated to fight against oxidants [2]. Therefore, augmentation of antioxidant condition in the cell environment instinctively occurs to repair the imbalance and protect from oxidatively-stressed environment.

Oxidative stress and HIV

Obviously, reactive oxygen species (ROS) are one of the second messengers that can promote the nuclear factor (NF)-κb cascade elevating HIV replication through control of gene transcription. In fact, both oxidative stress and inflammatory cascade play a critical role in the development of AIDS. Some complications in AIDS patients seem to be originated through elevation of ROS and the deregulation of endogenous antioxidant enzymes. Interestingly, changing the redox balances results in a clinically silent phase of HIV infection. The belief is that some patients are substantially resistant to HIV and remain seronegative, although they have been exposed several times to HIV. Thus, it is not surprising to state that the pro-oxidative imbalance of the host cell redox is essential for complete assembly of virus proteins [3]. Regarding all the above reasons, antioxidants are potentially useful for the treatment and prevention of HIV-1 infection that lead to new and alternative strategy. Nowadays, balancing of the oxidative condition in HIV infection is a golden therapy in addition to the standard protocol for treatment of HIV-infected patients, because it can provide further protection against viruses (figure 1).

Role of vitamins in HIV-inhibition

There are many categories of antioxidant medicines, which have been developed to meet protection against progression of pathogens [4]. Among them, vitamins and trace elements are able to inhibit HIV expression, since they act almost nonspecificly and display a broad range of activity. Vitamins A, C and E are the hallmark antioxidants known, of which vitamins C and E are the major antioxidants in plasma. It has been demonstrated that vitamin C can suppress the HIV replication via inhibiting reverse transcriptase activity, while vitamin E can prevent lipid peroxidation. In nature, vitamin E is the major antioxidant present in the mitochondria, microsomes and lipoproteins that can suppress the activation of NF-κb. It is recommended to decrease free radicals in HIV infected patients, since concentrations of oxidized DNA bases and lipid peroxidation in HIV-infected patients increase. Literature have revealed that antioxidant supplements could alter the asymptomatic stable chronic hyperlactatemia existing in AIDS patients, which were under HAART (highly active antiretroviral therapy) including NRTI (nucleoside analog reverse transcriptase inhibitors) for a long time [5,6].

The important point is that the levels of these natural antioxidants are too low in AIDS patients. In a recent study in sub-Sahara Africa, micronutrient deficiency in HIV-positive patients was observed particularly for vitamins A, C, and E, beta-carotene, selenium and zinc, as well as polyphenols especially in women [7]. Children alongside adults in Africa are the group in risk to the HIV infection. Unfortunately, children have inadequate linear growth without proper weight gain due to malnutrition resulting from uncontrolled infection-HIV or in other cases consequential opportunistic infections like tuberculosis. As observed, little children commonly remain without main meals leading to restricted neurological development. It is suggested that lifestyle modification, exercise and diet may prevent these complications [8].

The researchers have revealed that multivitamin supplementation during pregnancy and lactation may cause a positive impact on ponderal growth

in children born to HIV-infected mothers [9]. However, there is no essential evidence to manifest a relation between vitamin A and an eventual higher heterosexual HIV transmission [10]. Another cross sectional study has concluded that the micronutrients malnutrition and wasting are critical in adults with pulmonary tuberculosis who have higher HIV load. But longitudinal studies are needed to support the results obtained, although there has been strong correlation between severe wasting and deficiencies in vitamins A, selenium and plasma carotenoids [11]. Since major depression has been observed abundantly in HIV-positive subjects particularly in HIV-positive pregnant women, multivitamin supplementation has been studied and demonstrated good protective effect on depression and on some characteristics of life quality. However, vitamin A showed no effect on these outcomes. It seems that such results should be further supported by investigation among patients who need antiretroviral therapy [12].

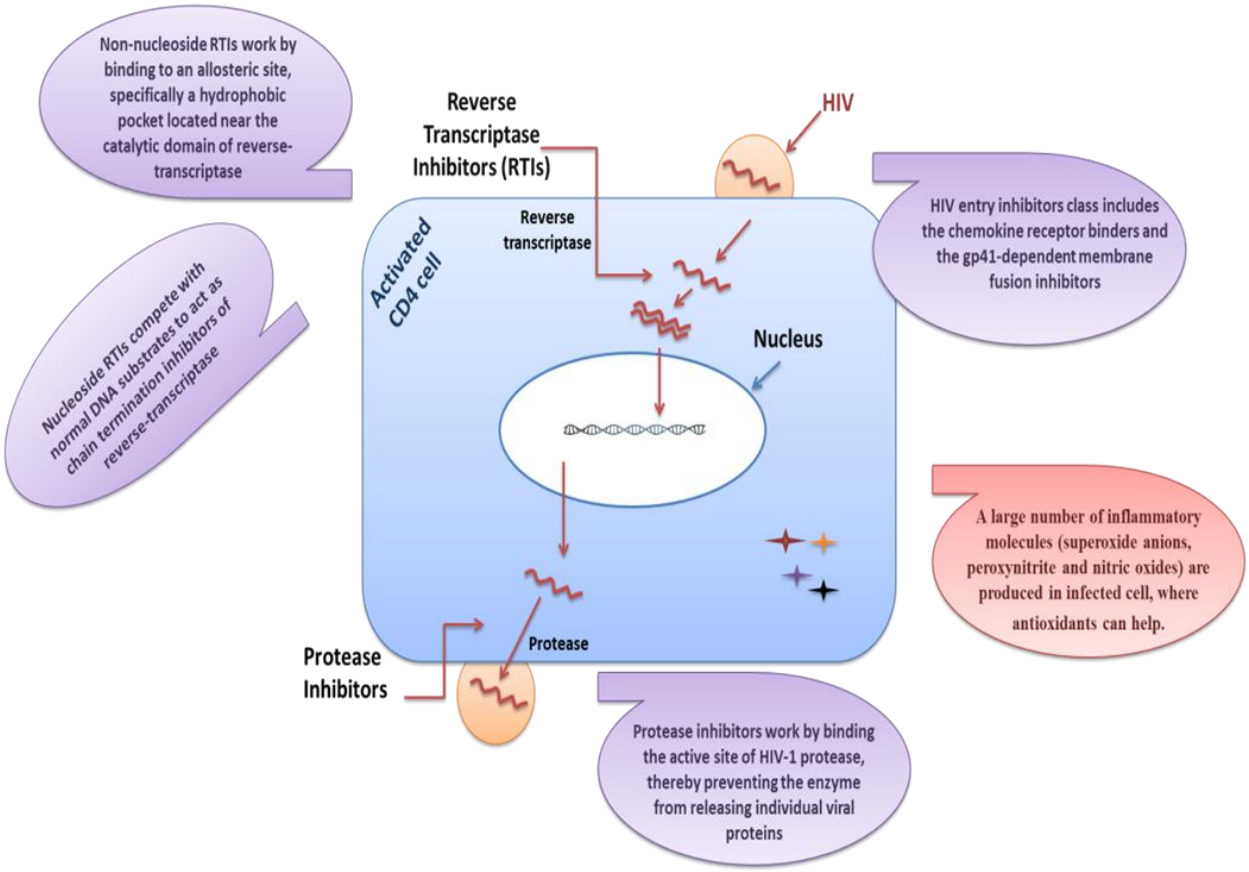

Figure 1. Different mechanisms of anti-HIV drugs and the role of antioxidants.

Role of micronutrients in HIV-inhibition

Like antioxidant deficiency, micronutrients deficiencies are correlated with HIV progress including reduced CD4 cell counts, and increased morbidity and mortality in HIV-positive persons. In a report to compare nutrient status of South African breastfeeding women by HIV status, the authors suggested a multiple micronutrient supplement therapy for HIV-positive persons, which should continue until improvement of dietary intake [13]. Meantime, other studies have reported that multiple micronutrient supplementation have no impact on viral load in seminal or cervicovaginal secretions [14]. It has also been reported that low level of serum carotene is common in HIV-positive patients which usually results in death among advanced AIDS patients. Surprisingly, supplement therapy could correct micronutrient deficiency and improve survival. However, the findings remain to be elucidated by defining the exact mechanism of action [15]. Selenium, a trace element is essential for the maintenance of human health. Selenium is able to enhance GSH peroxidase activity and inhibits TNF-α-induced HIV replication. Literature review has revealed that HIV-infected patients possess lower concentration of selenium in plasma associated with an enhanced risk of mortality [2]. Zinc deficiency also weakens immune function through decreasing interferon production, reducing NK cell activity, antibody formation and T-cell cytotoxic activity. Therefore, zinc therapy is recommended daily in HIV-1-positive subjects to improve $CD4^+$ cell counts [2]. Accordingly, IMOD is another good example of an antioxidant mixture of medicinal herbs and selenium that has been found effective in treating AIDS patients [16].

Role of polyphenols and other antioxidants in HIV-inhibition

Polyphenols are antioxidants naturally found in plants (including bioflavonoids, procyanidine, proanthocyanidine, leucoanthocyanidins, pyconogenol, and tannins), and may be effective in prevention or treatment of lipoprotein oxidation via scavenging free radicals. There are some herbal drugs effective in prevention and treatment of HIV-positive patients such as IMOD provided from a combination of *Rosa canina*, *Urtica dicica* and *Tanacetum vulgare* ethanol extracts, consisting selenium, carotene, flavonoids and urea, which are exposed to a pulsed electromagnetic field. To the best of our knowledge, the immunomodulatory mechanisms of IMOD have not been exactly explored, but it is reported to enhance CD4+ lymphocyte count after a period of one to three months therapy [16]. It seems that, in contrast to cancer, in which the role of antioxidants in chemoprevention and therapy is questionable and even may result in progression of disease [17,18], antioxidants play an important role in treatment of HIV-positive patients. This is due to the various effects of antioxidants to improve and maintain the oxidative balance of the body cells including CD4 cells to suppress the replication of the viruses. For instance, epigallocatechin-3-gallate (EGCG) is one of the main polyphenols of green tea, which is reported to show antiviral activity [19]. The authors have mentioned that they have employed peripheral blood lymphocytes incubated with either LAI/IIIB or Bal HIV strains along with increasing doses of EGCG. The results have revealed that this compound could strongly suppress the replication of both strains, which was evaluated by reverse transcriptase and p24 assays on the cell supernatants.

Furthermore, the putative anti-HIV activity of caffeic acid derivatives has been reported. Additionally, derivatives including chicoric, rosmarinic and lithospermic acids have been suggested to be considered as the future lead compounds that can act multi-targeting. Also, the plants and vegetables containing them can be potent nutritional therapeutic supplementation source [20]. Moreover, due to the role of beta-chemokine receptors (CCR2b, CCR3 and CCR5), and the alpha-chemokine receptors (CXCR1, CXCR2 and CXCR4) as entry co-receptors for HIV-1, it has been hypothesized that flavonoids

may possibly act by interfering at the HIV co-receptor level. In one study, the investigators evaluated the effect of flavonoid constituents of a grape seed extract on the expression of HIV-1 co-entry receptors using immune-competent mononuclear leukocytes. The authors have concluded that the mentioned extract significantly down regulated the expression of the HIV-1 entry co-receptors (CCR2b, CCR3 and CCR5) dose-dependently [21].

Previously in last decade, flavonoids from six different classes (chrysin, acacetin and apigenin) have been reported to suppress HIV expression in TNF-alpha-treated OM-10.1 cultures with favorable potencies. Among them, chrysin also inhibited HIV expression in response to PMA in OM-10.1 cells, in ACH-2 cells stimulated with either TNF-alpha or PMA, and in 8E5 cultures [22]. Taken together and regarding such example reports above, it seems that numerous polyphenol antioxidants are able to assist fighting against HIV, although underlying mechanisms are not necessarily related to their antioxidant potentials.

Conclusion

Today, antioxidant supplements including vitamins A, C and E are usually prescribed to people with HIV complications. As a new strategy for highly active anti-retroviral therapies, antioxidants could find a place to improve and extend lifespan of the AIDS patients, since these supportive elements of a regimen are able to suppress HIV and restore immune function as much as possible with the least toxic side effects. Although the beneficial capability of antioxidants for helping to fight against HIV is mechanistically approved, bibliography has demonstrated that there is a controversy in real impacts of antioxidant supplements on treatment of HIV-positive persons. It seems that research data are conflicting and some investigations suffer from a lack of rigor. For instance, some limited studies have shown no correlation between lipid alteration and levels of the antioxidant nutritional components such as selenium, vitamins A, C and E, but on the other side, there are many reports demonstrating beneficial impacts of dietary supplements on these patients. It is still questionable how to effectively prescribe single vitamins as drugs, and caution is needed when taking large amounts of these compounds is recommended. Meanwhile, the use of vitamins in high pharmacological doses is still poorly documented. Beside the natural vitamins and micronutrients, efficient herbal medicines compose various polyphenols, which may act as antioxidative agents.

Undoubtedly, antioxidants and micronutrient supplements have been considered as a costly and short-term strategy to improve antioxidant deficiency. If local diets combine with adequate nutritional education, they can provide a low-cost and long-term strategy to reduce oxidative stress, prevent micronutrient deficiency, and slow down AIDS progression. This strategy may be applicable and beneficial particularly in countries around the west, central, and south coast of Africa, which are rich in natural food resources. It seems that a healthy diet is the best way to insure proper nutrient intake, since it contains many nutrients not available in pills.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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