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ORIGINAL ARTICLE

Serum levels of antioxidants and its supplementation in people living with HIV: integrative review

Níveis séricos de antioxidantes e sua suplementação em pessoas vivendo com HIV: revisão integrativa

Aline Roberta Rodrigues da Silva[1], **Patrícia Dias de Brito**[2,*]

[1]*Nutrition Department, National Institute of Infectious Diseases Evandro Chagas, Oswaldo Cruz Foundation. Rio de Janeiro, RJ, Brazil.*

[2]*Clinical Research in Nutrition and Infectious Diseases Group, Nutrition Department, National Institute of Infectious Diseases Evandro Chagas, Oswaldo Cruz Foundation. Rio de Janeiro, RJ, Brazil.*

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KEYWORDS

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ABSTRACT

Objective: To conduct an integrative review of serum levels of antioxidants and the effects of their supplementation on people living with HIV (PLHIV).
Methods: A research was performed in the electronic databases LILACS and MEDLINE, using the descriptors "HIV" AND "antioxidants"; 110 publications were identified, 92 of which were available in the MEDLINE database and 3 in the LILACS database. After applying the exclusion criteria, 8 articles were selected for final evaluation.
Results: The studies selected for the review were divided into 4 prospective observational studies and 4 clinical trials with supplementation of antioxidants or food sources of antioxidants. We observed that the initiation of antiretroviral therapy and its prolonged use negatively influenced the parameters of oxidative stress, and that deficiency of antioxidants was associated with more significant damage to mitochondrial DNA. Supplementation of foods that are sources of antioxidants, such as dark chocolate and spirulina, has had beneficial effects on serum lipids and antioxidant capacity.
Conclusion: Clinical trials with a more robust methodology, supplementation of isolated nutrients, for more extended periods of intervention, and with the assessment of food consumption are necessary to elucidate their effects on oxidative stress in PLHIV faced with factors such as the use of antiretroviral therapy and changes in metabolic rates of this population.

*Corresponding author:
Instituto Nacional de Infectologia Evandro Chagas/Fiocruz
Addr.: Avenida Brasil, 4365. Manguinhos. Rio de Janeiro, RJ, Brasil | CEP: 21.040-360.
Phone: +55 21 3865-9602 / 21 986940571
E-mail: patricia.brito@ini.fiocruz.br (Brito PD)

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PALAVRAS-CHAVE

Antioxidantes
Infecções por HIV
Nutrientes
Suplementos nutricionais

RESUMO

Objetivo: Realizar uma revisão integrativa sobre os níveis séricos de antioxidantes e os efeitos da sua suplementação em pessoas vivendo com HIV (PVHIV).
Métodos: Foi realizado levantamento nas bases de dados eletrônicas LILACS e MEDLINE, por meio dos descritores "*HIV*" AND "*antioxidants*". Foram identificadas 110 publicações, sendo 92 disponíveis na base de dados MEDLINE e 3 na base de dados LILACS. Após aplicação dos critérios de exclusão, foram selecionados 8 artigos para avaliação final.
Resultados: Os estudos selecionados para a revisão se dividiam em 4 estudos prospectivos observacionais e 4 ensaios clínicos com suplementação de antioxidantes ou de alimentos fontes de antioxidantes. Foi observado que o início da terapia antirretroviral e seu uso prolongado influenciaram negativamente os parâmetros de estresse oxidativo (EO), e que a deficiência de antioxidantes estava associada a um maior dano ao DNA mitocondrial. A suplementação de alimentos fontes de antioxidantes, como chocolate amargo e spirulina, obteve efeitos benéficos sobre os lipídios séricos e a capacidade antioxidante.
Conclusão: Ensaios clínicos com metodologia mais robusta, suplementação de nutrientes isolados, por maiores períodos de intervenção, e com avaliação do consumo alimentar, são necessários para elucidar seus efeitos sobre o EO em PVHIV diante de fatores como o uso de terapia antirretroviral e alterações metabólicas dessa população.

INTRODUCTION

Antiretroviral therapy (ART) for treating HIV infection suppresses viral replication in the body[1], improving the quality of life and increasing the survival of people living with HIV (PLHIV), as it reduces the occurrence of opportunistic infections, hospitalizations, and the number of deaths[2-4].

The latest report from the Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that in 2018 approximately 37.9 million people were living with HIV, with just over 60% using ART. For this reason, the disease is currently considered one of the biggest public health issues in the world[5].

Initially, multiple nutrient deficiencies were among the most prevalent clinical complications in PLHIV[6,7]. However, there has been an improvement in serum micronutrient levels with combined ART, among other reasons, due to improved appetite and increased food intake, although not consistently enough to correct the deficiency[8,9].

The concern with the adequacy of serum micronutrient levels in PLHIV is justified by their participation in the immune and antioxidant systems[10] and the increased oxidative stress (OS) in HIV infection. This OS generates a potentially toxic accumulation of oxygen radicals, worsened by the deficiency of antioxidant micronutrients, leading to an inflammatory state that promotes an increased virus replication[6].

Antioxidants are substances or nutrients that, present in low concentration compared with the oxidizable substrate, can effectively delay or inhibit its oxidation[11,12]. Changing the balance between oxidants and antioxidants, known as the redox state[11], promotes OS with an increase in reactive oxygen species (ROS)[2,12] that promotes damage to DNA, polysaccharides and proteins, immune dysfunction, T-cell apoptosis, and induction of tumor necrosis factor (TNF)-α[2,13].

In HIV infection, the redox state is altered from the early stages of the disease. In addition, ART, which is necessary for disease control, also interferes with the balance between oxidants and antioxidants by increasing lipoperoxidation markers and the OS[13]. Thus, PLHIV exhibits changes in glutathione metabolism, reduced serum and tissue levels of antioxidants (such as vitamins C and E), and increased levels of peroxidation products[2,14]. The excessive ROS production during the leukocytes and macrophages activation contributes to the progression of the infection and the increasing in the viral replication rate[2,13].

Therefore, antioxidants, substances/nutrients capable of delaying or inhibiting oxidation[11,12] are indispensable in restoring the state of equilibrium[2,12], decreasing infections and improving immune and cellular health in HIV infections and AIDS[11]. In this sense, therapeutic dietary intervention to attenuate oxidative disorders can be beneficial in PLHIV using ART. Among them are vitamins A, C, and E, the minerals zinc and selenium, the antioxidants glutathione and cysteine, and whey proteins capable of providing precursors for synthesizing glutathione. These compounds contribute to the recovery of the redox state and influence the immune capacity, inhibiting viral replication, potentiating the latency phase, and improving the clinical presentation[2,13].

Although antioxidants are discussed in the scientific literature and widely used as a dietary supplement, their use in clinical practice as a complementary therapy in treating HIV and AIDS is still a topic to be explored to elucidate its potential beneficial effects on the immune system. Thus, an integrative review was conducted to discuss the serum levels of antioxidants and the effects of their supplementation on PLHIV, identifying the types and dosages of antioxidants used in HIV infection and verifying the main effects of antioxidants on the immune system.

METHODS

An integrative review was conducted to answer the following guiding question: "how are serum levels of antioxidants in PLHIV, and what are the results from their supplementation?". This question was planned using the PICO[15] method, in which the population corresponded to PLHIV, supplementation represented the intervention with or without comparison, and the

serum concentration of antioxidants was the outcome.

This type of review was chosen to discuss findings on the subject, given the heterogeneity of supplementation studies, and to identify gaps in the literature that hinder a strong recommendation on antioxidant supplementation for PLHIV. PRISMA-ScR guidelines[16] were followed to ensure methodological rigor and clarity in the presentation of results.

The bibliographic search was conducted between November and December 2019 on the LILACS and MEDLINE databases through PubMed and Virtual Health Library - Bireme - BVS. The search used the following descriptors: "HIV" AND "antioxidants". The inclusion criteria adopted were papers published from 2014 to 2019, with full-text availability in English, Portuguese or Spanish, performed on individuals over 18 years old with HIV/AIDS, whether or not using ART, addressing serum levels antioxidants and/or supplementation of nutrients and/or food sources of antioxidants. Observational studies and clinical trials were considered for the review. The publication time restriction excluded studies with PLHIV using older antiretrovirals, which were more toxic and could negatively affect the antioxidant system. Review articles, duplicates, in vitro or animal experiments, and publications whose sample was pediatric or uninfected with HIV were excluded.

First, a bibliographic search was conducted, after which two evaluators read all titles, and those that met the predefined criteria were selected. Subsequently, the abstracts of the chosen titles were read, and then the articles that would be read in full were defined. After reading the papers, those who met the inclusion criteria were selected. The following characteristics of each study were transcribed to a spreadsheet to be analyzed and interpreted: the type of study, country of publication, objective, the profile of the participants, methodology, main results, limitations.

In the initial screening, 110 publications were identified, of which 92 were available in the MEDLINE database and 3 in LILACS. Sixteen duplicates were excluded. Eighty did not meet the inclusion criteria after reading the title and abstract and were also excluded. Of the remaining 14 publications three were not available in full. However, after a complete reading of the 11 remaining articles, it was found that three did not meet the inclusion criteria; therefore eight articles were analyzed (Figure 1).

RESULTS

The selected studies were conducted in the American and African continents, in different countries, namely: Brazil (3), the United States of America (2), Nigeria (1), and Cameroon (2). The eight studies were divided into prospective observational studies[18-20,23] and clinical trials with supplementation of antioxidants (vitamins A and C17 and glutathione22) or food sources of antioxidants (dark chocolate and yerba mate[21] and Spirulina[24]). Table 1 presents the main findings of the selected articles and their limitations. Five studies included individuals up to 60 years of age[17-21], two[22,23] included individuals up to 65 years of age, and one study[24] did not provide information on the age of the participants.

DISCUSSION

Based on previous studies that showed that people living with HIV/AIDS have lower concentrations of antioxidants, disturbances in glutathione metabolism, and increased generation of ROS, researchers have advocated that OS contributes to the progression of HIV infection. HIV accelerates the inflammatory response and decreases the proliferation of immune cells. Based on these assumptions, several authors have been researching the modulating interference of antioxidants in the status and progression of disease infection in PLHIV[17].

This review showed that although there is a theoretical basis to indicate supplementation of antioxidants in PLHIV, there is still no robust evidence for this recommendation, given the variability in the methodology of clinical trials. Observational studies have shown that the onset of ART[18], prolonged use[20], and smoking[23] negatively influenced the parameters of OS and that deficiency of antioxidants was associated with more significant damage to mitochondrial DNA[19].

The observational study by Tasca et al.[18] evaluated the total antioxidant capacity (TAC), fat-soluble vitamins profile, lipid peroxidation, and DNA damage before and eight months after starting ART. After starting ART, individuals showed a reduction in TAC, retinol, alpha-tocopherol, and some carotenoids, besides a significant increase in DNA damage, especially in those who had a CD4 greater than 500 cells/mm^3. The authors suggested that the increase in OS results from the presence of the virus and ART administration, as it interferes with the redox state.

Martinez et al.[19] followed a cohort of mono-infected individuals with HIV and individuals co-infected with HIV and hepatitis C virus (HCV) for 34 months to assess serum zinc concentrations, DNA damage, and the score of hepatic fibrosis. The results showed an association between zinc deficiency, mitochondrial OS, and progression of liver fibrosis due to decreased antioxidant defenses.

In a cross-sectional observational study conducted in Brazil, Watanabe et al.[20] observed that prolonged use of ART increased plasma selenium levels and reduced selenomethionine. Also, individuals on ART had higher concentrations of MDA and GPX and lowered concentrations of GSH, which was associated with HIV status and their ability to induce OS.

To determine the effects of smoking on viral load (VL), cytokine production, and OS of PLHIV without the use of ART, Ande et al.[23] conducted a prospective study and observed that those considered moderate smokers had higher VL and increased OS. In determining mRNA levels for various antioxidants, the authors found no significant differences.

It was noticed that the observational studies presented a robust theoretical framework for generating the hypothesis, with well-defined objectives and outcomes, well-detailed methods, and an adequate description of the results. The main limitation found was not to present the limitations of the studies.

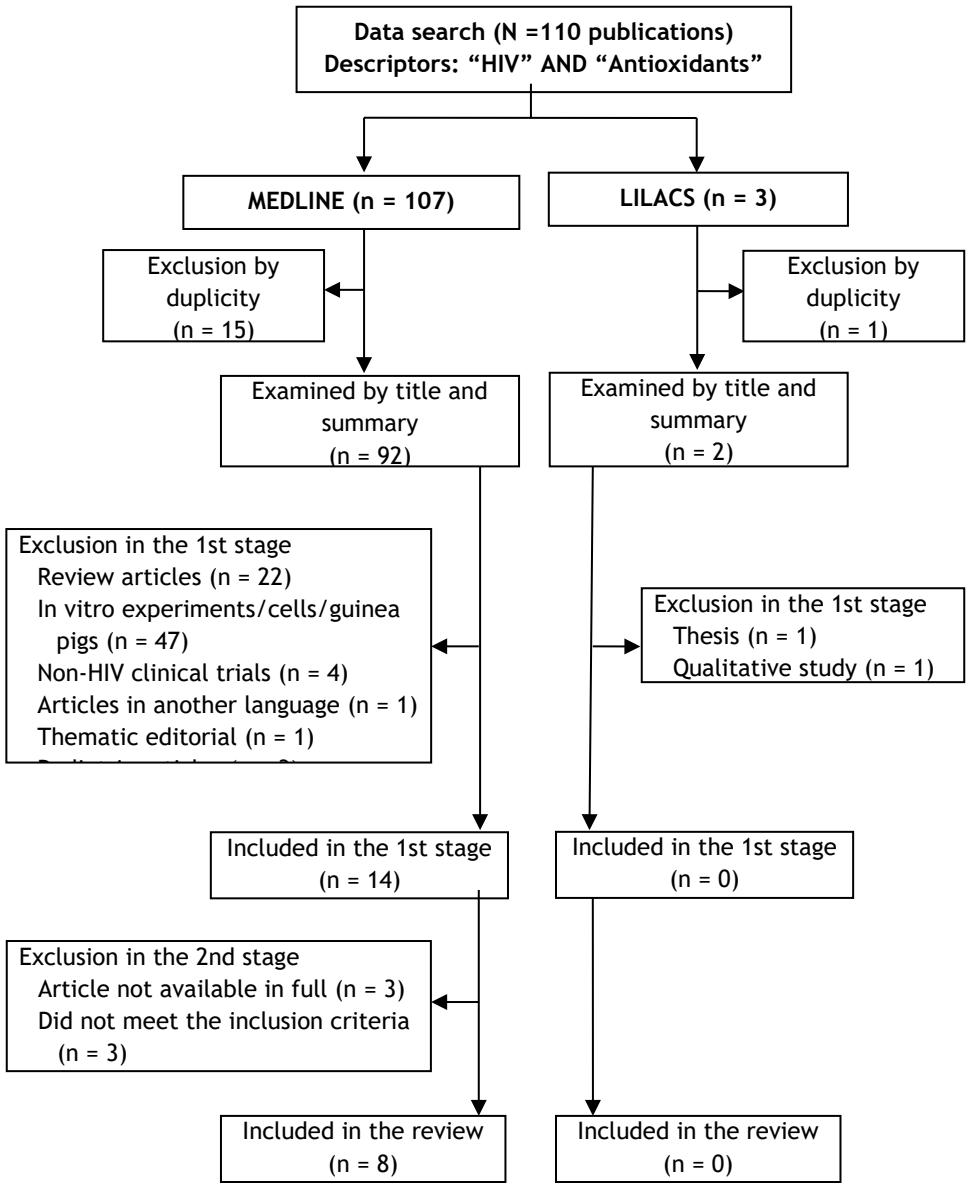

Figure 1 —- Flowchart of the stages of the bibliographic search.

Regarding the included clinical trials, the methodology was diverse, with heterogeneous supplementation protocols. Different nutrients and foods were used, and the supplementation time varied between 15 days and 13 weeks. Makinde et al.[17] conducted a clinical trial with HIV-infected Nigerian individuals and individuals co-infected with HIV and tuberculosis to determine OS parameters before and after supplementation with vitamin A (5,000 IU) and C (2,600 mg) during a month. The authors found significantly lower levels of superoxide dismutase (SOD) and catalase (CAT) and higher levels of malondialdehyde (MDA) after supplementation compared to baseline values. High levels of MDA indicate an increase in lipid peroxidation; thus, it was verified the inability of vitamin A and C supplementation to protect against OS in this population. Because it was a vulnerable population, probably in a situation of food insecurity, it was difficult to assume that the supplementation proposed would be sufficient to protect against OS, especially without presenting the sample's nutritional characteristics, including eating habits.

Another group of Brazilian authors conducted a clinical trial[21] to evaluate the effect of supplementation of dark chocolate (average of 2,148 mg of total phenols) and soluble yerba mate (average of 107 mg of total phenols and 84.24 mg of chlorogenic acid) on inflammatory and oxidative profile of PLHIV using ART. The results showed an increase in HDL-C concentrations after supplementation with dark chocolate, but there were no effects of yerba mate supplementation on inflammatory or oxidative markers. The authors justified the lack of response with yerba mate by the interference of the intervention period, the amount of supplement offered and polyphenols in them, metabolic and intestinal microbiota changes, and use of ART[21]. Note that the sample in this study consisted of individuals with viral suppression (controlled infection) due to the

Table 1 — Description of the articles included in the review.

Author / Year	Type of study	Objective	Methods	Results	Main limitations
Makinde et al., 2017[17]	Prospective randomized clinical trial	To determine the effect of vitamin A and C supplementation on oxidative stress in individuals with HIV and HIV-TB co-infected.	Dosage of OS parameters before and after supplementation of vitamins A and C for 1 month.	There was a reduction in SOD and CAT, and an increase in MDA after supplementation.	a) does not indicate the type of study in the title; b) the non-supplemented group did not receive a placebo; c) does not explain sample calculation or randomization; d) does not present a table of baseline characteristics of the participants; e) does not inform the registration number of the clinical trial; f) does not describe limitations.
Tasca et al., 2017[18]	Cross-sectional observational study	To evaluate the influence of the start of ART on the parameters of OS in HIV ATN individuals.	Analysis of TAC, profile of fat-soluble vitamins, lipid peroxidation (MDA and 8-isoprostane) and DNA damage before and 8 months after starting ART	Decrease in TAC, retinol, α-tocopherol and some carotenoids, in addition to significant increase in DNA damage after ART.	a) the type of study does not allow to establish cause-effect relationships; b) lack of a control group; c) small sample size; d) absence of dietary surveys or anthropometric measurements.
Martinez et al., 2017 [19]	Cross-sectional observational study	To investigate the relationship between plasma zinc, mitochondrial oxidative stress and progression of liver fibrosis in HIV individuals and HIV/HCV co-infected individuals.	Evaluation of the relationship between plasma zinc, DNA damage and fibrosis score for 34 months between the HIV and HIV / HCV groups.	Zinc deficiency was associated with the progression of liver fibrosis and greater damage to mitochondrial DNA.	a) the type of study does not allow to establish cause-effect relationships; b) authors do not describe limitations.
Watanabe et al., 2016[20]	Cross-sectional observational study	To evaluate the relationship between infection by HIV, the use of ART and the OS concentrations and selenium selenomethionine and antioxidant protection.	Evaluation of plasma selenium, erythrocytes, selenomethionine, GSH, GPX, and MDA in HIV- and HIV + with < or > 5 years of ART.	Higher concentrations of MDA and GPX and lower concentration of GSH in HIV +. Association of MDA, GPX and GSH with HIV status.	a) does not indicate the type of study in the title; b) does not explain sample calculation; c) does not describe limitations.

HIV: human immunodeficiency virus; TB: tuberculosis; SOD: superoxide dismutase; CAT: catalase; MDA: malondialdehyde ; ART: Antiretroviral therapy; OS: oxidative stress ; ATN: antiretroviral treatment-naıve; TAC: total antioxidant capacity; HCV: hepatites C Virus; GSH: glutathione; GSX: glutathione peroxidase activity .

Table 1 — Description of the articles included in the review (cont.).

Author / Year	Type of study	Objective	Methods	Results	Main limitations
Petrilli et al., 2016[21]	Placebo-controlled randomized clinical trial	To investigate the role of cocoa consumption and mate on oxidative and inflammatory biomarkers in HIV + individuals.	Analysis of inflammatory, oxidative and immunological parameters, after supplementation of dark chocolate or yerba mate for 15 days.	Increase in the average concentration of HDL-C after dark chocolate supplementation.	a) does not indicate the type of study in the title; b) does not explain sample calculation or randomization.
Ly et al., 2015[22]	Placebo-controlled randomized clinical trial	Evaluate GSH supplementation in HIV- and HIV + individuals.	Evaluation of levels of free radicals and cytokines after supplementation of GSH formulated in liposomes (lGSH) for 13 weeks.	Increased levels of IL-1b, IL-12, IFN-g and TNF-α, decreased levels of free radicals IL-10 and TGF-β.	a) does not indicate the type of study in the title; b) does not explain sample calculation or randomization; c) does not present a table of baseline characteristics of the participants; d) does not inform the registration number of the clinical trial; e) does not describe limitations.
Ande et al., 2015[23]	Cross-sectional observational study	To determine the effects of smoking on viral load (VL), cytokine production and OS in HIV + individuals without ART.	Investigation of cytokine production and OS via cytochrome P450 (CYP).	Higher VL and oxidative stress in HIV + smokers. The serum levels of antioxidants were unchanged.	a) does not indicate the type of study in the title; b) does not describe limitations.
Winter et al., 2014[24]	Placebo-controlled randomized clinical trial	Describe the effects of supplementation of 5 g/day of Spirulina in adult women with HIV in the pre highly active antiretroviral therapy (pre-HAART).	Evaluation of the antioxidant status through the total antioxidant capacity of the serum (TAOS) and analysis of renal function and reporting of concomitant events (anorexia, fatigue, nausea / vomiting, dry or productive cough, abdominal pain, diarrhea and constipation) after supplementation with Spirulina.	Only 43% reported a concomitant event. There was an increase in weight, antioxidant capacity and serum creatinine.	a) does not explain randomization; b) does not present a table of baseline characteristics of the participants.

HIV: human immunodeficiency virus; TB: tuberculosis; SOD: superoxide dismutase; CAT: catalase; MDA: malondialdehyde ; ART: Antiretroviral therapy; OS: oxidative stress ; ATN: antiretroviral treatment-naıve; TAC: total antioxidant capacity; HCV: hepatites C Virus; GSH: glutathione; GSX: glutathione peroxidase activity .

use of ART for at least six months, which reduces the interference of the disease itself on inflammatory and oxidative markers, reducing the bias of the interpretation of the results. When supplemented for 13 weeks with GSH formulated in liposomes (lGSH) in a clinical trial conducted by Ly et al.[22], PLHIV had a reduction in free radicals and immunosuppressive cytokines, demonstrating that, although an imbalance in cytokine profiles induced by HIV occurs, supplementation restores the immune response and can prevent opportunistic infections. Some study strengths can be highlighted: non-inclusion of a vulnerable population, use of placebo, and comparison with a control group (without HIV).

Winter et al.[24] conducted a clinical trial to assess the antioxidant status before and after spirulina supplementation in African women with HIV without ART. The authors found that, after supplementation, there was an increase in antioxidant capacity, a reduction in concomitant events and opportunistic infections, and a positive effect on weight stabilization. Although there are no data to support its use as an antiretroviral, its use as a supplement can reinforce the body's antioxidant action. This study was conducted with women who never used ART in a country with difficulty in accessing HIV treatment. The current recommendation for HIV treatment is the early start of ART, as soon as the diagnosis is confirmed[25]. Thus, the results of this study are limited in their extrapolation to other populations.

Although the bias assessment is not mandatory in the integrative review methodology[16], we consider it essential presenting some limitations observed in the included clinical trials, including the lack of information about the sample calculation and the randomization process, essential steps for an adequate analysis of the results, without bias. The lack of indication of the type of study in the title and a table with basic demographic and clinical data was also common. A limitation found in all clinical trials was the lack of assessment of the participants' food consumption. Thus, it is likely that the intake of other nutrients or foods may interfere with the study outcomes.

We consider as a limitation of this integrative review the search in only two bibliographic bases, which may have limited the results. However, due to the duplicity of articles found, we believe that the search in other databases would not expand the inclusion of studies considerably. This limitation was necessary to make the study viable and generate a quick response to guide nutritional assistance to PLHIV.

We suggest conducting more clinical trials with supplementation of antioxidants, with greater methodological rigor and more extended periods of intervention to elucidate its effects on OS in PLHIV faced with factors such as the use of ART and its metabolic changes.

CONCLUSION

The studies included in this integrative review, corroborating previous findings, demonstrated a decrease in important enzymatic (SOD and CAT) and non-enzymatic (GSH, selenium, carotenoids, and vitamins A and E) antioxidants, in addition to high levels of malonaldehyde, which reduces the defense antioxidant in people living with HIV.

Proposals for supplementing antioxidant vitamins to reverse the condition were ineffective against OS, as these results from the presence of the virus and the administration of ART, both interfering in the redox state.

Few clinical trials have found positive results with antioxidant supplementation. Supplementation with polyphenols through dark chocolate increased HDL-C concentrations, and supplements of liposomal GSH and spirulina resulted in the ability to restore the immune response, increase the antioxidant capacity, and prevent opportunistic infections.

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