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Review
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Use of antioxidants in patients with tuberculosis

Uso de antioxidantes en pacientes con tuberculosis

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ABSTRACT. Tuberculosis is a public health problem, statistics from the World Health Organization mentions that a quarter of the population is infected, but only 5 to 10% may develop the active tuberculosis. This infection mainly affects the lungs but can spread to other organs. When the pathogen enters the host, defense mechanisms are induced which activates the immune system and promotes the elimination of mycobacteria. The interaction of immune cells with the pathogen activates the release of cytokines and the production of reactive oxygen and nitrogen species. However, a continuous and exacerbated response leads to oxidative stress and chronic inflammation in the lung tissue, producing cellular and tissue damage. Despite having established anti-tuberculosis treatment, mycobacteria have defensive mechanisms to evade the host's immune response that permits them to survive for decades. The persistence of the pathogen contributes to the development of resistance to first-line drugs, increasing the mortality rate. Currently, several studies have shown that the use of antioxidants such as: vitamins A, C, and E, other than N-acetyl cysteine and some trace elements such as zinc and selenium used as complementary therapy together with anti-tuberculosis drugs improve the patient health. Antioxidants counteract the oxidation state, reduce the exacerbated inflammatory response in the host and enhance the effectiveness of first-line antibiotics. The objective of this review is to demonstrate the beneficial effect of various antioxidants in clinical studies to propose their use as complementary therapy.

Keywords: tuberculosis, oxidant stress, inflammation, antioxidants.

RESUMEN. La tuberculosis es un problema de salud pública, datos de la Organización Mundial de la Salud mencionan que una cuarta parte de la población está infectada, pero sólo de 5 a 10% desarrollará la tuberculosis activa. Cuando el patógeno entra al hospedero se inducen los mecanismos de defensa activando el sistema inmune, promoviendo la eliminación de las micobacterias. La interacción de las células con el patógeno activa la liberación de citocinas y se induce la producción de especies reactivas de oxígeno y nitrógeno. Sin embargo, una respuesta continua y exacerbada conlleva estrés oxidante e inflamación crónica en el tejido pulmonar, produciendo daño celular y tisular. A pesar de tener una terapia antituberculosis establecida, las micobacterias presentan mecanismos de defensa para evadir la respuesta inmune del hospedero, lo que le permite sobrevivir por décadas. La persistencia del patógeno contribuye al desarrollo de resistencia a los fármacos de primera línea, aumentando la tasa de mortalidad. Actualmente varios estudios han demostrado que el uso de antioxidantes como las vitaminas A, C y E, así como el N-acetilcisteína y algunos oligoelementos como el zinc y el selenio son utilizados como terapia complementaria junto con los fármacos antituberculosos, mejorando la salud del paciente. Los antioxidantes contrarrestan el estado de oxidación, disminuyen la respuesta inflamatoria exacerbada en el hospedero y potencian la eficacia de los antibióticos de primera línea. El objetivo de esta revisión es evidenciar el efecto benéfico de diversos antioxidantes en estudios clínicos, con el fin de proponer su uso como terapia complementaria.

Palabras clave: tuberculosis, estrés oxidante, inflamación, antioxidantes.

Abbreviations:

ATRA = transretinoic acid.
ERN = reactive nitrogen species.
GSH = glutathione.
GSNO = S-nitrosoglutathione.
IFN-γ = interferon gamma.
IL = interleukins.
IU = international units.
MDA = malondialdehyde.
NAC = N-acetylcysteine.
NF-κB = nuclear factor kappa core.
NK = natural killer.
PKC = protein kinase C.
ROS = reactive oxygen species.
TNF-α = tumor necrosis factor-alpha.

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INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*, which is transmitted by airborne transmission when a person with tuberculosis coughs, sneezes or spits, because it generates Flügge droplets containing mycobacteria. According to data reported by the World Health Organization, it is estimated that a quarter of the world's population is infected by this bacterium, but only 5-10% will develop signs and symptoms. In 2021, 10.6 million cases were reported worldwide.

Tuberculosis primarily affects the lungs, but can affect other sites in the body, when the mycobacteria enter the lung tissue, antigen presenting cells release interleukins (IL)-6 and -12, followed by the production of interferon gamma (IFN-γ), IL-23, IL-1β and IL-17 by lymphocytes, leading to activation of macrophages, which in turn produce tumor necrosis factor-alpha (TNF-α), and promote intracellular mycobacterial clearance. Macrophages induce the production of antimicrobial peptides and proteins, as well as reactive oxygen and nitrogen species (ROS and RNA) as a defense mechanism.[1] When ROS and RNS production is continuous and exacerbated, it leads to chronic inflammation in lung tissue creating oxidative stress, necrosis and cavitations in lung tissue.[2] Mycobacteria that manage to evade the immune response penetrate uninfected macrophages and replicate within them, forming a granuloma in the lungs.[3]

In most parts of the world, the standard treatment for pulmonary tuberculosis consists of a two-month intensive phase of isoniazid, rifampicin, pyrazinamide and ethambutol.[4] This is followed by a four-month maintenance phase of isoniazid and rifampicin. In this phase, the three-day-a-week schedule is taken.[5] Despite being an effective treatment for sensitive tuberculosis, it has been shown that these drugs can also produce oxidative stress.[6,7]

It has been shown that patients with tuberculosis present a chronic oxidative and inflammatory state before and during anti-tuberculosis therapy at least in the first two months of treatment. Various oxidation products have been detected in tuberculosis patients, for example hydrogen peroxide (H_2O_2)[8] and lipoperoxides such as malondialdehyde (MDA) and 8-isoprostane.[2] Decreased antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase,[9] as well as antioxidant molecules such as glutathione (GSH),[10] vitamin A, C and E, have also been observed.[11]

It has been shown that high levels of ROS and RNA in patients with pulmonary tuberculosis result in decreased immune response and antioxidant capacity, contributing to exacerbated inflammation leading to pulmonary dysfunction.[9] In addition, increased lipoperoxidation has been reported to alter the lipid profile of patients, resulting in decreased total cholesterol levels. Cholesterol is essential for the proper functioning of the immune system.[12] Lymphocytes require cholesterol to properly carry out their function (it induces differentiation and their cytotoxic effect).[13] Macrophages also require cholesterol for phagocytic function, cell motility, exocytosis and endocytosis.[14] Thus, cholesterol depletion by lipoperoxidation leads to immune cell dysfunction during tuberculosis.

The main effectors of this increase in ROS and ERN are infected macrophages that generate respiratory burst; subsequently, as these molecules are not adequately neutralized, they lead to oxidative stress that leads to cellular damage affecting DNA, lipid membrane and proteins.[9] Antioxidants are substances that can counteract oxidative stress and prevent cellular and tissue damage.

The aim of this review is to demonstrate in clinical studies the synergistic/potentiating effects of six main antioxidants such as vitamin A, C, E, N-acetylcysteine (NAC), selenium (Se) and zinc (Zn), as complementary therapy to the antituberculosis scheme *(Figure 1)*.

ANTIOXIDANTS DECREASE LUNG DAMAGE IN TUBERCULOSIS PATIENTS

Use of vitamins with antioxidant activity

Vitamin A

Vitamin A is a fat-soluble molecule, which is obtained by the diet from animal products in the form of vitamin A (retinol and its derivatives) or as provitamin A (carotenoids) of plant origin, characterized by an unsaturated isoprenoid chain structure.[15] It has several functions in the human body; one of them is to maintain the homeostasis of epithelial tissues and mucous membranes, through its metabolite, retinoic acid formed from retinol[16] (circulating form of vitamin A). The main bioactive molecules are the oxidized 11-cis-retinal derivatives and transretinoic acid (ATRA).[15] ATRA favors the immune system, promoting the differentiation and function of immune cells (mainly T and B cells).[17]

Vitamin A deficiency is associated with a high rate of infections, particularly respiratory infections, which contributes to morbidity and mortality.[18] In relation to this, it was demonstrated in an *in vivo* model that epithelial cells obtained from nasopharyngeal secretions of pediatric patients with vitamin A deficiency show increased bacterial adherence on the cell surface after 15 hours of co-incubation of the epithelial cells with *Klebsiella pneumoniae*, which represents a risk factor for acquiring a respiratory infection.[18]

In a clinical study carried out in Indonesia, two groups of 15 patients each were formed, the control group only received anti-tuberculosis treatment, while the other group additionally received complementary therapy with

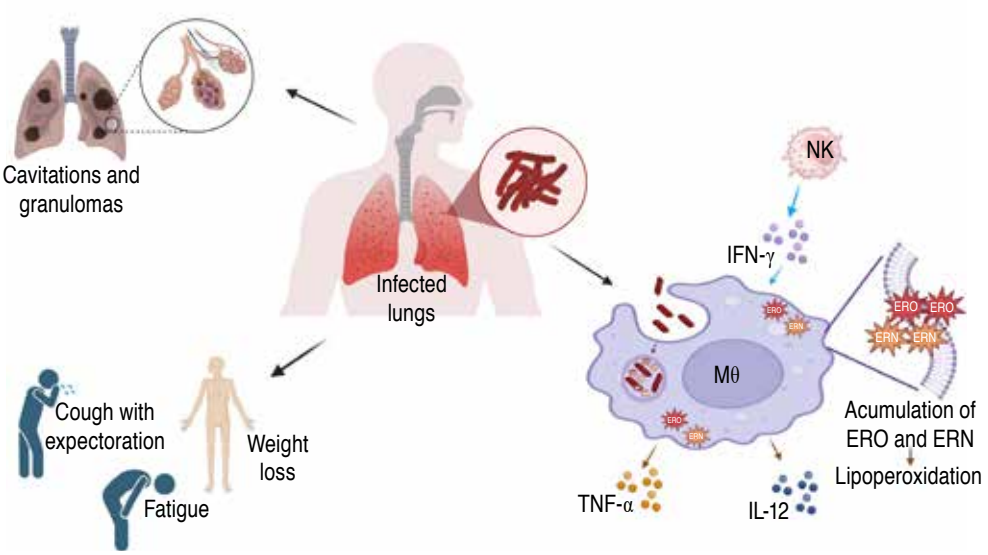

Figure 1:
Effects of tuberculosis on humans. Image created at BioRender.com.

vitamin A. It was demonstrated that the patients with complementary therapy decreased the bacterial load since, in the analysis of the smear tests, the patients became negative in 2.4 weeks after supplementation with vitamin A, compared to the placebo group, which became negative up to 4.1 weeks on average.[19]

In another study, a comparison was made between the placebo group and the group receiving supplemental therapy with vitamin A at a daily dose of 5,000 IU (international units) orally and Zn at a daily dose of 15 mg orally for six months. The use of these antioxidants was shown to improve the efficacy of antituberculosis drugs. In addition, the patients with complementary therapy at two weeks had negative smear microscopy in up to 23% (n = 40 patients) compared to the placebo group with 13%.[20] Another aspect that improved after two months was the decrease in the size of cavitations analyzed in the chest X-Ray, in addition to the 5% increase in body weight. Additionally, at six months of complementary treatment they had a gain of 16.7% of their initial body weight 20 *(Figure 2)*.

Vitamin C

Vitamin C or ascorbic acid is a water-soluble molecule, a six-carbon lactone of 2-keto-L-gluconic acid, with an endiol grouping (two hydroxyl groups at the ends of a double bond between C2 and C3).[21]

Vitamin C has an important role in the immune system, as it induces microbicidal activity, cell migration, phagocytosis and the generation of extracellular traps in neutrophils, induces the differentiation of natural killer cells,[22] increases the proliferation of lymphocytes.[23]

In *in vivo* studies, vitamin C maintains intracellular redox balance by using ascorbate as an electron acceptor, neutralizing various ROS such as superoxides, hydroxyl radicals, singlet oxygen and hypochlorous acid, generated by metabolic respiration and mitochondrial oxidative phosphorylation.[23] Its antioxidant capacity is achieved at a physiological dose between 75-120 mg/day.[24]

Vitamin C and E levels as well as glutathione reductase have been shown to be decreased during tuberculosis infection.[11] In a study conducted in India, they demonstrated that when using vitamin C as an adjuvant, patients showed significant increase in hemoglobin percentage (% Hb) with 53.5% at the end of six months, they also gained weight by 5% at two months and 13.1% at six months with respect to the initial mean. Likewise, baseline vitamin C and cholesterol levels increased compared to the group that only received anti-tuberculosis treatment at the end of six months of therapy.[25] In fact, it has been shown that the combined administration of vitamins C and E with anti-tuberculosis drugs enhances the efficacy of treatment[26] *(Figure 3)*.

Vitamin E

Vitamin E is a fat-soluble molecule, containing eight isomers: four tocopherols (α-, β-, γ-, and δ-tocopherol) and four tocotrienols (α-, β-, γ-, and δ-tocotrienols), its name depends on the number and location of the methyl groups on the chromanol ring, tocotrienols have an isoprenoid side chain, whereas tocopherols have a phytyl chain.[27]

Vitamin E is an important antioxidant, found mainly in cell membranes, it has a protective function against lipoperoxidation, since oxidation of low-density lipoproteins leads to increased cholesterol uptake by macrophages, increasing lipoperoxidation products and stimulating atherosclerotic processes.[27] Thus, the protective function of

vitamin E plays its essential role by decreasing membrane free radicals, preventing efflux to the cytoplasm and intracellular damage.[28] Vitamin E has been shown to inhibit protein kinase C (PKC) activity by increasing PKC-α dephosphorylation through activation of protein phosphatase A2, resulting in inhibition of platelet aggregation, reduced proliferation of macrophages, neutrophils, and vascular smooth muscle cells. A decrease in superoxide production in neutrophils and macrophages has also been observed.[29]

In a study carried out in India, the beneficial effect of vitamin E as an adjunctive therapy in patients with tuberculosis for six months was determined, demonstrating that the use of vitamin E as an adjunct significantly increased the percentage of hemoglobin (% Hb) with 40.7% at the end of six months. Patients gained weight 6.6% at two months and 16.6% at six months with respect to the initial mean. They also increased baseline vitamin E and cholesterol levels compared to the control group that received only anti-tuberculosis treatment at the end of six months of therapy.[25]

In another case-control study, the group treated with anti-tuberculosis therapy that received vitamin E as adjunctive therapy, at a dose of 140 mg orally daily for two months, showed a significant decrease of 63% in the levels

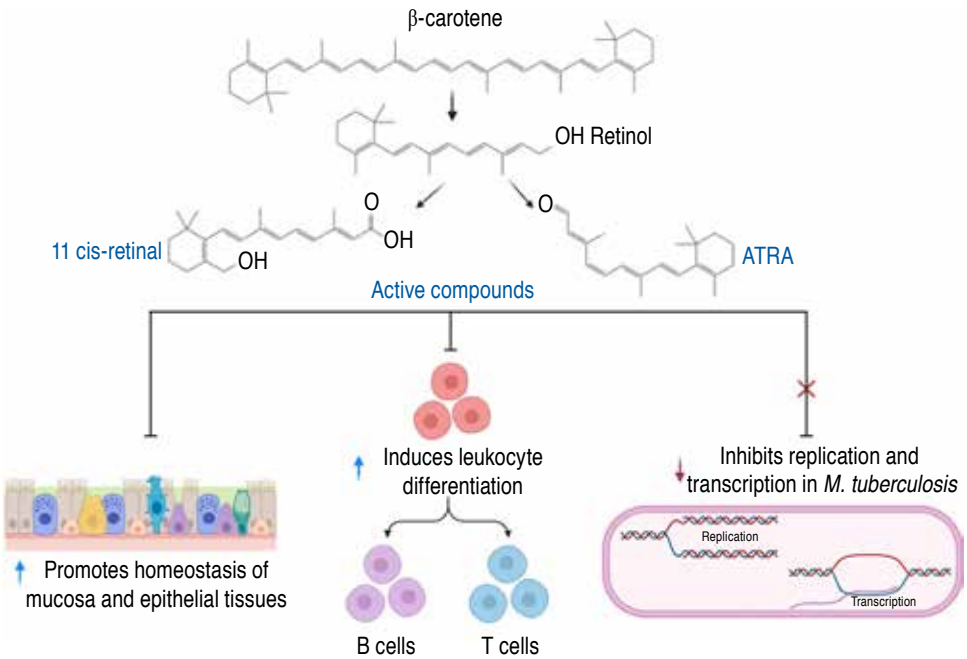

Figure 2:

Effect of vitamin A during tuberculosis. 11 cis-retinal and ATRA (all-trans retinoic acid) are active compounds derived from retinol. These compounds allow homeostasis of mucosa and epithelial tissues during an infection, promote lymphocyte differentiation and inhibit bacterial replication and transcription.
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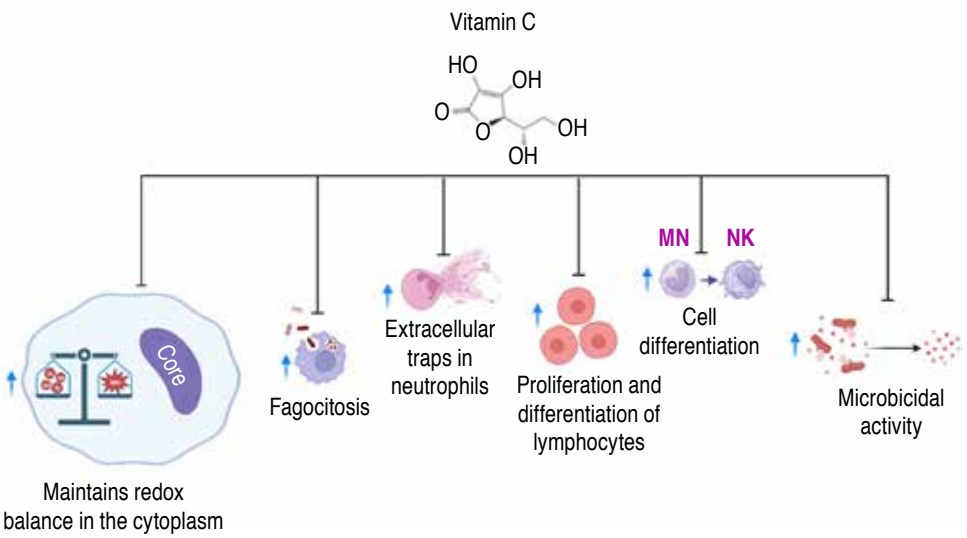

Figure 3:

Cellular effect of vitamin C during tuberculosis. Vitamin C maintains intracellular redox balance, induces phagocytosis and the generation of extracellular DNA traps in neutrophils. In addition, it promotes NK cell differentiation and inhibits bacterial growth.
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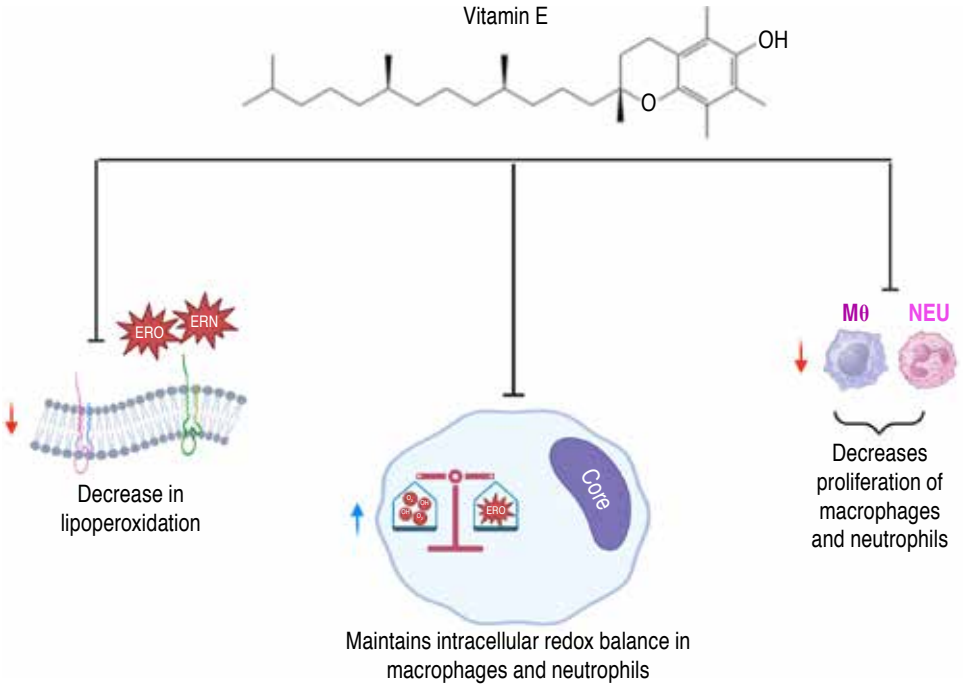

Figure 4:

Antioxidant mode of action of vitamin E. It is capable of neutralizing ROS and ERN, prevents lipoperoxidation of cell membranes, maintains redox balance and decreases the proliferation of neutrophils (NEU) and macrophages (Mθ) avoiding exacerbated inflammation.
Image made in BioRender.com.

of globular segmental velocity, with respect to their initial value, compared to the control group, which decreased by 34.5%. There was also a significant increase of 29% in serum vitamin E levels with respect to their initial value, while the control group increased by 4.9%. On the other hand, to determine the levels of oxidation in the patients, they analyzed the concentration of MDA, showing that after two months of treatment there was a 40% decrease with respect to its initial value, compared to the control group, which decreased to 13.3%.[28]

It is important to mention that the dosage of vitamin C and E has not been standardized based on their toxicity, so it is necessary to establish the optimal dose for their administration in patients with tuberculosis, so that they can be applied in a standardized manner as complementary therapy *(Figure 4)*.

N-acetylcysteine (NAC)

It is an antioxidant that directly neutralizes ROS and is a precursor and inducer of endogenous GSH.[30] It plays a crucial role in cellular defense against oxidative stress by stimulating GSH. NAC increases GSH levels in macrophages, this induces the formation of S-nitrosoglutathione (GSNO).[31] GSNO is an endogenous generator of nitric oxide. The latter has a direct antibacterial effect, generating oxidative stress in mycobacteria and damaging their cellular constituents.[32]

NAC has been shown to decrease the TH2-type cytokine response,[31] reduce IL-4 production and the humoral response.[33] In another study, NAC enhances the TH1 response, induces IFN-γ production, contributes to the control of mycobacterial replication, and improves the efficacy of antituberculosis drugs.[31]

In a study conducted in India in patients with tuberculosis with adjuvant therapy with NAC, at a daily dose of 600 mg orally for two months, it was shown that after three weeks the patients showed a significant recovery, since 95.83% were negative in the bacilloscopies and there was a decrease of 87% in pulmonary infiltration compared to the placebo group with 58.35 and 33%, respectively.[31]

In another study conducted in Brazil, using NAC as adjunctive therapy at a dose of 600 mg orally twice a day for eight weeks, showed that 61.1% of patients with NAC had negative smear tests compared to 33.3% in the control group. Regarding radiological analysis, 45% of the group that received NAC improved the radiological image compared to 30.8% of the control group, with no significant adverse effects.[34]

In a study conducted in Iran, they evaluated the hepatoprotective effect of NAC in two groups of patients: the control, which only received anti-tuberculosis therapy, and the other group with NAC supplementation, at a dose of 600 mg orally twice a day for two weeks. They measured two liver damage marker enzymes: alanine aminotransferase and aspartate aminotransferase. At baseline there were no significant differences, but at weeks one and two the control group significantly increased both enzymes. This group developed 37.5% hepatotoxicity due to the anti-tuberculosis therapy, while the group supplemented with NAC maintained constant values of both enzymes, avoiding liver damage[35] *(Figure 5)*.

Selenium (Se)

It is an essential trace element, since it interacts with proteins in the form of cofactors; selenium is cotranslationally incorporated into the polypeptide chain as part of the amino acid selenocysteine, forming selenoproteins, which have essential functions in the cell.[36]

Various selenoproteins are involved in the activation, proliferation and differentiation of cells involved in the innate and adaptive immune response. They are also involved in immune regulation, which is crucial to prevent exacerbated inflammation.[37] Several antioxidant enzymes have been shown to contain selenocysteine, such as glutathione peroxidase and thioredoxin synthetases, and their function is dependent on Se levels. In fact, a relationship between Se deficiency and increased susceptibility to tuberculosis has been suggested.[38]

In new strategies to eradicate multidrug-resistant strains of *Mycobacterium tuberculosis*, nanomedicine has been used, mainly the administration of metallic nanoparticles containing selenium.[39] Selenium has been proposed as a complementary therapy, as it has several mechanisms of action, it has been suggested that it has a bactericidal effect, as it affects the cell envelope of the mycobacteria, which facilitates the incorporation of antibiotics into the cytoplasm, prevents permanence in the phagosome and facilitates phagosome-lysosomal fusion of *Mycobacterium tuberculosis*, activating the macrophage bactericidal system and inducing autophagy through PI3K/Akt/mTOR signaling.[39]

In a double-blind clinical study conducted in Tanzania, 887 patients with pulmonary tuberculosis were enrolled and assigned to two groups: the placebo group comprising 471 patients and the complementary therapy group comprising 416 patients, where a dose of 100 μg of Se was used; after one month of treatment, patients significantly reduced the risk of reinfection by 45% during the rest of the treatment. In addition, treatment failure was reduced by up to 34%.[40] In another study in Pakistan, 80 patients with newly diagnosed pulmonary tuberculosis (not older than two months) were randomly divided into two groups: the control and the supplemented group with 40 patients each. The group supplemented with Se, at a dose of 100 μg/day orally for six months, showed a significant decrease in the leukocyte count compared to the placebo group, demonstrating control of the infection. In addition, it was evidenced that the concentration of Se in blood increased significantly up to 106% in comparison with the control group that only increased 6.1%. With respect to oxidation status, MDA levels decreased by up to 25.3% in the supplemented group, compared to the placebo group which decreased serum levels by 17.8%.[41] Based on the above, Se is a suitable supplement during the treatment of tuberculosis.

Zinc (Zn)

It is an essential trace element that plays a fundamental role in several physiological processes, such as immune function and wound healing. It is known to be involved in the development and function of immune cells, participating in the survival, proliferation and differentiation of monocytes, polymorphonuclear cells, natural killer (NK) cells, as well as T and B lymphocytes.[42]

Zn is an essential component of signal transduction pathways that eliminate pathogens and lead to the formation of neutrophil extracellular traps, it is also involved in modulating the proinflammatory response by inhibiting the translocation to the nucleus of nuclear factor kappa (NF-

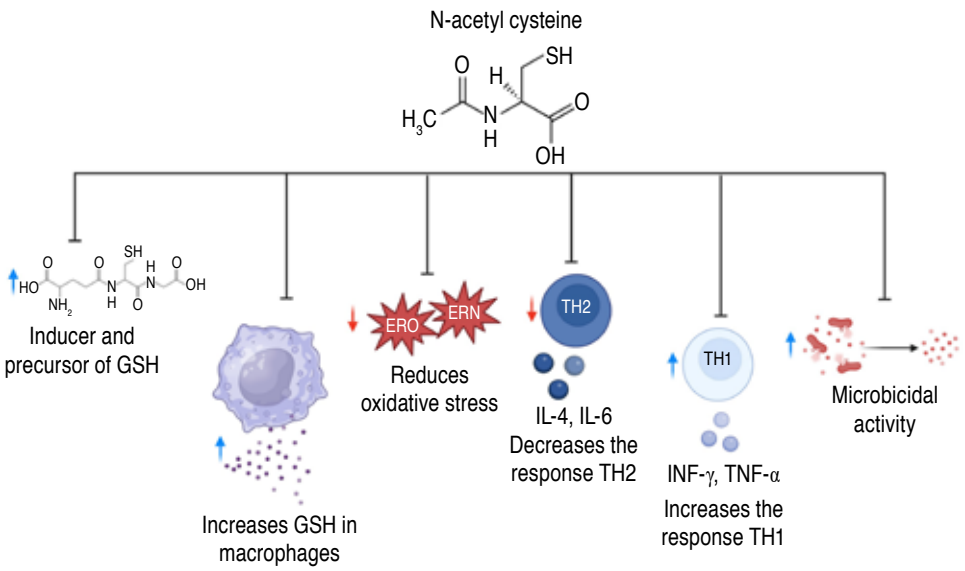

Figure 5:

Mode of antioxidant action of N-acetylcysteine. The main mechanism is to induce the production of endogenous glutathione in macrophages and directly neutralize ROS and ERN. It decreases the TH2 response and induces the TH1 response, generating a bactericidal effect and inducing INF-γ and TNF-α. Image made at BioRender.com.

κB), a transcription factor that induces the proinflammatory response.[43]

Several studies have shown that Zn plays an essential role in the metabolism of vitamin A, since in patients with tuberculosis, serum Zn levels are decreased, affecting the intestinal absorption of retinol.[44] However, when receiving vitamin A (5,000 IU) and Zn (15 mg) as adjunctive therapy in patients with tuberculosis after two months of treatment, the patients´ clinical status improved significantly, the number and size of cavitations decreased significantly.[45] In a study in India, it was shown that when receiving adjunctive therapy with Zn there was clinical improvement, the patients gained weight and there was a negative conversion in the sputum smear test.[46]

CONCLUSIONS

Based on the studies carried out in different countries, it was demonstrated that patients who use antioxidants improve their symptomatology, gain weight significantly and improve their health compared to patients who only receive their antituberculosis therapy. The use of antioxidants decreases lung damage, since it is possible to reduce the area and size of cavitations generated by the infection. In addition, the patient ceases to be bacilliferous more quickly compared to patients who do not receive antioxidants; this prevents the spread of mycobacteria to people who are in close contact with the patient.

Regarding the proinflammatory state and the imbalance in the redox state, it was shown that antioxidants contribute to homeostasis early, since they decrease the exacerbated inflammatory state, as well as the oxidation state, considerably decrease the concentration of lipoperoxides and increase the level of endogenous antioxidants such as glutathione.

REFERENCES

1. Ravesloot-Chavez MM, Van Dis E, Stanley SA. The innate immune response to *Mycobacterium tuberculosis* infection. Annu Rev Immunol. 2021;39:611-637. doi: 10.1146/annurev-immunol-093019-010426.
2. Guzmán-Beltrán S, Carreto-Binaghi LE, Carranza C, Torres M, Gonzalez Y, Muñoz-Torrico M, *et al.* Oxidative stress and inflammatory mediators in exhaled breath condensate of patients with pulmonary tuberculosis. A pilot study with a Biomarker Perspective. Antioxidants (Basel). 2021;10(10):1572. doi: 10.3390/antiox10101572.
3. Vázquez RN, Stwart LG, Quesada LL, Falcón AY. Evasión de la respuesta inmune: una lección del *Mycobacterium tuberculosis*. Rev Arch Med Camagüey. 2015;19(4):419-427. Available in: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1025-02552015000400014&lng=es&tlng=es
4. Soler N. Tratamiento de la tuberculosis pulmonar: estado actual. Med Integr. 2001;38(5): 232-239. Available in: https://www.elsevier.es/es-revista-medicina-integral-63-articulo-tratamiento-tuberculosis-pulmonar-estado-actual-13018827
5. Caruso E, Mangan JM, Maiuri A, Bouwkamp B, DeLuca N. Tuberculosis testing and latent tuberculosis infection treatment practices among health care providers - United States, 2020-2022. MMWR Morb Mortal Wkly Rep. 2023;72(44):1183-1189. doi: 10.15585/mmwr.mm7244a2.
6. Hou W, Nsengimana B, Yan C, Nashan B, Han S. Involvement of endoplasmic reticulum stress in rifampicin-induced liver injury. Front Pharmacol. 2022;13:1022809. doi: 10.3389/fphar.2022.1022809.
7. Preziosi P. Isoniazid: metabolic aspects and toxicological correlates. Curr Drug Metab. 2007;8(8): 839-851. doi: 10.2174/138920007782798216.
8. Amaral EP, Vinhaes CL, Oliveira-de-Souza D, Nogueira B, Akrami KM, Andrade BB. The interplay between systemic inflammation, oxidative stress, and tissue remodeling in tuberculosis. Antioxid Redox Signal. 2021;34(6):471-485. doi: 10.1089/ars.2020.8124.
9. Vidhya R, Rathnakumar K, Balu V, Pugalendi KV. Oxidative stress, antioxidant status and lipid profile in pulmonary tuberculosis patients before and after anti-tubercular therapy. Indian J Tuberc. 2019;66(3):375-381. doi: 10.1016/j.ijtb.2018.11.002.
10. Parchwani D, Singh SP, Patel D. Total antioxidant status and lipid peroxides in patients with pulmonary tuberculosis. Natl J Community Med. 2011;2(2):225-228. Available in: https://njcmindia.com/index.php/file/article/view/1886#:~:text=https%3A//njcmindia.com/index.php/file/article/view/1886
11. Vijayamalini M, Manoharan S. Lipid peroxidation, vitamins C, E and reduced glutathione levels in patients with pulmonary tuberculosis. Cell Biochem Funct. 2004;22(1):19-22. doi: 10.1002/cbf.1039.
12. Pérez-Guzmán C, Vargas MH. Hypocholesterolemia: a major risk factor for developing pulmonary tuberculosis? Med Hypotheses. 2006;66(6):1220-1230. doi: 10.1016/j.mehy.2005.12.041.
13. Pérez-Guzmán C, Vargas MH, Torres-Cruz A, Villarreal-Velarde H. La hipocolesterolemia: un hallazgo frecuente que se asocia a la tuberculosis. Rev Inst Nal Enf Resp Mex. 2002;15(1):7-11.
14. Parivakkam Mani A, Shanmugapriya K, Depak Kanna K, Yadav S. Assessment of lipid profile in patients with pulmonary tuberculosis: an observational study. Cureus. 2023;15(5):e39244. doi: 10.7759/cureus.39244.
15. Carazo A, Macáková K, Matousová K, Krcmová LK, Protti M, Mladenka P. Vitamin A update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. Nutrients. 2021;13(5):1703. doi: 10.3390/nu13051703.
16. Roche FC, Harris-Tryon TA. Illuminating the role of vitamin A in skin innate immunity and the skin microbiome: a narrative review. Nutrients. 2021;13(2):302. doi: 10.3390/nu13020302.
17. Podell BK, Aibana O, Huang CC, DiLisio JE, Harris MC, Ackart DF, *et al.* The impact of vitamin A deficiency on tuberculosis progression. Clin Infect Dis. 2022;75(12):2178-2185. doi: 10.1093/cid/ciac326.
18. Chandra RK. Increased bacterial binding to respiratory epithelial cells in vitamin A deficiency. BMJ. 1988;297(6652):834-835. doi: 10.1136/bmj.297.6652.834.
19. Sari DK, Marpaung AP, Siagian P, Arrasyid NK. Vitamin A supplementation in pulmonary tuberculosis patients on acceleration of Sputum conversion in Medan city. Open Access Maced J Med Sci. 2019;7(20):3505-3508. doi: 10.3889/oamjms.2019.688.
20. Karyadi E, West CE, Schultink W, Nelwan RH, Gross R, Amin Z, *et al.* A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr. 2002;75(4):720-727. doi: 10.1093/ajcn/75.4.720.

21. Oro JR de X, Donnamaría MC. Acción farmacológica, biofisicoquímica y estructura dinámica de la vitamina C. Acta Farm Bonaerense. 2006;25(1):145-154. Available in: http://sedici.unlp.edu.ar/handle/10915/6814
22. Mauro-Martín IS, Garicano-Vilar E. Papel de la vitamina C y los β-glucanos sobre el sistema inmunitario. Rev Esp Nutr Hum Diet. 2015;19(4):238-245. Available in: https://dx.doi.org/10.14306/renhyd.19.4.173
23. Leelahavanichkul A, Somparn P, Bootprapan T, Tu H, Tangtanatakul P, Nuengjumnong R, *et al.* High-dose ascorbate with low-dose amphotericin B attenuates severity of disease in a model of the reappearance of candidemia during sepsis in the mouse. Am J Physiol Regul Integr Comp Physiol. 2015;309(3):R223-R234. doi: 10.1152/ajpregu.00238.2014.
24. Kaźmierczak-Barańska J, Boguszewska K, Adamus-Grabicka A, Karwowski BT. Two faces of vitamin C-Antioxidative and pro-oxidative agent. Nutrients. 2020;12(5):1501. doi: 10.3390/nu12051501.
25. Madhavi M, Samudram P, Kumar AH, Victor L. Effect of antioxidant vitamins C and E supplementation on its plasma levels and on lipid profile in pulmonary tuberculosis patients. Am J Infect Dis. 2009;5(3):263-272. doi: 10.3844/ajidsp.2009.263.272.
26. Vilcheze C, Kim J, Jacobs WR Jr. Vitamin C potentiates the killing of *Mycobacterium tuberculosis* by the first-line tuberculosis drugs isoniazid and rifampin in mice. Antimicrob Agents Chemother. 2018;62(3):e02165-e02117. doi: 10.1128/aac.02165-17.
27. Miyazawa T, Burdeos GC, Itaya M, Nakagawa K, Miyazawa T. Vitamin E: regulatory redox interactions. IUBMB Life. 2019;71(4):430-441. doi: 10.1002/iub.2008.
28. Seyedrezazadeh E, Ostadrahimi A, Mahboob S, Assadi Y, Ghaemmagami J, Pourmogaddam M. Effect of vitamin E and selenium supplementation on oxidative stress status in pulmonary tuberculosis patients. Respirology. 2008;13(2):294-298. doi: 10.1111/j.1440-1843.2007.01200.x.
29. Lee GY, Han SN. The role of vitamin E in immunity. Nutrients. 2018;10(11):1614. doi: 10.3390/nu10111614.
30. Gillissen A. Actualizan el uso terapéutico de la N-Acetilcisteína y los mecanismos de acción involucrados. Pneumologie. 2011;65(9):549-557.
31. Mahakalkar SM, Nagrale D, Gaur S, Urade C, Murhar B, Turankar A. N-acetylcysteine as an add-on to directly observed therapy short-I therapy in fresh pulmonary tuberculosis patients: a randomized, placebo-controlled, double-blinded study. Perspect Clin Res. 2017;8(3):132-136. doi: 10.4103/2229-3485.210450.
32. Qian H, Ye Z, Pi L, Ao J. Roles and current applications of S-nitrosoglutathione in anti-infective biomaterials. Mater Today Bio. 2022;16:100419. doi: 10.1016/j.mtbio.2022.100419.
33. Hernández AS. Células colaboradoras (TH1, TH2, TH17) y reguladoras (Treg, TH3, NKT) en la artritis reumatoide. Reumatol Clin. 2009;5(1):1-5. doi: 10.1016/j.reuma.2008.11.012.
34. Safe IP, Lacerda MVG, Printes VS, Praia Marins AF, Rebelo Rabelo AL, Costa AA, *et al.* Safety and efficacy of N-acetylcysteine in hospitalized patients with HIV-associated tuberculosis: An open-label, randomized, phase II trial (RIPENACTB Study). PLoS One. 2020;15(6):e0235381. doi: 10.1371/journal.pone.0235381.
35. Baniasadi S, Eftekhari P, Tabarsi P, Fahimi F, Raoufy MR, Masjedi MR, *et al.* Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity. Eur J Gastroenterol Hepatol. 2010;22(10):1235-1238. doi: 10.1097/MEG.0b013e32833aa11b.
36. Zoidis E, Seremelis I, Kontopoulos N, Danezis GP. Selenium-dependent antioxidant enzymes: actions and properties of selenoproteins. Antioxidants (Basel). 2018;7(5):66. doi: 10.3390/antiox7050066.
37. Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2012;16(7):705-743. doi: 10.1089/ars.2011.4145.
38. Muzembo BA, Mbendi NC, Ngatu NR, Suzuki T, Wada K, Ikeda S. Serum selenium levels in tuberculosis patients: A systematic review and meta-analysis. J Trace Elem Med Biol. 2018;50:257-262. doi: 10.1016/j.jtemb.2018.07.008.
39. Ifijen IH, Atoe B, Ekun RO, Ighodaro A, Odiachi IJ. Treatments of *Mycobacterium tuberculosis* and *Toxoplasma gondii* with selenium nanoparticles. Bionanoscience. 2023;13(1):249-277. doi: 10.1007/s12668-023-01059-4.
40. Villamor E, Mugusi F, Urassa W, Bosch RJ, Saathoff E, Matsumoto K, *et al.* A trial of the effect of micronutrient supplementation on treatment outcome, T cell counts, morbidity, and mortality in adults with pulmonary tuberculosis. J Infect Dis. 2008;197(11):1499-1505. doi: 10.1086/587846.
41. Hussain MI, Ahmed W, Nasir M, Mushtaq MH, Sheikh AA, Shaheen AY, *et al.* Immune modulatory and anti-oxidative effect of selenium against pulmonary tuberculosis. Pak J Pharm Sci. 2019;32(2 Supplementary):779-784.
42. Bonaventura P, Benedetti G, Albarede F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev. 2015;14(4):277-285. doi: 10.1016/j.autrev.2014.11.008.
43. Gammoh NZ, Rink L. Zinc in infection and inflammation. Nutrients. 2017;9(6):624. doi: 10.3390/nu9060624.
44. Ali W, Ahmad I, Srivastava VK, Prasad R, Kushwaha RA, Saleem M. Serum zinc levels and its association with vitamin A levels among tuberculosis patients. J Nat Sci Biol Med. 2014;5(1):130-134. doi: 10.4103/0976-9668.127310.
45. Visser ME, Grewal HM, Swart EC, Dhansay MA, Walzl G, Swanevelder S, *et al.* The effect of vitamin A and zinc supplementation on treatment outcomes in pulmonary tuberculosis: a randomized controlled trial. Am J Clin Nutr. 2011;93(1):93-100. doi: 10.3945/ajcn.110.001784.
46. Lawson L, Thacher TD, Yassin MA, Onuoha NA, Usman A, Emenyonu NE, *et al.* Randomized controlled trial of zinc and vitamin A as co-adjuvants for the treatment of pulmonary tuberculosis. Trop Med Int Health. 2010;15(12):1481-1490. doi: 10.1111/j.1365-3156.2010.02638.x.

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