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Role of Antioxidants in the Prevention of Hepatotoxicity Induced by Anti Tubercular Drugs

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Abstract

Tuberculosis (TB), an emerging infection in human beings and is now the leading cause of deaths worldwide. Anti-tubercular drugs are available for treating Tuberculosis (TB). Hepatotoxicity is the major side effect associated with anti-tubercular drugs. Anti-tubercular drugs cause hepatotoxicity or Drug Induced Liver Injury (DILI) mainly due to excess free radical formation. The risk of hepatotoxicity due to anti-tubercular drugs can be prevented by neutralizing the free radicals with antioxidants. Mycobacterium also causes immunosuppression due to oxidative stress (free radical accumulation), antioxidants can reduce the oxidative stress induced immunosuppression. Estimation of malondialdehyde, Electron Spin Resonance (ESR) and Spin trapping technique are useful to specify radicals or the location at which the radicals are produced and to find the radical concentration. So use of antioxidants along with anti-tubercular drugs can prevent Drug Induced Liver Injury (DILI) or hepatotoxicity and oxidative stress caused by Mycobacterium and helps in successful completion of anti-tubercular therapy.

Keywords: Tuberculosis; Mycobacterium; Free radicals; Antioxidants; Drug induced liver injury; Immunosuppression; Malondialdehyde; Electron spin resonance; Spin trapping technique

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Introduction

Tuberculosis is the major emerging infection in developing countries like India [1]. The drugs that are used for treating tuberculosis are called anti-tubercular drugs (Isoniazid, Rifampicin, Ethambutol, Pyrazinamide etc., but hepatotoxicity is the major serious adverse effect of anti-tubercular drugs and leading to discontinuation of therapy in 11% of tuberculosis patients [2]. The incidence of hepatotoxicity varies from 2% to 36% depending upon the country. Use of anti-tubercular drugs leads to the production of Reactive Oxygen Species (ROS) or free radicals which cause the destruction of hepatocytes leading to Drug Induced Liver Injury (DILI) [3]. Free radicals are highly reactive and are capable of damaging almost all types of bimolecules, (Proteins, Carbohydrates, Lipids and Nucleic Acids) by lipid peroxidation, oxidation of proteins, DNA damage and cytoskeleton damage. As the drugs are metabolized in the liver, liver becomes the major organ affected by free radicals due to the availability of high radical concentration there. Macrophages serve as a natural habitat to mycobacterium tuberculosis (Mtb). Mycobacterium tuberculosis (Mtb) corrupts the macrophage's mechanism of intercellular killing and antigen presentation, leading to development of tuberculosis (TB). Here we describe mechanism of mycobacterium tuberculosis (Mtb) uptake by the macrophages and address key macrophage functions that are targeted by mycobacterium tuberculosis (Mtb). Specific effector molecules enabling this pathogen to escapes host immune response. The macrophage function described in this review include fusion between phagosomes and lysosomes, which leads to the production of free radicals or Reactive Oxygen Species (ROS) which causes immunosuppression [4,5]. These Reactive Oxygen Species (ROS) are produced both during physiological and pathological conditions. The reactive oxygen species produced during physiological conditions are neutralized by biological antioxidants, but the levels of biological antioxidants are not sufficient enough to neutralize the excess reactive oxygen species produced during pathological conditions (especially TB). So use of supplemental antioxidants in patients with tuberculosis can inhibit the actions of Reactive Oxygen Species (ROS) and Oxidative Stress [6,7].

Methods and Methodology

How can we detect the free radicals present in our body?

Estimation of malondialdehyde is the best methods for estimating oxidative stress apart from this; Electron Spin Resonance (ESR) and Spin trapping technique are useful to specify radicals or the location at which the radicals are produced and to find the radical concentration.

1. Malondialdehyde as a marker: Malondialdehyde is the most extensively studied products of lipid peroxidation, and is used as a biochemical marker for the assessment of lipid peroxidation. Malondialdehyde reacts with thiobarbituric acid and produces red colored products known as Thiobarbituric Acid Reactive Substances (TBARS) which can be measured calorimetrically.

2. The estimation of serum malondialdehyde is often used to assess oxidative stress and free radical damage to the body [8].

3. Electron Spin Resonance (ESR): it is an appropriate method for identifying the production of free radicals in the living system and it has become an important tool for the detection and identification of free radicals [9].

4. Spin trapping technique: in this technique some of the reagents are used for the detection of free radicals. In this oxygen radicals are trapped by 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) or Alpha-Phenyl-N-t-butylnitrone (PBN), and the DMPO and PBN spin adduct signal was measured quantitatively by an ESR spectrometer [9,10].

With these methods it is possible to specify the radicals or the location at which the radicals are produced.

Discussion

How antioxidants act?

Antioxidants act by neutralizing the free radicals produced in our body.

Mechanism of action of biological antioxidants [1]:

Step 1: $O_2^- + O_2^- + 2H^+ \xrightarrow{superoxidedismutase} H_2O_2 + O_2$

Step 2: $2H_2O_2 \xrightarrow{catalase} 2H_2O + O_2$

Step 3: $H_2O_2 + 2GSH \xrightarrow{glutathioneperoxidase} 2H_2O + GSSG$

$GSSG + NADPH + H^+ \xrightarrow{glutathionereductase} 2GSH + NADP^+$

O_2^-, H_2O_2, OH^- → damages the biomolecules if not neutralized [11,12].

Mechanism of action of antioxidant supplements

Selenium: Selenium shows many beneficial effects on health by producing selenoproteins. The selenocysteine is an amino acid involved in the synthesis of many enzymes namely glutathione peroxidase, thioredoxin reductases.

Superoxide dismutase: This enzyme is directly available from food sources and sometimes taken from cow. This superoxide dismutase acts by neutralizing the superoxide.

Glutathione: Glutathione is the cofactor for the enzyme glutathione peroxidase, as a result this supplemental glutathione increases its levels in the body there by increasing the levels of glutathione peroxidase in the body. This glutathione peroxidase is useful for the conversion of reactive hydrogen peroxide (H_2O_2) into water (H_2O).

Vitamin E: Vitamin E acts by terminating the lipid peroxidation. When vitamin E reacts with highly reactive lipid radicals they produce stable vitamin E radicals. When these radicals become stable they can't react with the biomolecules and can't cause any damage [11-13].

Some other examples of anti-oxidant supplements are Lycopene, Acetyl cysteine, melatonin, alpha lipoic acid, reduced glutathione, silymarin, carvedilol, pirfenidone, Vitamin-E and C, Selenium all these antioxidant supplements act by playing a vital role in the synthesis of biological antioxidants. These antioxidants are safe to use as they do not have any interactions with the anti-tubercular drugs [12-14]. Some of the anti-oxidants and their dietary sources are mentioned in **Table 1**.

Table 1 Anti-oxidants and their dietary sources.

Anti-Oxidant	Dietary Source
Reduced Glutathione	Beef, Fish, Poultry, Broccoli, Cauliflower,, Mustard Greens
Superoxide Dismutase	Broccoli, Cabbage, Barley Grass
Vitamin E (Tocopherol)	Unprocessed Vegetable Oils, Whole Grains, Legumes.
Vitamin C (Ascorbic Acid)	Citrus Fruits, Guava, Cabbage, Spinach, Melons.
Beta Carotene (Provitamin A)	Carrots, Spinach, Turnip, Apricots
Selenium	Sea Foods, Meat, Whole Grains
Alpha Lipoic Acid	Red Meat, Liver, Yeast
Lycopene	Tomatoes, Papaya, Pink Guava, Water Melons

Conclusion

As the free radicals or reactive oxygen species produced by the anti tubercular drugs are neutralized by anti oxidants, there will be no cell destruction and no oxidative stress induced immunosuppression. So by using anti oxidants as an adjuvant therapy along with anti tubercular therapy, we can restrict the occurrence of Drug Induced Liver Injury (DILI). Apart from that, the patient can successfully complete the anti tubercular therapy which minimizes the hospital stay and cost to the patient.

References

1 Sandhu, Gursimrat K (2011) Tuberculosis: current situation, challenges and overview of its control programs in India. J Glob Infect 3: 143-150.

2 Eris-Gulbay B, Gurkan OU, Yıldız OA, Onen Z, Erkekol FO, et al. (2006) Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis. Respir Med 100: 1934-1842.

3 https://www.ncbi.nlm.nih.gov/books/NBK547852/

4 Yew WW, Chang KC, Chan DP (2018) Oxidative Stress and First-Line Anti Tuberculosis Drug-Induced Hepatotoxicity. Antimicrob Agents Chemother 62: e02637-17.

5 Bannister JV, Bannister WH (1985) Production of oxygen-centered radicals by neutrophils and macrophages as studied by Electron Spin Resonance (ESR). Environ Health Perspect 64: 37-43.

6 Burton, Graham J, Jauniaux E (2011) Oxidative stress. Best Pract Res Clin Obstet Gynaecol 25: 287-299.

7 Frederick A. Villamena, Zweier JL (2004) Detection of Reactive Oxygen and Nitrogen Species by EPR Spin Trapping. Antioxid Redox Signal.

8 Marrocco I, Altieri F, Peluso I (2017) Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. Oxid Med Cell Longev.

9 Lee MC (2013) Assessment of oxidative stress and antioxidant property using electron spin resonance (ESR) spectroscopy. J Clin Biochem Nutr 52: 1-8.

10 Athar N (2017) Spin Trapping: A Review for the Study of Obesity Related Oxidative Stress and Na+/K+-ATPase. J Clin Cellular Immunol 8: 505.

11 Satyanarayana U, Chakrapani U (2017) Free radicals and antioxidants. Biochemistry (5thedn).

12 Kurutas EB (2015) The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutr J.

13 Ware M (2018) How can antioxidants benefit our health? Medical News Today.

14 Soh AZ, Chee CBE, Wang YT, Yuan JM, Koh WP. Dietary Intake of Antioxidant Vitamins and Carotenoids and Risk of Developing Active Tuberculosis in a Prospective Population-Based Cohort Study. Am J Epidemiol 186: 491-500.