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The Perspectives of Methylene Blue in Decelerating Aging Through the Restoration of Cellular Energy Potential

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Abstract. Methylene blue is a powerful inhibitor of free electrons, which recharge the cells' batteries in the mitochondria. When the cells' energy potential is high, this helps to slow down the aging process and increase life expectancy. Methylene blue's ability to increase the body's energy potential and thus decelerate aging makes it a promising drug in the present context when the age pattern of the population is changing due to declining birth rates that are already below the population replacement level. This paper explains how methylene blue functions as an anti-aging agent, examines the phases of the aging process in relation to the decline in cellular energy levels, and provides guidelines on the appropriate duration of methylene blue use for older population groups.

***Keywords*:** methylene blue, frailty index, cells' energy potential, human aging, electron transport chain, cellular battery.

1. INTRODUCTION

Aging is a gradual and irreversible pathophysiological process characterized by the deterioration of tissue and cellular functions, which produces multiple age-related conditions, such as metabolic diseases [18]. The mitochondrial theory of aging [4] postulates that aging is a consequence of the cellular oxidative damage produced by free radicals. Since free radicals accelerate aging, antioxidants that supply them with electrons may, by contrast, slow down the age-related deterioration. Methylene blue is a powerful antioxidant that specifically targets mitochondria, where it neutralizes reactive oxygen species (ROS), a specific type of free radicals, and thus protects cells from oxidative damage. Thus, methylene blue may help to slow down the aging of the body [16].

Current research on the use of methylene blue for the treatment of metabolic diseases associated with the mitochondrial dysfunction is mostly focused on therapeutic promise of methylene blue for age-related neurodegenerative disorders such as Alzheimer's disease and dementia [5, 12, 17]. The research on the potential uses of methylene blue as an anti-aging agent is yet in its nascent stage, although there are indications that it can delay cellular senescence and extend the cells' lifespan [15], thus increasing human life expectancy. This context calls for the use of mathematical modeling methods that may contribute to the prospective research and lay the ground for further in silico experiments and clinical trials.

The present study shows that the effectiveness of treatment using methylene blue depends on the duration of its use and needs to be determined based on the age of the patient. Upon that, the paper proposes a function that allows calculating the duration of use of methylene blue depending on a person's age.

The paper is organized as follows. The following section describes the components of the respiratory electron transport chain, or electron transport chain (ETC) of the mitochondria, based on [9]. It further presents a block chart of electron flow along the ETC. This flowchart helps to identify the key points of electron leakage that produces oxidative stress, which is the main cause of aging according to mitochondrial theory.

The third section describes a block chart of electron flow along the ETC with the inclusion of methylene blue, demonstrating how it neutralizes free radicals that produce oxidative damage.

The fourth section outlines the phases of the aging process and the corresponding rates of aging at each stage, as determined by the Frailty Index [10]. These rates are depicted on a curve, which provides the foundation for determining the ideal timing to begin anti-aging methylene blue therapy, as well as the potential length of this treatment.

The concluding section discusses the perspectives of methylene blue as promising anti-aging agent in the current demographic and economic context, and the need for further research using mathematical modeling.

2. COMPONENTS OF THE RESPIRATORY ELECTRON TRANSPORT CHAIN IN MITOCHONDRIA

Respiratory electron transport chain (ETC) comprises three protein complexes (I, II, III), complex (IV) and two complexes serving as electron carriers: ubiquinone (coenzyme CoQ) and cytochrome c oxidase (Cyt-c), which are embedded in the mitochondrial inner membrane. H^+ are protons generated through oxidation reactions. The variation in H^+ concentration across the membrane creates a pressure difference between the interior and exterior, which enables electrons e^- (t) to exit the ETC. This process powers the cell's "battery" (complex V) [9].

Figure 1 shows the components of the ETC within the mitochondrial membrane, presented as a block chart that depicts the flow of electrons from their generation in complexes I and II to the battery in complex V.

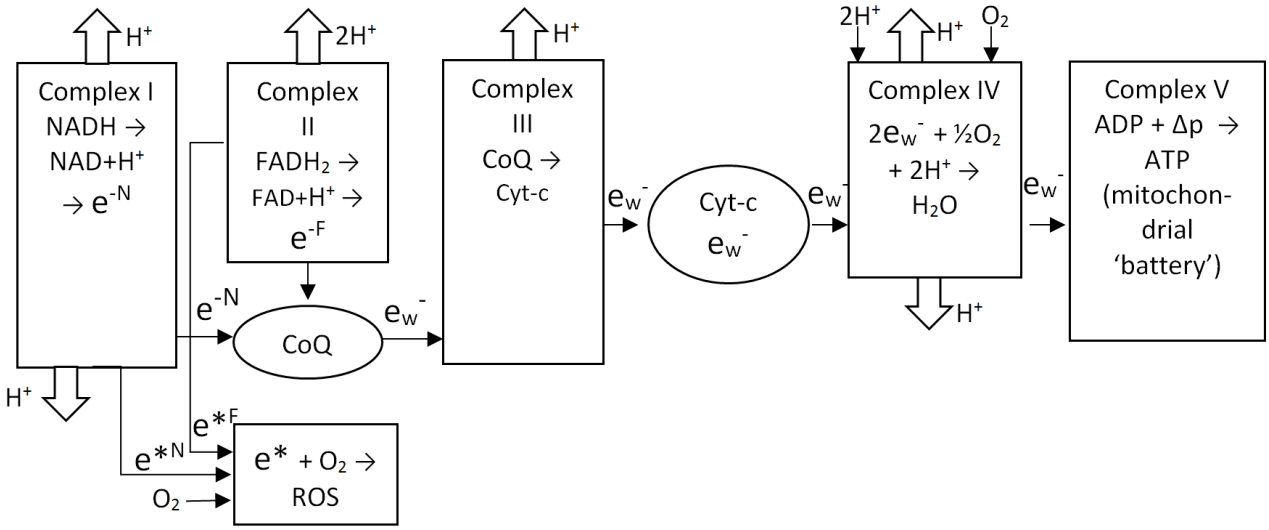

Fig. 1. Block chart showing the progression of electrons through the respiratory electron transport chain in the inner membrane of the mitochondria, including the block that represents the free radical formation (ROS) [2]

Complex I: Reactive oxygen species trigger an oxidation reaction involving NADH, which in turn generates NAD and H^+, thereby enabling the transfer of electrons e^{-N} through the inner mitochondrial membrane into the intracellular fluid: [NADH + O_2 = NAD + $H^+ \rightarrow e^{-N}$].

Complex II: This complex functions similarly to complex I. Reactive oxygen species produce oxidation reaction involving FADH2, producing FAD + $2H_2$ and facilitating the transition of electrons e^{-F} through the inner mitochondrial membrane into the intracellular fluid: [FADH2 + O_2 = FAD + $2H_2 \rightarrow e^{-F}$].

As a result, complexes I and II produce a total sum of electrons, which is calculated from the equation:

$$e^{-sum}(t) = (e^{-N}(t) + e^{-F}(t)),$$

where t is time (number of days),
e^{-N} is the number of electrons generated in complex I,
e^{-F} is the number of electrons generated in complex II.

The number of electrons that are included in the ETC to charge the battery of *complex V* is determined by the equation:

$$e_w^- (t) = e^{-sum} (t) K_w \ ,$$

where *Kw* is the coefficient that determines the proportion of electrons that is included in the ETC.

Other electrons generated in complexes I and II that were not included in the ETC transform into free electrons e^-*(t). Their number is defined as the difference between the total number of electrons formed in complexes I and II and the number of those electrons that joined the ETC:

$$e^*(t) = e^{-sum} (t) – e_w^- (t).$$

Free negatively charged electrons are used to form free radicals ROS(t). Their number is calculated from the equation:

$$ROS(t) = K_{ROS}\, e^*(t) \ ,$$

where K_{ROS} is the rate of capture of free electrons $e^*(t)$ for the generation of free radicals.

Complex III is the third protein complex in the mitochondrial ETC. It passes the electrons to cytochrome-c oxidase (Cyt-c) and further to Complex IV.

In complex IV, electrons e^- catalyze reaction with molecular oxygen O_2 and hydrogen $2H^+$, producing water inside mitochondrial matrix and the exit of electrons from the ETC into the battery in complex V: $[2e^- + ½\ O_2 + 2H^+ = H_2O \rightarrow e_w^-]$.

The transition of electrons is facilitated due to the differences in concentration of protons H^+ inside and outside the mitochondrial membrane. These varying concentrations produce pressure difference (ΔP) outside and inside the membrane. Inside the membrane the concentration of H^+ is lower than outside, and this enables the transition of electrons $e_w^-(t)$ from the ETC to the battery in complex V. When the battery is charged, the concentrations of H^+ inside and outside the mitochondrion are equalized. This is a characteristic of the normal functioning of a healthy body.

The battery as the main source of energy for all body cells requires constant supply of electrons that come from the ETC. The next section describes how methylene blue is included in the ETC as an alternative electron shuttle, and how it neutralizes free radicals that produce oxidative damage to the cells.

3. INCLUDING METHYLENE BLUE IN THE RESPIRATORY ELECTRON TRANSPORT CHAIN IN THE MITOCHONDRION

Methylene blue is a crystalline substance in the form of a powder. When dissolved in water, it gives the water a blue color, and its molecules gain a positive charge under the influence of oxygen. Once they enter the body through the gastrointestinal tract, they easily penetrate into the intercellular fluid of the mitochondria. As positively charged molecular particles, methylene blue in the intercellular fluid of the mitochondria attracts negatively charged free electrons e*(t) that have leaked from the ETC, and transfers them to cytochrome-c oxidase, which delivers them further along the ETC to complex IV and then to the battery in complex V (Fig. 2).

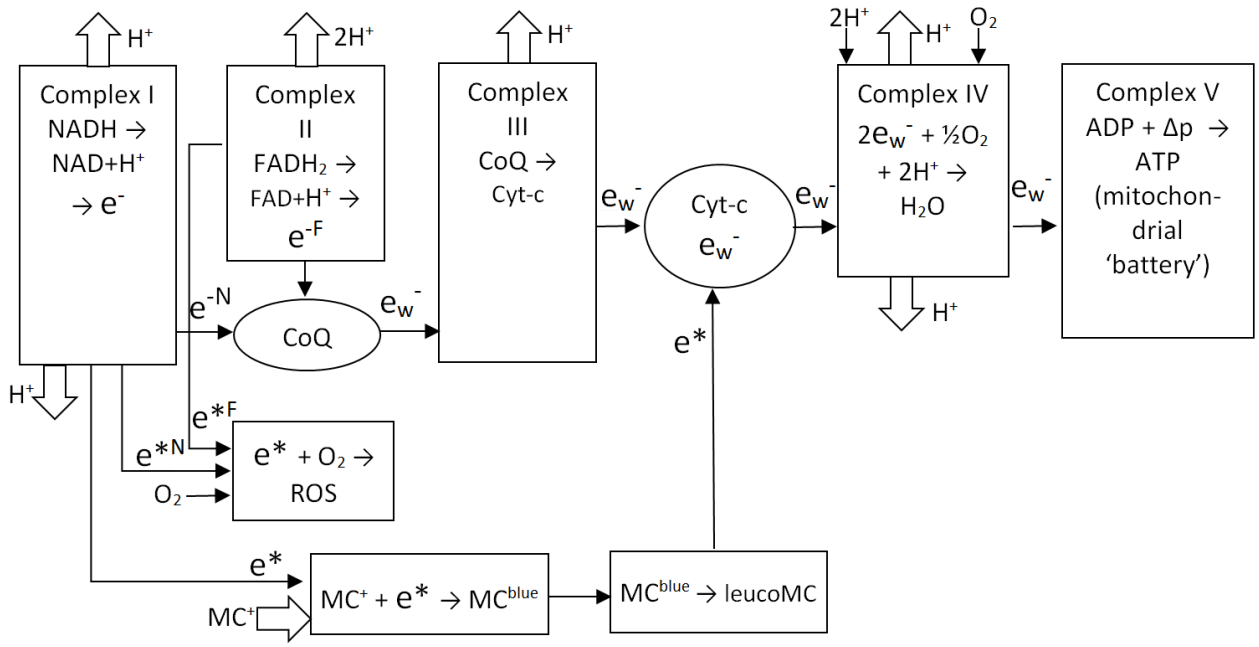

Fig. 2. Block chart showing the inclusion of methylene blue in the operation of the respiratory electron transport chain [2]

The battery in complex V is charged using only the electrons involved in the ETC: $e_w^-(t)$. The free electrons that leaked from the ETC, e*(t), are the primary source of ROS(t). Methylene blue accepts part of these electrons and returns them back to the ETC, thus reducing the negative impact of ROS.

The number of added free electrons depends on the methylene blue dosage, and is calculated using the following formula:

$$e^*_{mc}(t) = D_{mc}\, e^*(t),$$

where $e^*_{mc}(t)$ is a number of added free electrons that will be returned to the battery to enable its recharging,
D is a dosage of methylene blue administered to the body,
$e^*(t)$ is a number of free electrons that did not enter the ETC and remain in the intracellular fluid.

By adding a number of free electrons e*, methylene blue reduces their count, and therefore the number of free radicals (ROS) is also reduced:

$$ROS = K_{ROS}\,(e^* - e^*_{mc}),$$

where e* is free electrons that did not enter the respiratory electron transport chain,
e^*_{mc} – is a part of free electrons e* added to methylene blue.

Methylene blue is not included in the immediate functioning of the ETC. Its function is to increase the number of electrons that charge the battery in complex V (Fig. 2). As the body ages, the reduction of energy potential in the batteries affects all body cells. Thus the function of methylene blue can be compared to the charger for a low battery.

Methylene blue acts as a potent inhibitor of free electrons, thereby contributing to a reduction in the number of free radicals. This, in turn, helps to slow down the degradation of the body and the aging effects [1, 16]. However, the aging process includes several stages with different dynamics of degradation. Understanding the specifics of these stages may help to define the possible start dates and the duration of treatment using methylene blue as an anti-aging agent. The stages of the aging process and their specifics are described in the following section.

4. STAGES OF THE AGING PROCESS AND METHYLENE BLUE ADMINISTRATION

A comprehensive indicator that can be used as a proxy measure of individual aging is the Frailty Index (FI), which quantifies the accumulation of age-related health deficits [7]. Health deficits are defined broadly, covering both biological and clinical characteristics that include functional health status, chronic illness diagnoses, symptoms, cognitive conditions, etc. These deficits ultimately point to the decrease in the cells' energy potential.

The accumulation of deficits originates from the interaction between the damages to the organism produced by both internal and external sources and its capacity to repair or withstand such damages. Accordingly, the number of deficits is the product of the intensity of the environmental stresses, or damages, and the recovery time [8]. An individual's ability to recover from these stresses diminishes with age. Consequently, increase in recovery time leads to the progressive accumulation of deficits. In quantitative terms, this registers as the increase in the FI.

A recent study by Pridham et al. [10] using data from large longitudinal cohorts, the Health and Retirement Study (HRS) and the English Longitudinal Study of Ageing (ELSA), with a total sample of 47592 individuals, indicates four distinct stages of the aging process that are marked by varying rates of increase of the FI [10, p.5].

The first stage (before 45-50 years) is when the slope of the FI growth curve is low. In this stage, the ability to resist and repair damage is strong, and the average recovery periods are low (approx. 1-2 months).

The second stage (from 50 to 70 years) corresponds to the initial stage of aging when the FI starts to increase gradually until the age of about 70 years. This indicates the age-associated acceleration in recovery time.

The third stage (from 70 to 80 years) is when the rates of increase in the FI rapidly accumulate. This stage includes a tipping point of 75 years, when damage and repair rates are equal, followed by a period of accumulating health deficits after age 75.

The fourth stage (after 80 years) is when the rates of FI growth slow down after reaching high values in the third stage of the aging process, and the aged individuals are prone to high vulnerability to the environmental damages. However, they can still maintain sufficient health if they are not subjected to environmental stressors and take measures to combat the increase in their recovery times, which may include the use of methylene blue as an agent that can help restore the energy potential of cells.

This dynamics of the FI increase aligns with the Gompertz function [8], referred to in this study as $FI(T_v)$, where T_v is age. Stages of the aging process may serve as the guideline to approximate a curve indicating critical transitions in FI dynamics, and therefore reflecting the increases in recovery time, which ultimately indicates the decrease in the cellular energy potential levels. Thus, the rates of FI acceleration equivalently describe the rates of decline in the energy potential of the cells' batteries depending on the age of the individual. Accordingly, the beginning of the use of methylene blue and the duration of its intake directly depends on the age of the individual (Fig. 3).

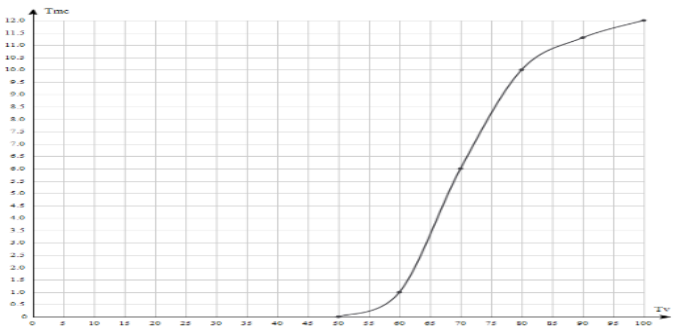

Fig. 3. Dynamics of the duration of methylene blue intake depending on the age of the person to restore the cells' battery charge

The calculation of the duration of taking methylene blue $P_{mc}(Tv)$ after 50 years, when the aging process accelerates, is determined in accordance with the dynamics of the FI increase from the equation:

$$P_{mc}\ (T_v) = 1 - FI(T_v),$$

where 1 corresponds to 12 months of taking the drug, i.e. the maximum duration of one year.

Evidently, as FI increases, indicating the loss of the cells' energy potential, the duration of methylene blue administration needs to be prolonged accordingly.

Currently there are no established treatment protocols that specify the dosages for age-related metabolic diseases, although there are indications that small dosages <2 mg/kg are safe [13]. In small dosages, methylene blue can be taken for a prolonged period, enabling the cells to gradually recover their energy potential. However, in order to increase the active age of an individual, especially to facilitate their ability to continue working after retirement age, it is recommended to start taking small doses of methylene blue as early as age 50 in order to prepare the body for the critical age of 73-76 years without significant deterioration of health.

5. CONCLUSION

As methylene blue is a specific mitochondrial-targeting antioxidant that restores cellular energy production while simultaneously intercepting free radicals to reduce oxidative stress, its ability to increase the energy potential of the body and thus slow down the aging process makes it a promising drug in the context of transforming age structure of the population and the trends towards population aging.

Due to the decrease in the birth rate, which, according to expert estimates, falls below the level of population reproduction [14], the age structure of the population is currently shifting towards an increase in the number of older age groups.

According to Rosstat estimates [11], by 2031 the working age population will decrease to about 55% of the total population. This implies an increased workload, which may fall on the shoulders of higher age groups.

This perspective calls for the means to increase active life expectancy and promote good health for older age groups of the population. Methylene blue has a potential to extend healthspan – the period of life spent in good health – rather than just lifespan through its ability to increase the energy potential of the cells.

Mathematical modeling makes it possible to describe physiological and pathological processes in the human body, increasing the accuracy and reliability of diagnosis and forecasting the results of the use of various drugs [6]. Currently, there is a growing number of studies on the use of methylene blue for the treatment of various diseases of metabolic origin, and the scope of its application is expanding. This implies the need for using mathematical modeling to calculate its application modes, which determines further research directions.

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