

Methylene blue caps

Background

Methylene blue is a medication used to manage and treat methemoglobinemia (e.g., a condition when Fe²⁺ of hemoglobin gets oxidized to Fe³⁺, reducing the oxygen-carrying capacity of hemoglobin), vasoplegic syndrome, Plasmodium falciparum, and ifosfamide-induced encephalopathy.^{5,6} Furthermore, methylene blue is used for diagnostic purposes as a powerful mapping tool for sentinel lymph node charting in breast procedures and parathyroid gland charting during parathyroidectomies.⁵ The chemical structure of methylene blue is presented below.⁷

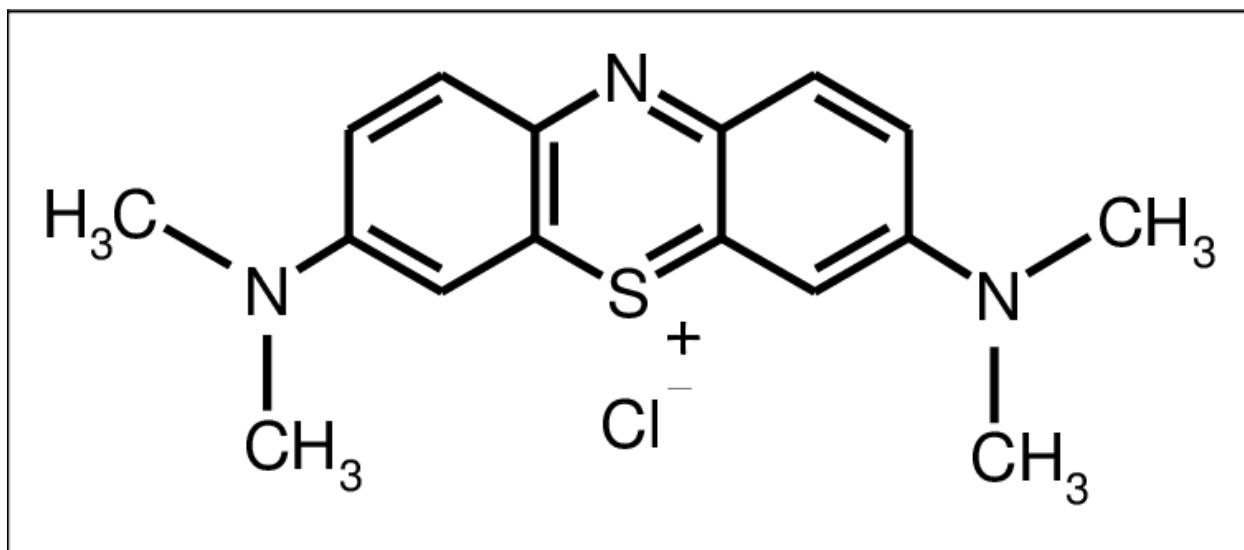


Figure 2. Chemical structure of methylene blue (p. 622).⁷

Source: Sharifi Pajaie, S. H., Archin, S., & Asadpour, G. (2018). Optimization of process parameters by response surface methodology for methylene blue removal using cellulose dusts. *Civil Engineering Journal*, 4(3), 620. <https://doi.org/10.28991/cej-0309121>, Canonical URL: <https://creativecommons.org/licenses/by/4.0/> (No changes were made).⁷

Methylene blue exerts its primary biological mechanism of action by attenuating the oxidized form of hemoglobin Fe³⁺ during a state of methemoglobinemia to Fe²⁺.⁵ Consequently, this improves the oxygen-binding capacity of hemoglobin and promotes enhanced oxygen delivery to tissues.⁵ Methylene blue promotes vasoconstriction of blood vessels by impeding of vascular smooth muscle relaxation caused by reducing the amount of cyclic guanosine monophosphate-specific phosphodiesterase (cGMP) necessary for nitrous oxide release, conducted by prohibiting the

enzymes, endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), and guanylate cyclase.⁸

Research

Methylene blue prevents nitric oxide synthase and guanylate cyclase and has various applications in medicine.¹ Previous findings suggest brief and reproducible blood pressure and cardiac function improvement in septic shock, ameliorates hypoxia and hyperdynamic circulation in cirrhosis of the liver and severe hepatopulmonary syndrome, and links to improvements in hypotension related to many clinical conditions.^{1,2,3,4} Vitamin C is suggested to demonstrate comparable properties like methylene blue as an alternative treatment option for methemoglobinemia, and physicians may explore links between the two as possible methods to amplify treatment effects.⁵ There is evidence to suggest methylene blue may play a role in malaria treatment via improving the chloroquine response, e.g., lessening its resistance and impeding *Plasmodium falciparum* glutathione reductase, an enzyme created by the *Plasmodium* species that inhibits the formation of byproducts and activates the body's immune response.^{8,9}



Photo by: David Gabrielyan on Unsplash (changes made).²¹

Methylene blue is gaining attention for a wide array of medicinal uses, e.g., as an anti-aging drug.¹⁰ Apart from previously stated applications in malaria, methemoglobinemia, and surgical staining, researchers are interested to learn more about the promising anti-oxidative properties of the drug.

¹⁰ There is evidence to suggest that methylene blue demonstrates the ability to bypass complex I/III activity in mitochondria and moderate oxidative stress. ¹⁰ Mitochondrial dysregulation is a hallmark of natural aging that affects the brain and skin, among other tissues, leading to increasing oxidative stress and many downstream phenotypical changes over time. ¹⁰ In other words, dysfunctional mitochondria promote a reduction in Adenosine triphosphate (ATP) production (the source of energy for use and storage at the cellular level) and an increase in reactive oxygen species (ROS) production, producing additional mitochondrial damage. ^{10, 11} This process speeds up natural aging and because methylene blue enhances mitochondrial function and mitigates the ROS damage cycle, it is likely a good contender for use in anti-aging therapies. ^{10, 12, 13}

Brain Diseases' Treatment

Methylene blue demonstrates promise for brain diseases' treatment. ¹⁰ Oxidative metabolism is a primary energy source for brain activity and brain aging promotes mitochondrial dysfunction that is associated with neuronal loss. ^{10, 14} Factors such as these have been observed in brain diseases like traumatic brain injuries, Alzheimer's disease (AD), and Parkinson's disease (PD). ^{10, 15} Methylene blue is highly lipophilic and able to efficiently cross the blood-brain barrier (BBB), demonstrates strong attraction for mitochondria, is shown to decrease production of free radicals rather than scavenging them, and in acting as an electron donor can increase oxygen consumption in vivo. ^{10, 16, 17, 18, 19, 20}

Hashmi et al. (2023) performed a comprehensive review of randomized control trials to uncover potential benefits of methylene blue in Alzheimer's disease (AD) treatment. ²² The existence of intracellular tangles of neurofibrillary tissues (NFTs) and extracellular amyloid- β plaques within the brain are hallmark characteristics found in AD. ²² Electronic databases were used in the investigation, e.g., PubMed and Scopus, and only randomized controlled trials (RCTs) in humans that investigated the potential benefits of MB in treating AD were included. ²² A total of six RCTs were included in their research. ^{22, 23, 24, 25, 26, 27, 28}

The authors' results suggest five out of six RCTs included in their investigation found methylene blue to improve cognitive performance and memory while decreasing beta-amyloid plaque (plaques form when protein pieces called beta-amyloid bunch together) buildup in AD patients. ²² Amyloid- β buildup is an associated feature of AD. ²² It is presumed MB's potent antioxidant properties and related ability to mitigate inflammatory stress and oxidative damage in the brain (two factors associated with AD progression) contribute to potential benefits in AD treatment. ²²

Covid-19 Management

Recently, some researchers have attempted to repurpose methylene blue in covid-19 management. ²⁹ Current covid-19 treatment primarily uses antiviral and anti-cytokine drugs, purported to have low efficacy due to inability to inhibit free radical and cytokine production simultaneously. ²⁹ As

a versatile molecule, MB is the only drug known to reduce the extreme production of reactive species and cytokines simultaneously, a hyper-inflammatory condition caused by the disease associated with serious complications.^{29,31} In a medical center investigation, ($n = 80$) patients with severe covid-19 were randomly assigned to receive oral MB with standard care ($n = 40$) or standard care only ($n = 40$) with the primary outcome measures as oxygen saturation and respiratory rate improvements on days three and five.^{29, 32} Findings suggest the methylene blue group demonstrated statistically significant improvements in both oxygen saturation and respiratory rates on days three and five.^{29, 32} Cagno et al. (2021) found that methylene blue displays virucidal preventive or therapeutic activity against Sars-Cov-2 and the compound's efficacy may be amplified in combination with immune serum due to existence of immunoglobulins against Sars-Cov-2.³³

Conclusion

Methylene blue (MB), e.g., methylthioninium chloride, is a salt used as a lab-grown dye and for various uses as a medication. MB or methylthionine chloride, chemically (3,7-bis(dimethyl amino) phenothiazine-5-ium chloride), is a tricyclic phenothiazine dye with a deep blue color.^{29, 30} The small molecular weight of methylene blue allows for swift delivery into tissues.¹⁰ The U.S. Food and Drug Administration has approved methylene blue for other indications, and it is a low-cost molecule.²⁹ In neurological conditions specifically, researchers cite the promotion of oxygenation in cells as the biological mechanism of action of MB – the enhanced oxygenation causes oxygen and respiration levels to rise, which increases glucose uptake and ATP production.³⁴ In addition to treatment effects found in brain diseases and covid-19 management, MB has demonstrated anti-aging benefits in fibroblast treatment that can increase lifespan and cell proliferation, e.g., attenuating aging markers, resulting in the appearance of healthy and youthful skin.^{10, 35}

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