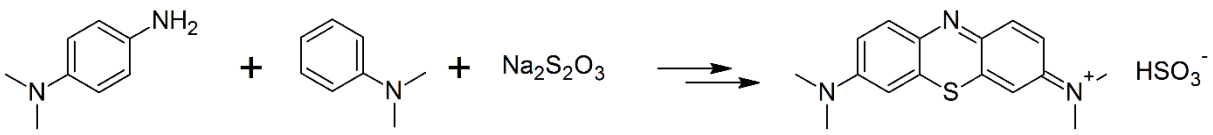
Methylene Blue for the treatment of fatigue, brain fog and Bartonella infections

Methylene Blue (MB)

Summary

1. **MB at concentrations of 0.39mg/kg maybe sufficient to inhibit the growth of Bartonella**
2. **MB at higher concentrations of 9.55mg/kg is required to kill stationary cells according to the John Hopkins study. However even higher dosages of 13 mg/kg for a minimum of 7 days, which are similar to dosages for malaria maybe be more effective against Bartonella henselae.**
3. **MB at a concentration of 0.5 to 4mg/kg could potentially overcome inhibiting factors which contribute to mitochondrial dysfunction resulting in fatigue by getting around a number of steps in the electron transport chain. Higher MB concentrations seem to be negative for this function**
4. **Using Nicotinamide dinucleotide riboside with MB may enhance this positive effect**
5. **MB at 0.5mg to 4mg/kg is being used to improve cognitive function and memory which could address "brain fog" in Tick borne infections.**

Background



Methylene Blue

Methylene blue (MB) is an oxidation-reduction agent. The intravenous form of MB is approved by the FDA for the treatment of paediatric and adult patients with acquired methemoglobinemia. MB was the very first fully synthetic drug used in medicine. In 1891 it was applied by Paul Guttmann and Paul Ehrlich for the treatment of malaria, and this application has recently been revived.

MB was used for a wide variety of medical and hygienic indications. Among others, it was added to the medication of psychiatric patients in order to study their compliance which could be monitored by the observable colour of the urine. These studies led to the discovery that MB has antidepressant and further positive psychotropic effects. Thus, MB became the lead compound for other drugs including chlorpromazine and the tricyclic antidepressants.

Current uses (Refs 1 – 2)

It is currently available as an injection, IV form and in an oral form. Its main mode of action is as a selective inhibitor of nitric oxide (NO) synthase and of soluble guanylate cyclase, however, it is being used in healthcare for its other mechanisms.

Table 1 Dosage of MB in different clinical conditions

Therapeutic indication	Dosages	Mode of action
Inherited methemoglobinemia Acute methemoglobinemia	50–250 mg/day (for a lifetime) 1.3 mg/kg (i.v. over 20 minutes)	MB acts by reacting within RBC to form leukomethylene blue, which is a reducing agent of oxidized hemoglobin converting the ferric ion back to its oxygen-carrying ferrous state
Ifosfamid-induced neurotoxicity	50 mg/day p.o. or i.v.	Alternate electron acceptor. Acts to reverse the NADH inhibition caused by gluconeogenesis in the liver while blocking the transformation of chloroethylamine into chloroacetaldehyde.
Prevention of urinary tract infections in elderly patients	Orally 3 x 65 mg/day	MB is an antiseptic and is related to a group of drugs called monoamine oxidase inhibitors (MAO inhibitors).
Alzheimer's disease	60 mg/day	A mechanistic study found that methylene blue oxidizes cysteine sulfhydryl groups on tau to keep tau monomeric. Anti-inflammatory or neuroprotective effects mediated by the Nrf2/antioxidant response element (ARE); another reported insoluble tau reduction and a learning and memory benefit when given early.
Pediatric malaria and Adult malaria	12 mg/kg p.o. for 3 days 12mg/kg oral for 7 days (HIGH DOSE)	A specific inhibitor of P.falciparum glutathione reductase has the potential to reverse CQ resistance and it prevents the polymerization of haem into haemozoin similar to 4-amino-quinoline antimalarials

The Case for Methylene Blue in treating Bartonella, fatigue and brain fog

MB for Bartonella (References Nos. 11 –14)

The use of MB for bartonella is based on research carried out at John Hopkins University where it was reported that whilst the currently used drugs for treating bartonellosis, including rifampycin, and azithromycin, doxycycline, and ciprofloxacin, had very low minimal inhibitory concentration (MIC) against growing B. henselae (Table 1), they had relatively poor activity against stationary phase B. henselae (Table 2). Obviously, there are other Bartonella sp. but the following discussion will be used as a general guide for Bartonella sp.

Table 1

Minimal inhibitory concentrations (MICs) of select drug candidates against *B. henselae* [a].

Antibiotics	MIC (μg/mL)	C_{max} (μg/mL)
Rifampin	0.01	15.6
Azithromycin	0.04–0.08	0.57 ± 0.23
Pyrvinium pamoate	0.04–0.08	0.003
Methylene blue	0.08–0.16	3.91
Doxycycline	0.08–0.16	1.5–7.0

Stationary phase B. henselae

When a time-kill drug exposure assay was performed against a 5-day-old *B. henselae* stationary phase culture at concentrations of their respective C_{max} it was shown that, pyrvinium pamoate, methylene blue and daptomycin were the most active agents and rapidly killed *B. henselae* with no detectable CFU after 1-day exposure. The Cmax required for MB was reported to be 5mcg/ml or 5,000 ng/ml. Other active hits, including clotrimazole, gentamicin, and streptomycin, could lead to eradication of *B. henselae* cells without viable cells being recovered after exposure for 3 days (Table 2). Berberine showed some activity but not as high as some of the other compounds tested.

Table 2

Evaluation of select drug candidates against a 5-day old stationary phase B. henselae culture at their respective maximum drug concentration in serum (Cmax) values.

Antimicrobial Agents	**Con. of Drug Exposure (µg/mL)**	**CFU per mL after Drug Exposure**	
		1 Day	**3 Day**
Control *	0	$3.67 \pm 2.08 \times 10^7$	$1.33 \pm 0.11 \times 10^6$
Rifampin	10	$2.10 \pm 0.85 \times 10^5$	$8.67 \pm 0.46 \times 10^3$
Azithromycin	2	$3.00 \pm 1.00 \times 10^6$	$5.33 \pm 2.31 \times 10^5$
Doxycycline	5	$5.33 \pm 1.53 \times 10^6$	$1.00 \pm 0.40 \times 10^6$
Erythromycin	1	$3.00 \pm 1.00 \times 10^6$	$1.00 \pm 0.20 \times 10^6$
Gentamicin	10	$1.00 \pm 0.17 \times 10^4$	0
Streptomycin	25	$7.33 \pm 2.08 \times 10^4$	0
Methylene blue	**5**	**0**	**0**
Daptomycin	**60**	**0**	**0**
Pyrvinium pamoate	**5**	**0**	**0**
Clotrimazole	25	$2.00 \pm 1.73 \times 10^3$	0
Miconazole	6	$2.07 \pm 0.38 \times 10^6$	$2.13 \pm 0.31 \times 10^5$
Berberine	1	$3.40 \pm 0.27 \times 10^6$	$1.00 \pm 0.00 \times 10^6$

Cmax is maximum drug concentrations in serum were from the literature.

MB shows great activity against B. henselae. This is in addition to MB having been shown to have good activity against stationary phase Borrelia burgdorferi too. Furthermore, MB was also shown to have an antifungal effect (Candida sp) through its effect on redox and membrane disruption. As the membrane is a target of persister drugs, it maybe that MB could disrupt membranes of B. henselae.

Log phase B.henselae

To further demonstrate the efficacy of the top drugs, they were tested against 1-day-old log phase cultures of B.henselae. The results were similar in that, pyrvinium pamoate, methylene blue, and daptomycin were the most active agents against log phase *B. henselae*, with no colony being detected on agar plate after treatment for 1 day and 3 days. However, the concentrations were not reported.

Bartonella biofilms

There is no information regarding its efficacy in this area

Dosages (References Nos. 15 – 17)

Dosages have yet to be determined in clinical trials with humans and therefore this remains a challenge. However, we have existing information that may provide a guide to the dosages required.

To determine the dosage levels required for Bartonella, we may be able to use the data from the John Hopkins study which showed Cmax levels required to kill stationary cells. MB was shown to be effective at 5,000ng/ml. We need to assume that lower doses will be effective against growing cells as the Cmax was not reported, other than the MIC which was 80 to 160ng/ml.

We are also assuming that there is a relationship between in vitro studies and in vitro dosages. This is an assumption that is not based on any published data so maybe completely erroneous.

Research carried out comparing intravenous and oral doses of MB in humans showed that a single IV dose of 50mg compared to a single oral dose of 500mg in 16 healthy individuals (9 males and 7 females) with a mean weight of 67kg resulted in the following Cmax in plasma and blood.

Table 4. Cmax in human plasma and blood after a single dose of MB taken as IV or oral

	Cmax (ng/ml) in plasma	Cmax (ng/ml) in blood	John Hopkins study. Cmax to **inhibit** B. Henselae growth (80 - 160ng/ml). To achieve this the single dose required (mg)	John Hopkins study. Cmax to **kill** B. Henselae (5,000ng/ml). To achieve this the single dose required (mg)	Dosages optimised for Malaria (Bountongo et al 2010) mg/kg for 7days
IV dose 50mg	748	1,418	11mg or 0.16mg/kg	334 or 4.98mg/kg	
Oral dose 500mg	3,905	3,957	26mg or 0.39mg/kg	640 or 9.55mg/kg	13.22 mg/kg (tablets)

The plasma half -life of both forms was about 18.3h. Based on this data it can be seen that to achieve the Cmax dosages of 5,000ng/ml reported by John Hopkins to kill stationary B. henselae cells, the required oral dose is about 640mg for a 67kg individual which is 9.55mg/kg. This is lower than the malaria dosages reported at 13.22 mg/kg for 7 days. However, it is also clear that the MB is required to cross the blood brain barrier as well as act intracellularly. This may suggest that the higher dosages of 13.22 mg/kg required for malaria may be what is required to kill persister or stationary B. Henselae cells in the body.

In contrast, it maybe that lower doses could be sufficient too, as the in vitro concentrations of Disulfiram which were effective in the lab were much higher than the actual doses required currently for Borrelia and Babesia in humans.

Duration of dosage

At this stage unknown, however low dosages of 100mg to 300 mg per day for long periods may not be an issue. 300mg has been used for 19 months with only moderate side effects in psychiatric hospitals.

100mg per day is the current dose used by the LLMD's in USA for Dapsone therapy. However, it seems that there is recognition currently, that it may help with Bartonella too.

Higher dosages in malaria such as 13.22mg/kg were used for 7 days only (780mg per day). Dosages higher than 13.22mg/kg from 30 to 90 days have been reported previously.

Human clinical trials are required to establish the dose levels in humans. However, until that is carried out it is prudent to stay at dose levels which are known to be safe. Low doses of 0.5 to 4mg/kg maybe taken for long periods under the supervision of a medical professional. High doses of 13.22mg/kg need to be monitored more closely especially if it is used over a long period. It maybe that a patient could start on 100mg/day and then titrate up every 10days to 300mg. Titrating to higher levels could be made once the patient is on 300mg for 10 days. Note that 780mg per day in 59kg individuals was well tolerated for 7 days.

Pulsing

There may be a role for pulsing MB, we know that low dosages are beneficial for mitochondria and brain function but high doses are required for Bartonella. A pulsing regime maybe designed with your healthcare professional.

Combination with other antibiotics or Disulfiram

No reports of the use of MB with antibiotics, however it seems prudent to include them with MB in any treatment regime at least at the beginning.

Disulfiram is been used together with MB (needs to be confirmed again.)

Furthermore, the efficacy of MB against Bartonella biofilms has not been studied yet.

Supplementation

In addition, it was reported that adding MB to an artemisinin-based combination therapy reinforced the particular beneficial effects of the artemisinins, i.e., it further accelerated the elimination of asexual P. falciparum parasites and reduced P. falciparum gametocytes. Therefore, supplementation with artemisinin maybe desirable in any therapy used for B. henselae too.

In summary dosages of 9.55mg/kg to 13.22 mg/kg are probably indicated for the treatment of stationary cells of B. henselae for a minimum period of 7 days.

Non clinical trials (Facebook Methylene Blue for bartonella group and Beating Bartonella group)

A summary of the dosages taken by various members is shown below, this table is expected to grow in the following weeks as more people try and source MB from a reputable source.

Table 1 Methylene Blue - Dosage, weight and herx reactions

No.	Weight(lbs)	Dosage (mg)	Dosage mg/lb	Dosage mg/kg	[1]Frequency (days)	[2]Herx intensity	Comments	Results	Other treatments	Source of MB
1001	150	36	0.24	0.53	1	0	Taking for few years, unknown infections	Dramatically better	Unknown	NA
1002	188	100	0.53	1.17	1	NA	Diagnosed with Bart, going to start with 50mg	NA	NA	Infuserve America
1003	165	100	0.61	1.33	1	3		Thinks that it will help	1% solution, 20mg per day at the moment, started at 40mg and herxed badly and back to 20mg and building up. Recommended for Bart.	https://www.ebay.com.au/p/Kordon-Methylene-Blue-general-Disease-Prevention-Treatment-for-Aquarium-4oz/21011029811
1004	130	100	0.77	1.69	1	1	Yet to start.			Science Methylene blue Ebay: https://tinyurl.com/y2otz7ps
1005	60	50	0.83	1.83	1	1	Yet to start		Rifabutin, Clarithomycin to be replaced by Minocycline	Infuserve America (14y old)
1006	120	100	0.83	1.83	1	3		Brain fog, depressed, headache and night sweats		
1007	100	100	1.00	2.20	1	1	Diagnosed 4y ago, bart, lyme and mould.	Nausea, after 4days increased energy and mental clarity, best in 4y	Rifampin 600mg per day, GFS 500mg, Doxy 200mg, Azithro 500mg. Nystatin, S.boulardii and other probiotics	Infuserve America

[1]Frequency 1 will be every day, 2 every other day etc
[2]Herx intensity From 0 (none) to 3 (intense) based on the comments seen, please PM me if you think differently
NA Not available

It has been reported that one of the main LLMD's is prescribing 100mg/day for Bartonella. At this stage it is difficult to ascertain the reasons for this dosage.

Safety of MB (Ref. 16 - 17)

In the historical studies, MB was usually given orally and often in high doses and for prolonged periods of time, both in children and in adults, and without reports of major safety problems. During World War I for example, some European soldiers received more than 400 g of MB over several weeks without major side effects, apart from moderate urogenital symptoms. Brazilian children were reported to tolerate 20–50 mg/ kg per day of MB very well for long periods of time. However, while MB given orally seems to be largely well tolerated, MB given intravenously must be applied with caution. Intravenous MB is often routinely given as the first-line treatment for acute acquired methemoglobinemia in doses of 1–2 mg/kg, but a dose of 7 mg/kg can lead to severe gastrointestinal symptoms. Moreover, a dose of 5 mg/kg has been reported to be associated with an altered mental status during parathyroidectomy.

In the African study on dosages (13.22mg/kg for 7 days), the main adverse events were dysuria, headache and gastro-intestinal symptoms. While headache and gastrointestinal symptoms may well be related to malaria illness itself, usually mild and self-limiting dysuria is known to be caused by MB. No signs of haemolysis and anaemia were observed in this population with and without G6PD deficiency, confirming previous results on the safety of MB in populations

MB sources

PLEASE USE THE COMPOUNDING PHARMACIES, THEY SHOULD BE PHARMACEUTICAL GRADE.

NOT PHARMA GRADE MEANS NOT MANUFACTURED IN A PHARMACEUTICAL FACILITY

USA

Infuserve America (compounding pharmacy in FL)

https://infuserveamerica.com/, Need prescription, definitely the safest source

Science bio products. COA provided with each batch. (NOT PHARMA GRADE)

https://science.bio/product/methylene-blue-powder/?fbclid=IwAR0HUk_SJd4-6L1wWvxApyLkZh3cZOUrPlP_Uel6wLJDdfFyTepW7dQpl8s

Europe (NOT PHARMA GRADE)

https://apcpure.com/ based in the UK, selling on Ebay

Methylene Blue BP73 ACS C.I.52015 25gm APC Pure, Probably British Pharmacopoeia standard

Global

Thermofisher with offices around the world (NOT CONFIRMED AS PHARMA GRADE)

https://www.thermofisher.com

Ask for their best grade, may meet pharmaceutical standards but please check

Canada

https//www.galenova.com (PHARMA GRADE)

Please note, other than Infuserve America and Stuart Ellis pharmacy, the rest are not selling them as pharmaceutical grade. You will require a compounding pharmacy to help you as you can't just take it as is.

MB contraindications and side effects (Ref. 18)

What is the most important information I should know about methylene blue?

Do not use methylene blue if you have used an MAO inhibitor such as furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine (Nardil), rasagiline (Azilect), selegiline (Eldepryl, Emsam, Zelapar), or tranylcypromine (Parnate) in the last 14 days. A dangerous drug interaction could occur, leading to serious side effects.

Many drugs can interact with methylene blue. Tell your doctor about all other medications you use. You may need to stop using certain medicines before using methylene blue (in some cases for up to 5 weeks before you start methylene blue). During your treatment with methylene blue, do not start or stop using any other medications unless your doctor tells you to.

You should not use this medication if you are allergic to methylene blue, or if you have severe kidney problems.

Before using methylene blue, tell your doctor if you have kidney disease, or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Also tell your doctor about all other medications you use, especially antacids, diuretics (water pills), sodium bicarbonate, or acetazolamide (Diamox).

If you take an antidepressant or psychiatric medication, call your doctor right away if you have signs of a serious drug interaction, including: confusion, memory problems, feeling hyperactive (mentally or physically), loss of coordination, muscle twitching, shivering, sweating, diarrhea, and/or fever.

Methylene blue will most likely cause your urine or stools to appear blue or green in color. This is a normal side effect of the medication and will not cause any harm.

This medication can cause you to have unusual results with certain medical tests. Tell any doctor who treats you that you are using methylene blue.

Call your doctor at once if you have a serious side effect such as severe vomiting or stomach pain, pain in your chest or behind your breast bone, pale or blue skin, high fever, fast or pounding heartbeats, trouble breathing, confusion, or feeling like you might pass out.

What should I discuss with my health care provider before taking methylene blue?

Do not use methylene blue if you have used an MAO inhibitor such as furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine (Nardil), rasagiline (Azilect), selegiline (Eldepryl, Emsam, Zelapar), or tranylcypromine (Parnate) in the last 14 days. A dangerous drug interaction could occur, leading to serious side effects.

Many drugs can interact with methylene blue. Tell your doctor about all other medications you use. You may need to stop using certain medicines before using methylene blue (in some cases for up to 5 weeks before you start methylene blue). However, do not stop taking any of your medications without your doctor's advice. This includes:

- meperidine (Demerol);
- diet pills, stimulants, cold or allergy medicines, ADHD medication;
- migraine or cluster headache medication such as almotriptan (Axert), frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex, Treximet), or zolmitriptan (Zomig);
- medication to treat Parkinson's disease or restless leg syndrome, such as carbidopa or levodopa (Lodosyn, Parcopa, Sinemet), pramipexole (Mirapex), or ropinirole (Requip);
- an "SSRI" antidepressant such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac, Sarafem, Symbyax), fluvoxamine (Luvox), paroxetine (Paxil), or sertraline (Zoloft);
- an "SNRI" antidepressant such as venlafaxine (Effexor), desvenlafaxine (Pristiq), or duloxetine (Cymbalta);
- a "tricyclic" antidepressant such as amitriptyline (Elavil, Vanatrip, Limbitrol), clomipramine (Anafranil), desipramine (Norpramin), doxepin (Sinequan), imipramine (Janimine, Tofranil), nortriptyline (Pamelor), protriptyline (Vivactil), or trimipramine (Surmontil); or
- other medications used to treat depression, anxiety, and other psychiatric conditions, such as bupropion (Wellbutrin, Zyban, Aplenzin), buspirone (BuSpar), maprotiline (Ludiomil), mirtazapine (Remeron), nefazodone, trazodone (Desyrel, Oleptro), or vilazodone (Viibryd).

You should not use this medication if you are allergic to methylene blue, or if you have severe kidney problems. To make sure you can safely use methylene blue, tell your doctor if you have any of these other conditions:

- kidney disease; or
- glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- FDA pregnancy category C. It is not known whether methylene blue will harm an unborn baby, but the medication may sometimes be used during pregnancy. Your doctor will determine whether or not this medication is safe or if it will harm the unborn baby. Before you are treated with methylene blue, tell your doctor if you are pregnant.

It is not known whether methylene blue passes into breast milk or if it could harm a nursing baby. Do not use this medication without telling your doctor if you are breast-feeding a baby.

How should I take methylene blue?

Use exactly as prescribed by your doctor. Do not use in larger or smaller amounts or for longer than recommended. Follow the directions on your prescription label.

The usual dose of oral methylene blue is 1 or 2 tablets after meals, 3 times per day.

Take the methylene blue tablet after a meal, with a full glass (8 ounces) of water.

To be sure this medication is helping your condition, your blood may need to be tested often. This will help your doctor determine how long to treat you with methylene blue. Visit your doctor regularly.

Methylene blue will most likely cause your urine or stools to appear blue or green in color. This is a normal side effect of the medication and will not cause any harm.

This medication can cause unusual results with certain medical tests. Tell any doctor who treats you that you are using methylene blue.

- Store methylene blue tablets at room temperature away from moisture, heat, and light.

What happens if I miss a dose?

Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What happens if I overdose?

Seek emergency medical attention
Overdose symptoms may include severe forms of some of the side effects listed in this medication guide.

What should I avoid while taking methylene blue?

Follow your doctor's instructions about any restrictions on food, beverages, or activity.

What are the possible side effects of methylene blue?

Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

Call your doctor at once if you have a serious side effect such as:

- severe nausea, vomiting, or stomach pain;
- pain in your chest or behind your breast bone;
- pale or blue skin;
- high fever, fast or pounding heartbeats, trouble breathing; or
- confusion, feeling like you might pass out.

Less serious side effects may include:

- mild bladder irritation;
- mild nausea, vomiting, diarrhea, upset stomach;
- dizziness;
- headache; or
- increased sweating.

What other drugs will affect methylene blue?

Tell your doctor about all other medications you use, especially:

- acetazolamide (Diamox);
- antacids;
- sodium bicarbonate; or
- a diuretic (water pill) such as hydrochlorothiazide, HCTZ, Accuretic, Aldactazide, Aldoril, Atacand HCT, Avalide, Capozide, Diovan HCT, Dyazide, HydroDiuril, Hyzaar, Inderide, Lopressor HCT, Lotensin HCT, Maxzide, Moduretic, Vaseretic, Zestoretic, Ziac, and others.

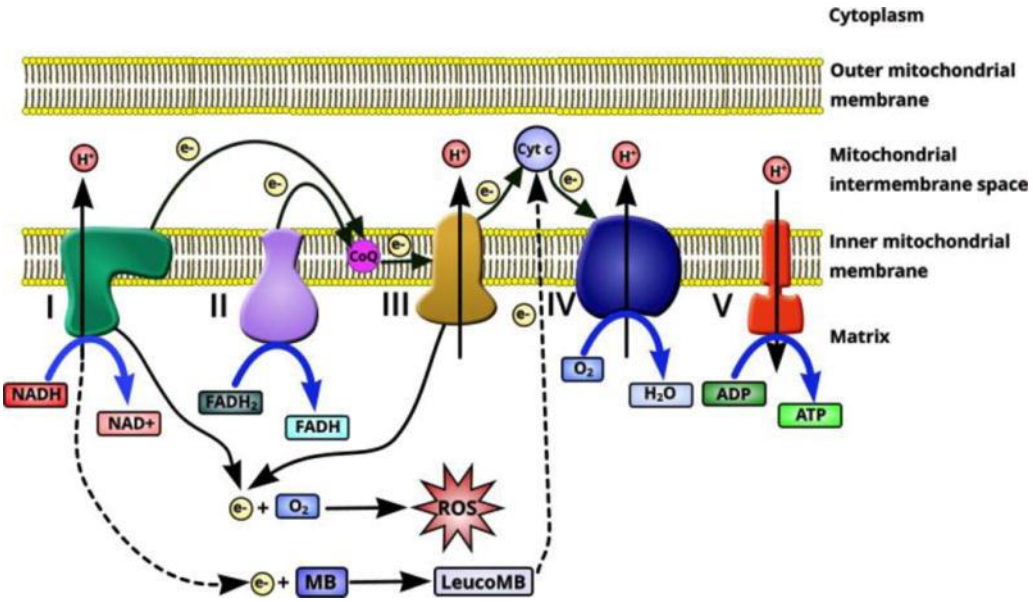
This list is not complete and other drugs may interact with methylene blue. Tell your doctor about all medications you use. This includes prescription, over-the-counter, vitamin, and herbal products. Do not start a new medication without telling your doctor.

MB for Fatigue (References Nos. 3 – 5)

It is a lipophilic compound that accumulates in the mitochondria driven by the mitochondrial membrane potential, and its major cellular target associated with the neuroprotective and cognitive-enhancing effect is assumed to be the mitochondrial metabolism. MB is highly permeable in biological membranes because of its solubility in both water and organic solvent, which permits it to freely enter the intracellular compartments like mitochondria, lysosomes and the nucleus.

However, what is interesting is its ability to donate electrons in the electron transport chain critical for ATP production (Fig 1).

Fig 1



Low-doses (0.5–4 mg/kg) of methylene blue stimulate mitochondrial respiration in vivo and are safe and effective in both animals and humans. This is carried out with methylene blue donating electrons to the electron transport chain. This is possible by a unique auto oxidizing redox chemical property. Foremost is the auto oxidizing property that allows methylene blue at low concentrations to form a redox equilibrium by cycling electrons (i.e., serving as both an electron donor and acceptor).

Electrons in the mitochondrial electron transfer chain are transferred from complex I – complex IV, providing the transmembrane potential to drive production of ATP by complex V. Electron leakage from complex I and complex III acts as the main cellular source of ROS production. MB has been demonstrated as an alternative mitochondrial electron transporter to reroute electrons directly from complex I to complex III, avoiding electrons leakage and subsequent ROS production. This significantly facilitates complex IV activity, increasing mitochondrial respiration

In other words, under normal physiological conditions the electrons that enter the electron transport chain come from electron donor molecules such as NADH and FADH2. These molecules derive from the Krebs cycle conversion of the food we eat. Methylene blue at low concentrations serves as another source of electrons for the electron transport chain that is part of mitochondrial respiration, leading to increased cytochrome oxidase activity, oxygen consumption and ATP production.

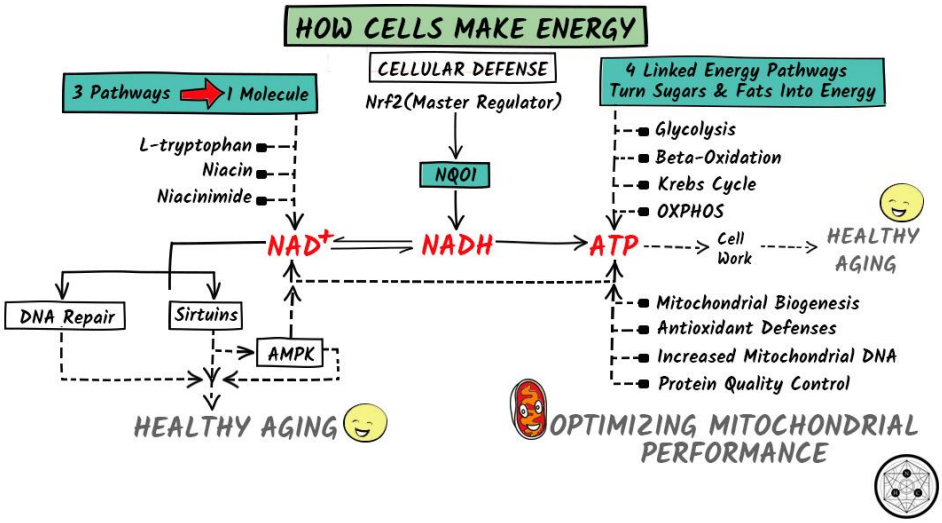
Even during complex I inhibition via rotenone MB can bypass ETC blockage at complex I and III, promoting respiration. Oxidative damage, a cause and consequence of mitochondrial dysfunction, impairs primarily complex IV as well as complex I. This blockage is also bypassed by MB, as it can significantly increase the activity of complex IV.

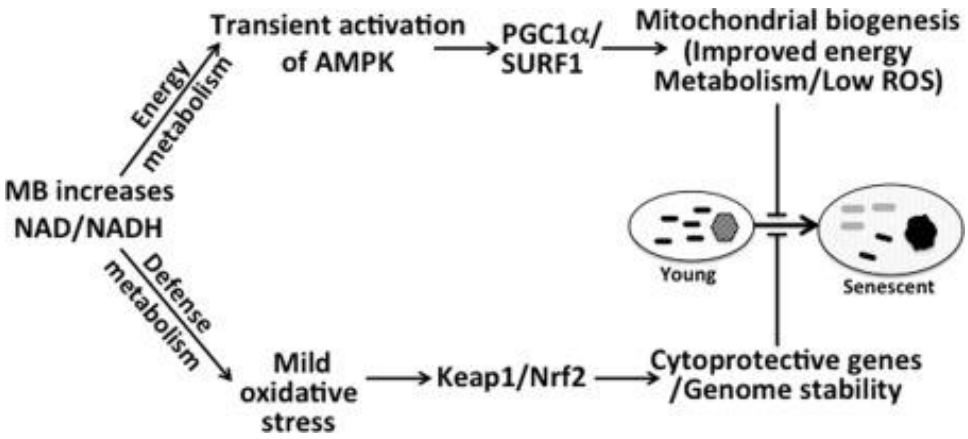
Therefore, MB could play a significant role in overcoming fatigue due to mitochondrial dysfunction.

Fatigue and Nicotinamide dinucleotide riboside (NR) in combination with MB (Reference No. 6)

The use of Nicotinamide dinucleotide riboside (NR) is considered to be of benefit as NR efficiently increases NAD+ levels in mammalian cells and tissues which means that the ratio of NAD to NADH is increased in mitochondria.

Figures 2 and 3





This increased ratio NAD+ enhances the production of electrons that are fed into the electron transport chain. NAD+ is an oxidizing agent as it accepts electrons from other molecules and becomes reduced. This reaction forms NADH, which can then be used as a reducing agent to donate electrons. MB acts as an electron acceptor from NADH at complex I. These electron transfer reactions are the main function of NAD+. Furthermore, it is as a donor of ADP-ribose moieties in ADP-ribosylation reactions, as a precursor of the second messenger molecule cyclic ADP-ribose, as well as acting as a substrate for bacterial DNA ligases and a group of enzymes called sirtuins that use NAD+ to remove acetyl groups from proteins.

NR therefore has a role to play in the electron transport chain and together with MB could overcome mitochondrial dysfunction and enhance the production of energy required to overcome fatigue.

MB for Brain fog ((References Nos. 7 – 10)

The brain is almost exclusively dependent on an uninterrupted supply of glucose and oxygen in order to generate energy to meet its physiological requirements. Due to this high energy demand and lack of energy reserves in the brain, short disturbances in the availability of oxygen and glucose can quickly impair energy production and cause metabolic failure.

The general concept is that by improving mitochondrial function and oxidative defences, neurons can function with improved efficiency and maintain proper health, improving basal function and stymieing cognitive decline associated with age and neurodegeneration.

Early work has shown that MB crosses the blood brain barrier resulting in improved spatial memory retention alongside long-lasting mitochondrial respiratory function, mediated through complex IV of the electron transport chain. In a human study, MB administration increased cerebrovascular reactivity in psychomotor vigilance task and a short-term memory test. This was accompanied with modest improvements in performance on the short-term memory test. Therefore, MB could potentially alleviate symptoms affecting the brain.

In summary, it's role as a mitochondrial enhancer and recycling antioxidant maybe of great significance in alleviating some of the symptoms such as brain fog in Tick borne infections.

References

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