

Review - Human and Animal Health

Methylene Blue for the Treatment of Health Conditions: a Scoping Review

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Editor-in-Chief: Paulo Vitor Farago

Associate Editor: Paulo Vitor Farago

Received: 2020.05.03; Accepted: 2020.09.10.

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HIGHLIGHTS

- This scoping review summarizes the findings of clinical trials using methylene blue (MB) for the treatment of various health conditions.
- This research method allowed mapping main findings, clarifying research topics, and identifying gaps in the literature.

Abstract: studies evaluating effective drugs for health conditions are of crucial importance for public health. Methylene blue (MB) is an accessible synthetic drug that presents low toxicity and has been used in several health areas due to its effectiveness. Objective: this scoping review aims to provide a comprehensive overview of relevant research regarding the use of MB for the treatment of health conditions. Methods: a five-stage framework Arksey and O'maley scoping review was conducted. The literature was searched in Cochrane Library database using Mesh term "methylene blue". Data were collected by two independent reviewers and submitted to descriptive synthesis. Results: The search resulted in 429 records, from which 16 were included after exclusion criteria were applied. The therapeutic use of MB was identified for acute conditions (malaria and septic shock), chronic conditions (discogenic back pain, bipolar disorder, refractory neuropathic pain, and post-traumatic stress disorder), and postoperative care (vasoplegic syndrome, and pain after haemorrhoidectomy, lumbar discectomy, and traumatic thoracolumbar fixation). Conclusion: there is much evidence emerging from clinical trials about the therapeutic use of MB for acute, chronic, and

postoperative conditions; however, many gaps were identified, which open further avenues for future research.

Keywords: methylene blue; therapeutic uses; therapy; clinical trials; scoping review.

INTRODUCTION

Methylthioninium chloride, also known as methylene blue (MB), was the first synthetic drug used in clinical therapy. With a wide range of use, MB has found applicability in several areas of Engineering, Biological Sciences, and Health Sciences [1-3]. Due to its anti-inflammatory, antioxidant, neuroprotective, and antiparasitic properties [4-8] MB has been considered a multifunctional drug with uses at preventive [4,6], curative [9], and postoperative [10-12] care. The main clinical indications of MB are for the treatment of malaria [8,11-13] and methemoglobinemia [14].

The pharmacokinetics, effects, and toxicity of MB have been major topics of investigation. Studies have shown that MB exhibits not only adequate absorption rates by the gastrointestinal tract, but also peak plasma concentrations occurring between one to two and five to six hours after oral and intravenous administration, respectively [15]. Because MB is hydrophilic, low-doses can cross the blood-brain barrier and act on brain mitochondrias, inducing greater energy production and decreasing cell toxicity. Additionally, MB acts as a redox mediator for nicotinamide adenine dinucleotide (NADH), oxidizing intramitochondrial substances and functioning as an alternative electron carrier [16]. Thus, MB can regulate the metabolism and homeostasis of mitochondrial reactive oxygen species, which play an important role in age-related neurodegenerative disorders [13].

The clinical use of MB can be classified according to its purposes as a diagnostic aid or as a medication for the treatment of several conditions. For diagnostic purposes, MB is used in the staining of microorganisms and as an intraoperative adjunct, identifying tissues and preventing iatrogenic complications [17-19]. Furthermore, it may be used in identification of abnormal areas and their targeting biopsy [20]. For treatment purposes, MB has antimicrobial properties [21] and has been used as an antidote in emergency and critical care [6,22,23]. Additionally, it can be administered as an adjuvant therapy, enhancing the outcomes of selected drugs or procedures [24-27]. MB has also been used as the main treatment strategy, being administered alone or combined with other therapies [4-7,10,12,16,22,28-36]

Studies evaluating effective drugs for health conditions are considered of crucial importance in public health. MB, being an accessible synthetic drug with low toxicity, has found uses in many different health areas. Also, effectiveness of MB has been commonly investigated in the literature [17,25,28,37,38]. Therefore, the aim of this scoping review was to identify and select relevant studies, to summarize and disseminate the findings, and to point out potential gaps within the literature on the therapeutic use of methylene blue for health conditions. The results of this scoping review are expected to identify the current state of research and provide evidences to support further clinical and review investigations on the topic.

MATERIAL AND METHODS

A scoping review is a relatively new type of literature search that focus on mapping the literature on a particular topic or research area and provide robust key concepts and evidences to support further investigations. We chose this approach because we did not aim to assess methodological quality of the studies, but rather map the current state of research on the topic and provide evidence for further systematic review and clinical studies [39,40].

For the purpose of this study, the methodological approach was based on the Arksey and O'Malley's five-stage framework for scoping reviews [41,42]. This methodology is underpinned by five stages, as follows: (1) identifying the research question, (2) identifying potentially relevant studies, (3) selecting eligible studies, (4) mapping the data, and (5) collating, summarizing, and reporting the findings [40-45].

The research question posed for this review was "what are the therapeutic applications of methylene blue?" We explored randomized clinical trials and focused on extracting key elements related to MB therapy: sample characteristics, clinical indications, dosing, route of administration, and treatment outcomes. The research question was expected to answer the purpose of this scoping review, as well as open further avenues for future clinical trials.

In order to be included in this scoping review the studies had to meet the following eligibility criteria: 1) any clinical trial published in English, Portuguese, or Spanish in a peer-reviewed journal; 2) studies investigating MB therapy administered alone or in combination with other medications. The exclusion criteria

were as follows: 1) non-interventional study design; 2) case reports or review articles; 3) studies that used MB for diagnostic purposes; 4) articles that reported MB-mediated photodynamic therapy; 5) conference proceedings and other non-refereed publications; and 6) if full text could not be retrieved.

The electronic search was carried out in the Cochrane Library database, which is recognized as the gold standard in evidence-based health care. Key term “Methylene blue” [Mesh] was used for the search. The review considered clinical trials published from January 2010 to April 2020. Two independent examiners conducted the electronic search and data extraction. Disagreements between them were resolved by a third examiner. The standardized data extraction tool from JBI-QARI software [45] was used to assist and facilitate data extraction and analysis. This meta aggregation software retrieves general details of the studies, for instance citations, population, phenomena of interest, context, methods, settings, and key findings. As data were extracted, the reviewers could identify potentially relevant studies related to the research question.

The results were collated, summarized, and reported. Thereafter, the two examiners included the clinical implications of the retrieved studies and recommendations for future research. This stage was conducted using consensus discussion. Finally, descriptive data synthesis was performed based on the findings.

RESULTS

A total of 429 articles were identified through database searching, with 415 remaining after exclusion of duplicates. Further screening of titles and abstracts against the inclusion criteria resulted in 381 being excluded. The remaining 34 studies were assessed for eligibility and the exclusion criteria applied. Among them, nine were excluded because they exhibited non-experimental designs, eight because they were conference proceedings, and one because it was published in a language other than English, Portuguese, or Spanish. Sixteen studies were selected for full-text analysis, met the criteria, and were included in the review [4,6,7,10-12,22,28-36]. Figure 1 shows a PRISMA flow diagram with a summary of the study selection process.

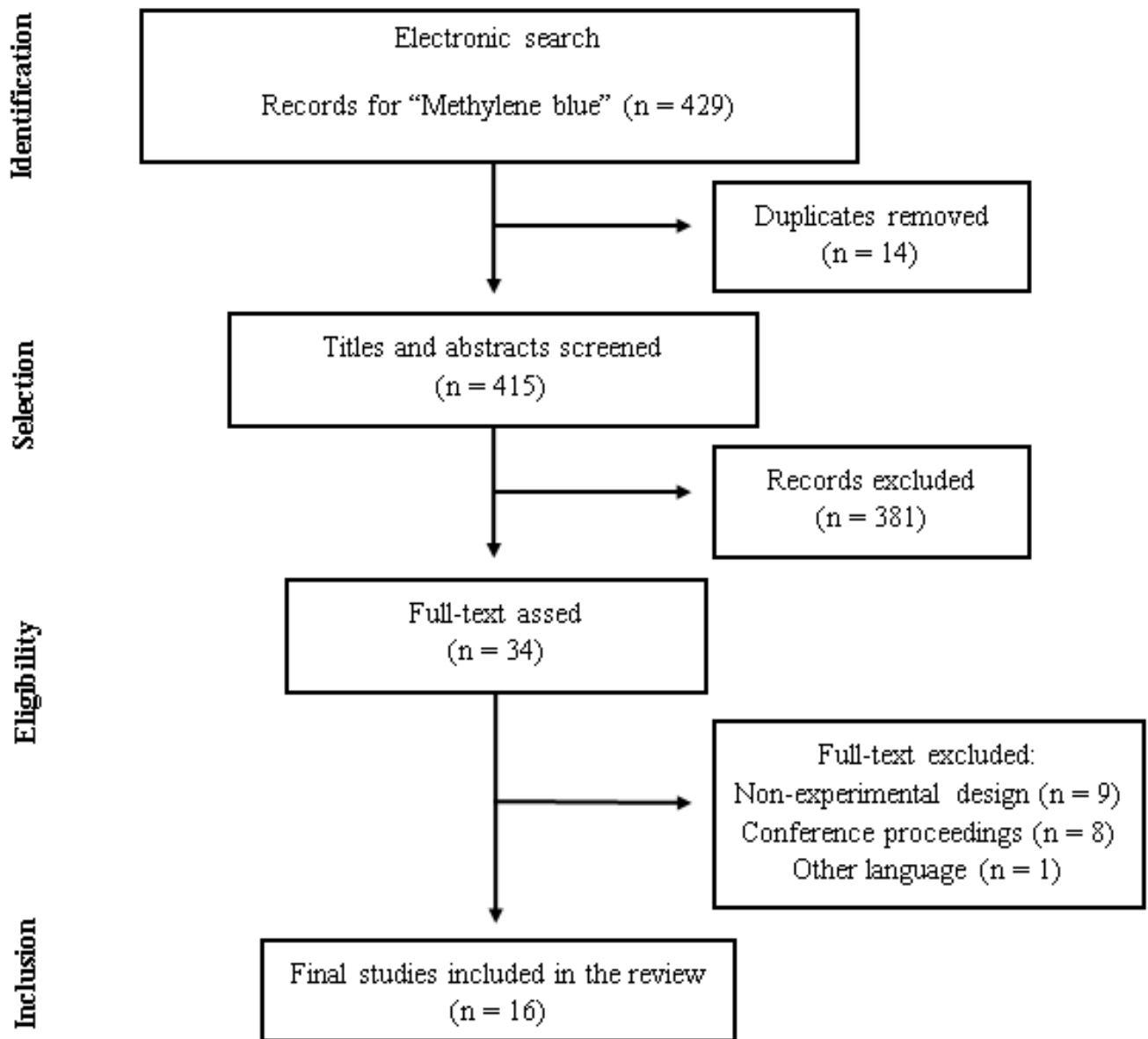


Figure 1. Flow diagram of the search and selection of articles to be included in the scoping review.

Among the included articles, fifteen were published in English language and one in Spanish. For the purpose of this review we charted them according to the therapeutic indication. With this regard, seven studies evaluated acute conditions, of which five were related to malaria [7,22,28,35,36] and two to septic shock [29,30]. Additionally, five studies evaluated chronic conditions, of which two were related to discogenic back pain [31,32] and one to bipolar disorder [4], one to refractory neuropathic pain [33], and one to post-traumatic stress disorder [6]. Moreover, four studies reported the use of MB for postoperative care related to vasoplegic syndrome [34], and pain after hemorrhoidectomy [10], lumbar discectomy [11], and traumatic thoracolumbar fixation [12].

An overview of the selected studies is exhibited in Tables 01, 02, and 03. These Tables evidence the authors and year of publication, population (sample number, gender, health condition, and country), purpose of the study, intervention (dosing, frequency, duration), and outcomes.

Table 1. Studies reporting the use of MB for acute conditions: malaria and septic shock.

Study	Population (n) / Country	Aim	Intervention / Administration route	Outcomes
Ahn et al. (2020) ²²	N = 15 Healthy male volunteers (Vietnam)	To evaluate whether MB can alter the pharmacokinetics of artesunate-amodiaquine (AS-AQ) and increase its antimalarial activity.	After the drugs were administered, blood samples from 7 patients were evaluated for <i>ex vivo</i> antimalarial activity against artemisinin-sensitive (MRA1239) and -resistant (MRA1240) <i>P. falciparum</i> lines. Randomization: Group 1: single dose of AS-AQ (200 mg AS + 540 mg AQ). Group 2: single dose of MB (325 mg) + AS-AQ (200 mg AS + 540 mg AQ). Oral administration	MB increased the antimalarial activity of AS-AQ, suggesting that the triple-drug tested may can be recommended to treat artemisinin-resistant malaria.
Jorge et al. (2019) ³⁵	N = 100 Children with uncomplicated falciparum malaria (Burkina Faso)	To evaluate the efficacy of MB and primaquine (PQ) combined with AS-AQ in the treatment of uncomplicated falciparum malaria.	Patients received weight-adjusted doses. Haematological recovery was assed at day seven. Group 1: AS-AQ (6.0–8.9 kg = 25 mg AS + 67.5 mg AQ; 9.0–17.9 kg = 50 mg AS + 135 mg AQ; >17.9 kg = 100 mg AS + 270 mg AQ). Group 2: daily dose of MB (15 mg/kg) for 3 days + AS-AQ (6.0–8.9 kg = 100 mg; 9.0–12.9 kg = 150 mg; 13.0–16.9 kg = 200 mg; 16.9 kg = 250 mg) PQ was administered at the last day of AS-AQ (day 2) (6.0–8.9 kg = 2 mg; 9.0–12.9 kg = 3 mg; 13.0-16.9 kg= 4 mg; 16.9 kg = 5 mg). Oral administration	Although non-inferiority could not be observed, MB combination exhibited significant secondary benefits and thus may be useful to reduce the transmission and risk for development of resistant falciparum malaria.
Coulibaly et al. (2015) ³⁶	N = 221 Children aged 6-59 months with uncomplicated falciparum malaria (Burkina Faso)	To assess the gametocytocidal effect, safety, and efficacy of AS-AQ combined with MB therapy in the treatment of uncomplicated falciparum malaria	Patients were randomly assigned to two groups and received weight-adjusted doses once a day for 3 days. Randomization: Group 1: AS-AQ (6.0-8.9 kg = 25 mg AS + 67.5 mg AQ; 9.0-17.9 kg = 50 mg AS + 135 mg AQ; >17.9 kg = 100 mg AS + 270 mg AQ). Group 2: AS-AQ (aforementioned weight-adjusted doses) + MB (15 mg/kg) (6.0–8.9 kg =100 mg MB; 9.0–12.9 kg = 150 mg MB; 13.0–16.9 kg = 200 mg MB; 6.9 kg = 250 mg MB). Oral administration	Gametocytes prevalence was significantly lower in patients treated with AS-AQ + MB compared to only AS-AQ and thus indicate that the combination may be useful for the treatment of falciparum malaria.

Table 1 (cont.)

Study	Population (n) / Country	Aim	Intervention / Administration route	Outcomes
Bounto go et al. (2010) ⁷	N = 60 Semi-immune adults with uncomplicated falciparum malaria (Burkina Faso)	To evaluate the efficacy of the therapy with MB in different dosing regimens in semi-immune adults with uncomplicated falciparum malaria.	Patients received MB monotherapy (390 mg) twice a day (after breakfast and supper). Clinical and parasitological responses were evaluated on day 28. Randomization: Group 1: MB administered for 7 days. Group 2: MB administered for 5 days. Group 3: MB administered for 3 days. Oral administration	MB activity against <i>P. falciparum</i> is slow; however, it appears to be effective following a seven-day administration. Therefore, MB should be combined with efficacious and rapidly drugs for the treatment of falciparum malaria.
Dicko et al. (2018) ²⁸	N = 80 Males aged 5 to 50 years with asymptomatic falciparum malaria (Mali)	To evaluate the efficacy and safety of PQ and MB for the prevention of human to mosquito transmission of <i>P. falciparum</i> .	Patients were randomly assigned to two groups and received weight-adjusted doses. Randomization: Group 1: single dose of sulfadoxine (500 mg)-pyrimethamine (25 mg) + amodiaquine (150 mg) for 3 days. Group 2: single dose of sulfadoxine (500 mg)-pyrimethamine (25 mg) + amodiaquine (150 mg) for 3 days + single low-dose of primaquine (0.25 mg/kg). Group 3: standard doses of dihydroartemisinin-piperaquine. Group 4: standard doses of dihydroartemisinin-piperaquine + MB (15 mg/kg) for 3 days. Oral administration	The combination of sulfadoxine-pyrimethamine with amodiaquine, as well as the combination of dihydroartemisinin-piperaquine with MB were highly effective to prevent the transmission of <i>P. falciparum</i> .
Juffermans et al. (2010) ²⁹	N = 15 Mechanically ventilated patients with septic shock (Netherlands)	To assess the risk-ratio of using MB as an adjuvant in the treatment of human septic shock.	Prior the study, patients received a standard protocol treatment, which included resuscitation with infusion of colloid fluids and administration of broad-spectrum antibiotics. Dose-finding investigation, global hemodynamics measurements, gasometrics, and gastric PCO ₂ were assessed before and after 20 minutes of MB administration. Randomization: Group 1: 1 mg / kg de AM. Group 2: 3 mg / kg de AM. Group 3: 7 mg / kg de AM. Intravenous administration	MB administered at a dosage of 1-3 mg/kg in patients with septic shock is adequate to transiently elevate arterial pressure. It is attributed to an increase in cardiac index and vascular resistance. High doses of MB, such as 7 mg/kg may compromise splanchnic perfusion adequacy.
Arzábalo et al. (2016) ³⁰	N = 60 Patients with septic shock (Mexico)	To assess the efficacy of MB as an adjuvant in the treatment of septic shock.	Blood pressure, lactate, base deficit, central venous oxygen saturation, and CO ₂ delta were assessed at baseline and after every hour. Noradrenaline dosage (mg), length of stay and mechanical ventilation, and mortality were evaluated. Group A: Single dose of MB (2 mg/kg) in 100 mL of 5% dextrose over 60 minutes. Group C: 100 mL of 5% dextrose over 60 minutes. Intravenous administration	MB may be used as a valuable adjuvant in the treatment of human septic shock.

Table 2. Studies reporting the use of MB for chronic conditions: discogenic low back pain, bipolar disorder, post-traumatic stress disorder, and refractory neuropathic pain

Study	Population (n) / Country	Aim	Intervention / Administration route	Outcomes
Kallewaard et al. (2019) ³¹	N = 84 Adults with discogenic low back pain for at least 6 months (Netherlands)	To evaluate the efficacy of intradiscal MB injection on discogenic back pain intensity.	Prior the procedure, patients received antibiotic prophylaxis (cephazolin 2 mg). MB was injected in the symptomatic disk and one control disk. The outcomes evaluated were reduction in pain and patients' general impression after 6 weeks and 3, 6, 12, and 24 months. Group 1: 1 mL of MB (10 mg/mL) + 0.5 mL of 2% lidocaine hydrochloride + 0.5 mL of contrast dye. Group 2: 1 mL of isotonic saline + 0.5 mL of 2% lidocaine hydrochloride. + 0.5 mL of contrast dye. Intravenous administration	The efficacy of MB in reducing discogenic back pain compared to saline hydrochloride was not confirmed.
Peng et al. (2010) ³²	N = 72 Adults with chronic low back pain without radiculopathy (China)	To evaluate the efficacy of intradiscal MB injection on discogenic low back pain.	Prior the procedure, discographies were performed under fluoroscopy. Patients with discogram-proven diseased disc were randomly allocated to two groups. Reevaluations were performed after 6, 12, and 24 months. Group 1: 1 mL of 1% MB (10 mg) + 1 mL of 2% lidocaine hydrochloride. Group 2: 1 mL of isotonic saline + 1 mL of 2% lidocaine hydrochloride. Intravenous administration	MB injection reduced pain intensity and Oswestry disability scores, as well as increased satisfaction rates compared to placebo treatment.
Alda et al. (2017) ⁴	N = 37 Adults with bipolar disorder partially stabilized with lamotrigine (Canada)	To assess the efficacy of MB as an adjuvant treatment of residual symptoms of bipolar disorder in patients treated with lamotrigine.	The administration of low and high doses of MB was performed using a crossover dose-response design (1-week titration, 12-weeks of treatment, 1-week of crossover, and 12-weeks of treatment). The order of MB administration (active-subtherapeutic, subtherapeutic-active) was randomly selected. Patients were evaluated in 2-weeks intervals for neurocognitive testing. Group 1 (low dose): capsules containing 5mg MB three times per day. Group 2 (high dose): capsules containing 65 mg MB three times per day. Oral administration	MB as an adjuvant drug for bipolar disorder improves residual symptoms of anxiety and depression.
Zoellner et al. (2017) ⁶	N = 42. Adults with a primary DSM-IV-TR diagnosis of posttraumatic stress disorder (USA)	To evaluate the outcomes of MB augmentation of exposed therapy for posttraumatic stress disorder.	Patients were submitted to daily imaginal exposure (50 minutes). Thereafter, MB or placebo was administered according to posttraumatic stress disorder severity. Group intervention: MB (260 mg) Group control: placebo containing an inert food dye Oral administration	MB has the potential to enhance the outcomes of imaginal exposure therapy for the treatment of posttraumatic stress disorder.
Miclescu, Svahn, and Gordh (2015) ³³	N = 10 Adults with refractory neuropathic pain for more than 12 months. (Sweden)	To evaluate the effect of MB therapy in refractory neuropathic pain.	Prior the procedure, placement of monitors for electrocardiography, blood pressure, and pulse oximetry was performed. MB was infused with 5% glucose (250 mL) over 60 minutes. Pain was assessed at baseline and after 60 minutes. Pain was recorded for the following 5 days with the aid of a diary. Group intervention: MB (2 mg/kg). Group control: MB (0.02 mg/kg). Intravenous administration	The administration of MB in patients with refractory neuropathic pain reduced pain level on the first two days after drug infusion.

Table 3. Studies reporting the use of MB for postoperative care: pain after hemorrhoidectomy, vasoplegic syndrome, and pain after lumbar discectomy and traumatic thoracolumbar fixation

Study	Population (n) / Country	Aim	Intervention / Administration route	Outcomes
Sim and Tam (2014) ¹⁰	N = 67 Adults with symptomatic third- and fourth-degree haemorrhoids that underwent elective diathermy haemorrhoidectomy (Singapore)	To verify if the administration of intradermal MB reduces postoperative pain of haemorrhoidectomy.	Patients were randomly allocated to two groups. Perianal intradermal administration was performed prior dissection. Pain levels were evaluated with a visual analogue pain score. Reevaluation was performed 2 and 6 weeks after. Secondary outcomes included postoperative complications, urinary retention, and reactions. Group MB: 4 mL of 1% MB + 16 mL of 0.5% marcaine Group placebo: 4 mL of saline solution + 16 mL of 0.5% Marcaine. Intravenous administration	The intradermal injection of MB reduced the initial postoperative pain of open haemorrhoidectomy. Furthermore, no secondary outcomes were observed.
Farrokhi et al. (2015) ¹¹	N = 50 Adults undergoing PPSF because of thoracolumbar fractures (Iran)	To evaluate the effects of MB on inhibiting postoperative pain and improving quality of life of patients submitted to PDSF.	After surgery, patients were administered MB or saline in the soft tissue around fusion site. Pain was assessed after 48 hours, 2, and 6 months with the aid of a visual analogue scale. Quality of life was assessed after 2 and 6 months. Group intervention: 1 mL of 0.5% MB. Group control: 1 mL of normal saline. Intravenous administration	MB injection on the surrounding tissues has potential in terms of safety, reducing pain, and functional outcomes following 6 months of surgery.
Farrokhi et al. (2016) ¹²	N = 115 Adults undergoing posterior pedicle screw fixation (PPSF) because of thoracolumbar fractures (Iran)	To assess the effects of MB on inhibiting postoperative low-back-pain.	After surgery, patients were administered MB or saline over the dural sac and surrounding soft tissues. Reevaluations were performed after 24 hours and 3 months. Group intervention: 1 mL of 0.5% MB. Group control: 1 mL of normal saline. Intravenous administration	MB injection on the dural sac and surrounding tissues has potential for reducing pain and enhancing functional outcomes.
Abdelazim et al. (2016) ³⁴	N = 40 Children diagnosed with vasoplegic syndrome after cardiopulmonary bypass (Egypt)	To compare the use of MB with norepinephrine in children who developed vasoplegic syndrome after cardiopulmonary bypass.	Norepinephrine was titrated according to the response of patients. Maximum dose considered was 2 µg/kg/min. Patients were assessed for heart rate, blood pressure, cardiac output and index, pulmonary artery pressure, and systematic vascular resistance. Group intervention: 1.5 mg/kg MB + norepinephrine infusion over 20 min. Group control: norepinephrine infusion over 20 min. Intravenous administration	Infusion of MB exhibited higher efficacy managing vasoplegic syndrome after cardiopulmonary bypass compared to only norepinephrine.

DISCUSSION

The present scoping review highlights positive outcomes reported by the majority of clinical trials included. Among the main benefits addressed is the fact that MB is a low-cost synthetic compound, which allows production on a large scale, regardless of supply or location of natural resources. Furthermore, low toxicity, appropriate pharmacokinetics, and low potential for drug resistance have been reported [7,22,28,35,36,46]. The findings we summarized in this review suggest that MB is a promising option for the treatment of high-prevalence health conditions, which has been considered a major concern in public health.

The summary presented in this section provides a panoramic overview of what is currently known about the use of MB in the treatment of health conditions. Data synthesis was performed based on MB applicability for health conditions, mechanism of action, pharmacokinetics, route of administration, dosing, and adverse or side effects.

Acute Clinical Conditions

Malaria

Studies evaluating MB in the treatment of malaria were the most reported in the literature. Malaria is an endemic infectious disease of high-prevalence in underdeveloped countries that poses a great threat to public health worldwide [47]. The disease is caused by intracellular protozoan parasites of the genus *Plasmodium* and transmitted through the bites of infective female *Anopheles* mosquitos [48]. The high prevalence of malaria has guided a research effort aiming to evaluate drugs with antimalarial activity. Among them, MB has been used as an adjuvant treatment because of its easy-access and low-cost compared to other antimalarial drugs, such as artesunate-amodiaquine and primaquine [7,26,28,35].

Children under five years of age are the most vulnerable group to malaria [48]. In this context, two studies included pediatric patients [35,36], two included adults [7,22] and one both populations [28]. MB dose adjustment was performed based on patient's age (varying from 45 to 390 mg) and administered orally as tablets or mini-tablets. Nevertheless, nausea and vomiting were reported as side effects associated with oral administration of MB, possibly due to the strong bitter taste of the tablets [35,36]. It may impose difficulties to be administered to pediatric patients. Considering this limitation, one study pointed out that when MB was administered with food and sweets, such as honey, it improved patients' acceptance and reduced vomiting frequency; however, this technique alone was not sufficient to eliminate the mentioned side effects [36]. Moreover, dose-related adverse reactions such as gastrointestinal disorders and dysuria may occur with the administration of 15 mg/kg/day MB for three days [22]. With regards to organoleptic properties, the use of MB against malaria is promising. The included studies presented interventions that resulted in notorious outcomes, for example elimination of *P. falciparum* in MB monotherapy [7] and enhanced effectiveness of other antimalarial drugs in MB-based combination therapy [22,28,35,36].

Septic shock

Septic shock is characterized by profound changes in the hemodynamic profile. These changes include increased cardiac output and persistent hypotension resulted from arterial vasodilation and overwhelming response to a systemic inflammatory reaction. The condition is the leading cause of non-coronary morbidity and mortality of patients admitted to intensive care units [29,30]. Even in the developed economies, septic shock has been a challenge for health agencies [49]. The high prevalence and mortality rate of this condition have supported studies aiming at different treatment approaches, among which the use of MB seems encouraging [29,30].

In septic shock patients, the administration of MB improves hemodynamic status through an increase of the cardiac index and systemic vascular resistance [29]. Furthermore, the two studies included in this review report that MB administration was safe and no adverse effects were observed. It is important to mention that safety was restricted to intravenous administration and at a dosage of 1 to 3 mg/kg [29,30]. Excessive doses of MB may result in adverse effects on visceral tissue perfusion. Doses higher than 40 mg/kg are expected to be lethal [29,30].

Chronic Clinical Conditions

Chronic Discogenic Low Back Pain

The use of MB in the treatment of chronic discogenic low back pain is commonly investigated [31,32,38]. This condition is characterized by the degeneration of intervertebral discs caused mostly by mechanical factors. The pain associated with the condition usually worsens upon sitting, coughing or sneezing, and relieves on standing up or walking. Pain radiation to the lower extremities and neurological symptoms such as numbness, weakness, and urinary incontinence are advanced signs of the disease [50]. The prevalence of discogenic low back pain worldwide is estimated at 11.9%, which results in high patient demand and costs of treatment [51]. MB administration may be an effective alternative treatment for the condition via denervation of small nociceptive fiber. Additionally, it acts reducing inflammatory processes of disc degeneration by inhibiting the production of nitric oxide [51]. Transient adverse effects were reported in the following six months after exposure and included increasing in pain, dizziness, radiating pain, urinary tract infection, and tiredness[31], corroborating another investigation[32].

Bipolar Disorder and Posttraumatic Stress Disorder

Methylene blue has been used for psychiatric disorders for more than 30 years. A significant reduction of residual symptoms of depression and anxiety in patients with bipolar disorder has been associated with the use of MB [4]. Bipolar disorder is a multifactorial illness with uncertain etiology characterized by changes in mood involving episodes of mania, neuropsychological deficits, and immunological / physiological changes. Worldwide, bipolar disorder affects 2.4% of the population, with prevalence estimated at 0.6% for type I, and 0.4% for type II [52]. Treatment consists of the use of mood stabilizers, atypical antipsychotics, and anticonvulsants, which vary according to the stage and symptoms of the condition [53].

Methylene blue has shown potential to improve symptoms of bipolar disorder. Due to its neuroprotective mechanisms, MB increases levels of serotonin / dopamine and inhibits nitric oxide synthase, thus contributing to neurogenesis and treatment of residual symptoms [4]. Therapy with an orally dose of 195 mg MB was well tolerated and presented only mild side-effects (chromaturia and fluid retention) [4].

Regarding post-traumatic stress disorder, MB has shown to be a promising adjuvant treatment. Its effect on psychological disorders has been widely addressed by the literature. A recent study showed that MB enhanced the effects of imaginal exposure therapy, in which a patient is asked to imagine feared scenes or situations [6]. It could be associated with the fact that MB improves memory retention and learning, in addition to having significant effect on the quality of life [6]. In the aforementioned study, an oral dose of 290 mg MB was administered and only mild side effects were observed. MB possesses antioxidant and neuroprotective properties that enhance mitochondrial oxidative metabolism, cerebral oxygen consumption, and improvement of memory consolidation. Therefore, MB may be very useful in the treatment of post-traumatic stress disorder, since it is characterized by mental health condition that is triggered by a frightening event or traumatic memories [6].

Refractory Neuropathic Pain

Patients with chronic pain have increased plasma levels of nitric oxide (NO) compared to healthy individuals. MB is a direct inhibitor of nitric oxide synthase, both constitutive and inducible, in addition to blocking the accumulation of cyclic guanosine monophosphate (cGMP) by inhibiting the enzyme guanylate cyclase [33]. The neuropathic pain mechanism involves the activation of NO- and cGMP-dependent signaling pathways, thus the effectiveness of MB is likely related to the inhibition of these processes [33]. Therefore, MB seems to be a promising alternative to the treatment of refractory neuropathic pain that does not respond well to conventional treatments.

The researchers administered MB at two different doses, as follows: 2 mg/kg of MB (10 mg/mL) or 0.02 mg/kg, both in 5% glucose solution. The glucose solution was chosen because precipitation has been reported in studies where MB has been diluted with sodium chloride. Eight of the patients in the MB group reported adverse effects, which included abdominal pain and nausea. There is no consensus among researchers regarding appropriate dosing of MB for the treatment of neuropathic pain; however, bolus dose of 2 mg/kg MB administered for one hour has been reported [33].

Post-Surgical Clinical Conditions

Pain after hemorrhoidectomy

Hemorrhoidal disease, commonly referred by the term “hemorrhoids”, is characterized by the dilation of submucosal blood vessels in the anorectal region because of an increased venous pressure in the rectal venous plexus [54]. It is a condition that affects quality of life of millions of people worldwide. Conservative treatments have been recommended and include changes in lifestyle and diet. On the other hand, in cases where surgical approach is required, considerable levels of postoperative pain have been reported, such as in open hemorrhoidectomy. In order to assess the reduction of postoperative pain after hemorrhoidectomy, studies have investigated the injection of local anesthetic combined with MB prior diathermy dissection [10]. The use of MB has been associated with a reduction in postoperative pain levels because it temporarily ablates perianal nerve endings. In addition, no significant adverse effects were encountered and therefore suggesting that MB is a promising drug for the pain control after hemorrhoidectomy. Nevertheless, further studies are needed to clarify the effectiveness and safety of MB administration for postoperative pain control of hemorrhoidectomy [10].

Pain after Lumbar Discectomy

Worldwide, low back pain is a widely prevalent disorder with high impact in patients' quality of life. Chronic low back pain may require surgical management. Among the surgical approaches, lumbar discectomy is a common procedure that consists of partially removing an intervertebral disc compressing the nerve root or spinal cord [55]. However, this procedure is associated with high levels of postoperative pain, which results in increased length of hospital stay and impacts on public health systems. As an alternative treatment, MB has been used to pain control after lumbar discectomy. Conventional procedures include intraoperative injections of local anesthetics and administration of opioid analgesics; however, these are often associated with constipation and delayed mobilization, in addition to not present adequate pain control. Farrokhi and coauthors [11] demonstrated that a single dose of 0.5% AM (1 mL) was effective in reducing postoperative pain and presented no adverse effects. These findings may be considered an important indicator of MB effectiveness.

Pain post fixation Thoraco-Lumbar

Thoracolumbar traumas or injuries can result in permanent impairment of function. Traumatic events put the patient at risk of suffering injuries as spinal fractures, which may require surgical treatments that can require posterior pedicle screw fixation. Patients submitted to this procedure often report postoperative pain. It has guided studies incorporating alternative approaches seeking to reduce pain levels. Among these, MB has shown to be a promising analgesic alternative to assess pain after thoracolumbar fixation [12].

Effective pain control after low back surgery contributes to improving patient's quality of life in the short term, but it can also contribute to the prevention of chronic pain and failed back surgery syndrome. Intradermal or intravenous injections of MB have no adverse reactions reported in the literature. In the studies included in this review, low doses were used to avoid high local concentration of the drug. Moreover, due to the neurotropic properties of MB, injections have been performed aiming at pain management. Based on this review we can state that epidural administration of 0.5% MB (1 mL) was effective for the control of postoperative pain after of thoracolumbar fixation. However, further studies related to the analgesic effect of MB are necessary in order for it to be consolidated for clinical use [12].

It is important to mention that the administration of MB aforementioned is simple to be performed and accessible, presenting similar results of pain relief when reproduced. However, there is a need for studies with larger samples and longer follow-up periods in order to better investigate the effect of MB in reducing postoperative pain and improving patients' quality of life.

Vasoplegic syndrome

Vasoplegic syndrome is a condition characterized by uncontrolled vasodilation that results in hypotension because of the low systemic vascular resistance. The etiology of the condition is multiple and diverse and may include septic, cardiogenic, neurogenic, and anaphylactic shock [34].

Conventional treatments of vasoplegic syndrome comprise fluid therapy and use of vasopressor agents such as phenylephrine, norepinephrine, and vasopressin. Nevertheless, these agents may induce adverse effects and increase in mortality rate. Thus, studies evaluating alternative approaches for the treatment of

vasoplegic syndrome are of fundamental importance. For instance, norepinephrine, used in the trial as a comparison drug, despite its adequate perfusion can reduce cardiac output and oxygen supply to tissues, in addition to reducing blood flow to compromised organs. As an alternative, MB was proposed because of its influence on the NO synthase, by inhibiting vasodilation on the vascular endothelium and consequently increasing mean arterial pressure [56]. MB was shown to be superior in terms of efficacy and safety compared to norepinephrine in the treatment of VS, however the authors recommend that further studies be done in order to compare it with other vasopressin drugs.

Limitations of this scoping review include the search on a single database. Nevertheless, it is important to mention that the search in the Cochrane Library comprises other databases such as Pubmed, Embase, and ClinicalTrials. Future studies evaluating MB treatment for health conditions are recommended in order to demonstrate its effectiveness and safety. Furthermore, further research should elucidate the mechanism of action of MB for each health condition evaluated.

CONCLUSION

Based on the findings of this scoping review it is possible to conclude that there is much evidence emerging from clinical trials about the therapeutic use of MB for acute, chronic and postoperative conditions; however, many gaps were identified, which open further avenues for future research.

Funding: This research received no external funding.

Acknowledgments: The authors acknowledge the multiprofessional residency in health program HU-UEPG.

Conflicts of Interest: The authors declare no conflict of interest.

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