Artigo de Revisão

https://www.revistardp.org.br https://doi.org/10.25118/2763-9037.2023.v13.443

Use of *Hericium erinaceus* as a potential therapeutic of mental disorders: a systematic review

Uso de Hericium erinaceus como potencial terapêutico de transtornos mentais: uma revisão sistemática

Uso de Hericium erinaceus como potencial terapéutico de los trastornos mentales: una revisión sistemática

Pietra McDonnell Matheus Cortonesi ORCID - Lattes

Laura Fogaça de Almeida - ORCID - Lattes

Rafael Monteiro Tancredi Pinheiro - ORCID - Lattes

Cintia de Azevedo-Marques Périco - ORCID - Lattes

João Maurício Castaldelli-Maia - ORCID - Lattes

ABSTRACT

Introduction: *Hericium erinaceus* (HE), often known as Lion's Mane, is an edible fungus that has been extensively explored for its many functions. The use of this mushroom in traditional Chinese medicine dates back many years, and it is now being tested in the treatment of cognitive decline and Alzheimer's disease, and mental diseases like depression, anxiety, schizophrenia. **Methods:** We followed 2020 PRISMA statement for systematic reviews. The three selected databases were Worldcat®, Cochrane Library®, and PubMed®. On March 7, 2022, a search for articles was conducted. The search sources' descriptions were *Hericium erinaceus* AND (mental disorders OR cognitive impairment OR depression OR anxiety). "English" was the sole filter applied to the data sources. **Results:** Three Japanese randomized double-blind controlled trials were included in the review. Although the data demonstrated that HE can be useful in treating symptoms of cognitive impairment and moderate cognitive impairment, it was not effective in treating depression/anxiety symptoms. **Conclusions:** More studies are needed in countries besides Japan, lasting at least 12 weeks, since shorter periods do not demonstrate significant

improvement of symptoms. Incorporating HE into a patient's daily diet may produce favorable benefits by alleviating cognitive decline.

Keywords: *Hericium erinaceus*, mental disorders, cognitive dysfunction.

RESUMO

Introdução: *Hericium erinaceus* (HE), muitas vezes conhecido como Lion´s Mane, é um fungo comestível que vem sendo amplamente explorado por suas diversas funções. O uso deste cogumelo na medicina tradicional chinesa remonta a muitos anos e agora está sendo testado no tratamento do declínio cognitivo e da doença de Alzheimer e doenças mentais como depressão, ansiedade, esquizofrenia. **Métodos:** Seguimos a declaração PRISMA de 2020 para revisões sistemáticas. As três bases de dados selecionadas foram Worldcat®, Cochrane Library® e PubMed®. Em 7 de março de 2022, foi realizada uma busca de artigos. As descrições das fontes de busca foram *Hericium erinaceus* E (transtornos mentais OU comprometimento cognitivo OU depressão OU ansiedade). "Inglês" foi o único filtro aplicado às fontes de dados. **Resultados:** Três ensaios controlados randomizados duplo-cegos japoneses foram incluídos na revisão. Embora os dados demonstrem que o HE pode ser útil no tratamento de sintomas de comprometimento cognitivo e comprometimento cognitivo moderado, ele não foi eficaz no tratamento de sintomas de depressão/ansiedade. **Conclusões:** São necessários mais estudos em outros países além do Japão, com duração mínima de 12 semanas, visto que períodos mais curtos não demonstraram melhorias significativas dos sintomas. A incorporação de HE na dieta diária de um paciente pode produzir benefícios favoráveis ao aliviar o declínio cognitivo.

Palavras-chave: *Hericium erinaceus*, transtornos mentais, disfunção cognitiva.

RESUMEN

Introducción: *Hericium erinaceus* (HE), a menudo conocido como Lion's Mane, es un hongo comestible que ha sido ampliamente explorado por sus múltiples funciones. El uso de este hongo en la medicina tradicional china se remonta a muchos años atrás, y ahora se está probando en el tratamiento del deterioro cognitivo y la enfermedad de Alzheimer, y enfermedades mentales como la depresión, la ansiedad y la esquizofrenia. **Métodos:** Seguimos la declaración PRISMA 2020 para revisiones sistemáticas. Las tres bases de datos seleccionadas fueron Worldcat®, Cochrane Library® y PubMed®. El 7 de marzo de 2022 se realizó una

búsqueda de artículos. Las descripciones de las fuentes de búsqueda fueron *Hericium erinaceus* AND (trastornos mentales OR deterioro cognitivo OR depresión OR ansiedad). "Inglés" fue el único filtro aplicado a las fuentes de datos. **Resultados:** Se incluyeron en la revisión tres ensayos controlados aleatorios doble ciego japoneses. Aunque los datos demostraron que HE puede ser útil en el tratamiento de síntomas de deterioro cognitivo y deterioro cognitivo moderado, no fue eficaz en el tratamiento de síntomas de depresión/ansiedad. **Conclusiones:** Se necesitan más estudios en otros países más allá de Japón, con una duración mínima de 12 semanas, ya que períodos más cortos no demuestran una mejoría significativa de los síntomas. La incorporación de HE en la dieta diaria de un paciente puede producir beneficios favorables al aliviar el deterioro cognitivo.

Palabras clave: *Hericium erinaceus*, trastornos mentales, disfunción cognitiva.

Como citar: Cortonesi PMM, Almeida LF, Pinheiro RMT, Périco CAM, Castaldelli-Maia JM. Use of *Hericium erinaceus* as a potential therapeutic of mental disorders: a systematic review. Debates em Psiquiatria, Rio de Janeiro. 2023;13:1-13. https://doi.org/10.25118/2763-9037.2023.v13.443

Conflito de interesses: declaram não haver

Fonte de financiamento: declaram não haver

Parecer CEP: não se aplica

Recebido em: 01/12/2022

Aprovado em: 25/12/2022

Publicado em: 11/02/2023

Introduction

There are several treatments that aim to control symptoms and promote life's quality, specific to each psychiatric disorder. Although the psychopharmacotherapy is largely used throughout whole world, it may often not fully control symptoms or lead to many adverse effects [1]. The research on innovative treatments for psychiatric disorders has been sparse for years, with a few exceptions, such as the use of orexin antagonists for insomnia [2]. However, in the last years, there has been

an increase in the numbers of studies in the area of psychedelic psychiatry, that investigate the effects of mescaline, dimethyltryptamine and psilocybin in the treatment of psychiatric disorders [3].

Before being placed in Schedule I of the UN Convention on Drugs in 1967, psychedelic drugs were widely used in psychiatry. Studies carried out before the prohibition indicated that its use was beneficial in patients who had the so-called "psychoneurotic" disorders. But that, however, was not so suitable for those with psychotic disorder or with a tendency to develop it. Since 2006, the number of studies on the use of psychedelics in non-psychotic psychiatric disorders has increased, bringing encouraging results that provided evidence of efficacy and safety [3].

With the advance of medical knowledge, many new therapeutics gain space and the possibility of applicability. Herbal medicine, for example, can be complementary to the treatment of some disorders, due to its low cost and fewer side effects [4]. Some psychoactive drugs are chemical substances that, in some way, alter the functioning of the mind, and that can be found also in some mushrooms [5].

The various activities of the edible fungus *Hericium erinaceus* (HE), also known as Lion's Mane, have been widely studied. This mushroom has a long history of usage in traditional Chinese medicine and is now being used to treat cognitive impairment and mental disorders such as depression and anxiety [6], Parkinson's disease [7], and Alzheimer's disease [8], in mice, specifically in Japan. Its use has apparently shown several health benefits such as antioxidative, antidiabetic, anticancer, anti-inflammatory, antimicrobial, antihyperglicemic, and hypolipidemic effects [4].

Bioactive compounds extracted from its fruiting body or mycelium of HE have been demonstrated to induce the synthesis of neurotrophic growth factor (NGF) and protect against neuronal cell death [4]. Recently, Saitsu et al. showed that oral intake of HE by humans improved cognitive functions and prevented neuronal deterioration. It is speculated that hericenones, one of the chemical compounds of this mushroom, have multiple effects on the brain neural networks and improve cognitive functions [9]. However, so far, only a few studies have investigated its use in mental disorders, and either each study only focused on a specific psychiatric disorder or these studies have established a direct causal relationship between exposure and outcome. Nevertheless, HE is used as

https://doi.org/10.25118/2763-9037.2023.v13.443

a nutritional supplement, and has not been compared or approved as a treatment to mental disorders.

This paper aims to conduct a systematic review of published studies on the use of HE in adults who have some kind of mental disorder and condense the results presented for each one of the mental disorders. Finally, this study will also discuss the direct relationship between the use of these mushroom derivatives and the results obtained in the studies.

Methods

A Systematic review studies - PRISMA 2020 model [10]. The chosen databases were PubMed®, Cochrane Library® and Worldcat®. The search for articles was carried out on the 7th of March 2022. The descriptors used for the search sources were: *Hericium erinaceus* AND (mental disorders OR cognitive impairment OR depression OR anxiety). The only filter used in the data sources was "English".

Data limit was not set for the studies, due the lack of information in the area. In the PubMed® database, 30 studies were found, in the Cochrane Library®, 5 studies and in Worldcat®, 75 studies. Overall, 110 studies were found. Of these 110 studies, 46 were repeated, therefore, at all, the title and abstract of 64 studies were read. The inclusion criteria were studies written in English performed on humans that analyze the effects of *Hericium erinaceus* in the treatment of psychological symptoms.

Were excluded studies that, for some reason, did not have a conclusion, literature review studies; animal studies; studies that evaluated a quality of different strains of H. erinaceus; and H. erinaceus as a treatment for any disease other than neuropsychiatric ones.

Of the 64 studies analyzed, 20 were excluded because they were review studies, 22 because they were animal studies, 11 that do not fit with no objective of the study (other use of the mushroom, other mushrooms, etc.) and 6 that, despite the use of H. erinaceus, addressed other diseases. 5 studies were selected for complete reading. Of these, two were excluded: one for not having a conclusion yet (study in open) and another for not having the article available for reading in full, even though we have contacted the author. In the end, 3 studies were included in the review.

Figure 1 shows the Preferred Report Items diagram for Systematic Reviews and Meta-Analyses (PRISMA), which summarizes the selection of studies.

The selection of studies was performed independently by the second author. The review, complete reading and data collection was performed by the first author. The information that we searched in the papers were: dose, time, tests applied, psychiatric symptoms presented by patients, total number of participants and outcome.

Results

In the 2010, Nagano et al. [11], in a randomized double-blind placebo-controlled trial, performed on 26 women with an age range of 41.3 ± 5.6 years, who presented depression and anxiety symptoms. The women in the control group ingested 4 cookies, each one with an amount of 0.5 g of *Hericium erinaceus* "flour", while those in the group placebo also ingested 4 cookies, without the *Hericium erinaceus*, for 4 weeks.

The scales used were the Japanese versions of the Kupperman Menopausal Index (KMI), Center of Depression for Epidemiological Studies (CES-D), Pittsburgh Sleep Quality Index (PSQI), and Undefined Complaints Index (ICI). The KMI scale (P = 0.09) did not show significant difference between the two groups, otherwise the CES-D scale indicated that the experimental group, after 4 weeks, scored less than when compared to the beginning of the study (P = 0.033), however, at the end, there was no significant difference between the groups.

The PSQI scale showed no significant difference between groups. The ICI scale showed a final mean rating lower than the average baseline (P = 0.004) in the HE group; regarding the "subscales", palpitation (P =0.032) and stimulus (P = 0.047), the final rating of the experimental group were significantly lower compared to the placebo group, since irritation (P = 0.076), anxiety (P = 0.067) and concentration (P = 0.09) trended to be lower in the experimental group than those who had placebo.

In another randomized double-blind placebo-controlled trial, Mori et al. [12] recruited 29 participants, men and women, aged between 50 and 80 years, with mild cognitive impairment. The study lasted a total of 22 weeks (2 weeks of preliminary trials, 16 weeks of HE ingestion, and 4 weeks of observation and follow-up). The intake was 250mg of 96% Yamabushitake. The scale used was the Revised Hasegawa Dementia Scale (HDS-R).

The study showed significant differences between the groups ($p < 0.001$) and between periods ($p < 0.001$) in the score of cognitive function. In the

https://doi.org/10.25118/2763-9037.2023.v13.443

8, 12, and 16 weeks of ingestion and 4 weeks of follow-up, the HE group had significantly higher scores compared to the placebo group, which means better cognition [13]. The Yamabushitake group scores increased with duration of ingestion, but during 4 weeks after the end of the 16-week intake, scores decreased significantly.

Saitsu et al. [9] realized a randomized, parallel-group comparative, double-blind, placebo-controlled study. The 31 participants showed cognitive impairment, all the participants were over 50 years old (average in HE 61.8 and in placebo 60.8), and ingested, for 12 weeks, 3.2g/day of HE. The tests used were Mini Mental State Examination (MMSE), Benton visual retention test, and Standard verbal paired-associate learning test (S-PA). In the MMSE the total scores of both groups increased with time, but only the HE group showed a significant increase comparing the tests before and after the study. Benton's test showed no improvement or significant difference between groups. The test S-PA also showed no difference or significant improvement in the groups ($P < 0.100$), nor did between groups.

The results obtained from the review are summarized in Table 1.

Discussion

As mentioned before, HE is a dietary supplement and, therefore, its use differs from a pharmacological treatment, but studies with these mushrooms have been growing in the last 5 years.

Nowadays, the mental disorders are being more related to an inflammatory systemic process, instead of an exclusive process of the central nervous system. The brain inflammation is highly correlated to the systemic inflammation, and this connection happens through pro-inflammatory cytokines (tumor necrosis factor α, interleukin-1, interleukin-6 and interferon- α and γ), this is mainly being observed in depression disorders [14].

The anti-inflammatory effects of the HE are important due to the systemic outcome, as the bioactive compounds found in it (hericenones and erinacines) improve neuro growth factor synthesis, therefore reducing the systemic inflammation and by that, controlling the depressive symptoms [4].

https://doi.org/10.25118/2763-9037.2023.v13.443

Studies also show that depression might be associated with brain-derived neurotrophic factor (BDNF), mainly by saying that some effective antidepressants increase BDNF mRNA in individuals that are under treatment for Major Depressive Disorder. In clinical studies with rats, the HE has shown to be an important promoter of nerve health by inducing the nerve growth factor, so it might as well have significant importance to the BDNF [15].

Other studies tell us that depressive disorders are correlated to depletion of serotonin, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis and alterations of the hippocampus [16]. Nerve damage present in rats were positively repaired with aqueous extract of HE (its effects are compared to those of vitamin B12), accelerating wound healing and treating peripheral nerve damage [17]. By that we could relate the use of HE, and its neurodegenerative effect, to repair the nerve injuries that possibly occur in depressive disorders [18].

The studies which were analyzed showed that the intake of *Hericium erinaceus* can provide significant improvements for mild cognitive impairment, cognitive impairment, and some improvement in the decrease of symptoms of depression and anxiety. Although the results are positive for depression/anxiety symptoms, it is shown that the use of HE is more effective to treat symptoms of cognitive impairment and mild cognitive impairment.

The dose of the intake and the time of ingestion are two important factors for the positive results: the studies that had the longer intake had better results. The number of patients analyzed in each study was similar to each other, but the doses of 250mg a day for 22 weeks are shown to be more effective than a higher dose of 2g a day but given for 4 weeks. Also, it is a fact that the dosage of 3.2g a day for the period of 12 weeks had a lower decrease of the symptoms than the lower dose with a period of 22 weeks. By that we can assume that lower doses applied for a longer period of time are showing better results than higher doses taken in less time.

In order to assume that the dietary supplementation with the *Hericium erinaceus* is beneficial for patients, more studies are still necessary, with a major number of participants. Despite that, the results of the studies suggest that the intake or the simple introduction of the *Hericium erinaceus* in a patient's regular diet might provide positive results by reducing the psychiatric symptoms and improving the quality of life in regard to the

https://doi.org/10.25118/2763-9037.2023.v13.443

patient's mental disorder. To the best of our knowledge, studies around indiscriminate use and potential risks of HE intake were not found. Although we can compare its abuse of substance to other mushroom chemicals like psilocybin, studies showed that it is safe to use in controlled dosage [19].

Referências

1. Fava GA, Tomba E, Bech P. Clinical pharmacopsychology: conceptual foundations and emerging tasks. Psychother Psychosom. 2017;86(3):134-40. https://doi.org/10.1159/000458458 PMID:28490035

2. Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic psychiatry's brave new world. Cell. 2020;181(1):24-8. https://doi.org/10.1016/j.cell.2020.03.020 - PMID:32243793

3. Rucker JJH, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology. 2018;142:200-18. https://doi.org/10.1016/j.neuropharm.2017.12.040 PMID:29284138

4. Chong PS, Fung ML, Wong KH, Lim LW. Therapeutic potential of *Hericium erinaceus* for depressive disorder. Int J Mol Sci. 2019;21(1):163. https://doi.org/10.3390/ijms21010163 PMID:31881712 - PMCID:PMC6982118

5. Inanaga K. Amycenone, a nootropic found in *Hericium erinaceum*. Personal Med Universe. 2012;1(1):13-7. https://doi.org/10.1016/j.pmu.2012.05.003

6. Ryu S, Kim HG, Kim JY, Kim SY, Cho KO. *Hericium erinaceus* extract reduces anxiety and depressive behaviors by promoting hippocampal neurogenesis in the adult mouse brain. J Med Food. 2018;21(2):174-80. https://doi.org/10.1089/jmf.2017.4006 PMID:29091526

7. Kuo HC, Lu CC, Shen CH, Tung SY, Hsieh MC, Lee KC, Lee LY, Chen CC, Teng CC, Huang WS, Chen TC, Lee KF. *Hericium erinaceus* mycelium and its isolated erinacine A protection from MPTP-induced

neurotoxicity through the ER stress, triggering an apoptosis cascade. J Transl Med. 2016;14:78. https://doi.org/10.1186/s12967-016-0831-y - PMID:26988860 PMCID:PMC4797317

8. Tsai-Teng T, Chin-Chu C, Li-Ya L, Wan-Ping C, Chung-Kuang L, Chien-Chang S, Chi-Ying HF, Chien-Chih C, Shiao YJ. Erinacine A-enriched *Hericium erinaceus* mycelium ameliorates Alzheimer's disease-related pathologies in APPswe/PS1dE9 transgenic mice. J Biomed Sci. 2016;23:49. https://doi.org/10.1186/s12929-016-0266-z - PMID:27350344 - PMCID:PMC4924315

9. Saitsu Y, Nishide A, Kikushima K, Shimizu K, Ohnuki K. Improvement of cognitive functions by oral intake of *Hericium erinaceus*. Biomed Res. 2019;40(4):125-31. https://doi.org/10.2220/biomedres.40.125 - PMID:31413233

10. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. https://doi.org/10.1136/bmj.n160 - PMID:33781993 PMCID:PMC8005925

11. Nagano M, Shimizu K, Kondo R, Hayashi C, Sato D, Kitagawa K, Ohnuki K. Reduction of depression and anxiety by 4 weeks *Hericium erinaceus* intake. Biomed Res. 2010;31(4):231-7. https://doi.org/10.2220/biomedres.31.231 - PMID:20834180

12. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. Phytother Res. 2009;23(3):367-72. https://doi.org/10.1002/ptr.2634 - PMID:18844328

13. Imai Y, Hasegawa K. The revised Hasegawa's Dementia Scale (HDS-R): evaluation of its usefulness as a screening test for dementia. J Hong Kong Coll Psychiatr. 1994; 4:20-24.

https://www.easap.asia/index.php/advanced-search/item/503-v4n2-9402-p20-24

14. Kohler O, Krogh J, Mors O, Benros ME. Inflammation in depression and the potential for anti-inflammatory treatment. Curr Neuropharmacol. 2016;14(7):732-42. https://doi.org/10.2174/1570159X14666151208113700 PMID:27640518 - PMCID:PMC5050394

15. Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors. 2004;22(3):123-31. https://doi.org/10.1080/08977190410001723308 - PMID:15518235 PMCID:PMC2504526

16. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C, Camus V. Neuroinflammation and depression: a review. Eur J Neurosci. 2021;53(1):151-71. https://doi.org/10.1111/ejn.14720 PMID:32150310

17. Wong KH, Naidu M, David RP, Bakar R, Sabaratnam V. Neuroregenerative potential of lion's mane mushroom, *Hericium erinaceus* (Bull.: Fr.) Pers. (higher Basidiomycetes), in the treatment of peripheral nerve injury. Int J Med Mushrooms. 2012;14(5):427-46. https://doi.org/10.1615/IntJMedMushr.v14.i5.10 - PMID:23510212

18. Li IC, Lee LY, Tzeng TT, Chen WP, Chen YP, Shiao YJ, Chen CC. Neurohealth properties of *Hericium erinaceus* mycelia enriched with erinacines. Behav Neurol. 2018;2018:5802634. https://doi.org/10.1155/2018/5802634 - PMID:29951133 PMCID:PMC5987239

19. Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, Mennenga SE, O'Donnell K, Owens LT, Podrebarac S, Rotrosen J, Toningan JS, Worth L. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry. 2022;79(10):953-62. https://doi.org/10.1001/jamapsychiatry.2022.2096 PMID:36001306 - PMCID:PMC9403854

Tabela 1. The results obtained from the review

Table 1: Results.

Study	Dose	Intake period	Tests	Psychic symptoms	Final N	Outcome
Reduction of depression and anxiety by 4 weeks Hericium erinaceus intake Nagano et al. 2010 Japan	2g/day	4 weeks	KMI, CES-D, PSQI, ICI	Anxiety and depression symptoms	26	KMI (P = 0.09) no significant difference of between the two groups CES-D (0.033) no significant difference of between the two groups with respect to a change before and after the trial PSQI no significant difference of between the two groups ICI (P = 0.004) significant improvement in the HE group and improvement in symptoms such as palpitation (P = 0.032) and incentive (0.047) between the two groups.
Improving Effects of the Mushroom Yamabushitake (Hericium erinaceus) on Mild Cognitive Impairment: A Double-blind Placebo-controlled Clinical Trial Mori et al. 2009 Japan	250mg/day	22 weeks	HDS-R	Cognitive function	29	Significant between-group differences($p < 0,001$) and between-period differences ($p < 0,001$) Significantly increased scores with the duration of intake of the HE, but during the 4 weeks after the termination of the 16 week intake, the scores decreased significantly.
Improvement of cognitive functions by oral intake of Hericium erinaceus Saitsu et al. 2019 Japan	3,2g/day	12 weeks	MMSE, S-PA, Benton Visual Retention Test	Cognitive impairment	31	MMSE significant increase in the HE group Benton no significant difference of between the 2 groups S-PA no statistically significant changes in both groups, and no significant differences between the two groups.

Kupperman Menopausal Index (KMI), Center of Depression for Epidemiological Studies (CES-D), Pittsburgh Sleep Quality Index (PSQI), Indefined Complaints Index (ICI), Revised Hasegawa Dementia Scale (HDS-R), Mini-Mental State Examination (MMSE) and Standard verbal paired-associate learning test (S-PA).

https://doi.org/10.25118/2763-9037.2023.v13.443

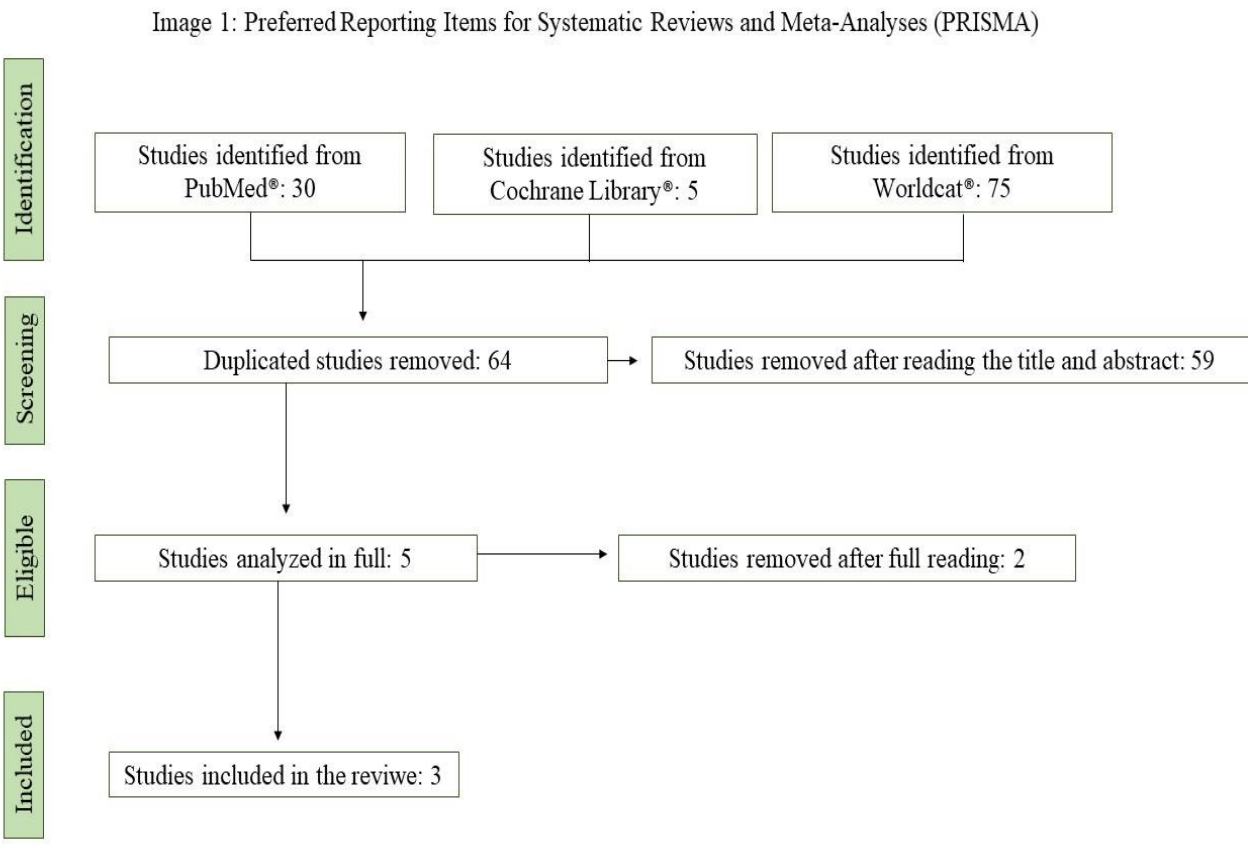

Figura 1. Preferred Report Items diagram for Systematic Reviews and Meta-Analyses (PRISMA)

https://doi.org/10.25118/2763-9037.2023.v13.443