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Efficacy of Mitochondrial-Based Interventions in the Management of Clinical Depression—A Systematic Review

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Abstract: Background: Depression, a multifaceted mental health condition, necessitates a multidimensional approach to treatment. This study aimed to elucidate the potential efficacy of various mitochondrial interventions, ranging from pharmacological treatments to lifestyle modifications, in alleviating depressive symptoms and enhancing overall mental well-being and assess the diverse range of mitochondrial assessments for managing depression by synthesizing findings from selected studies. **Methods:** A systematic compilation of studies, employing observational, interventional, and animal-based designs, was undertaken to elucidate the intricate relationship between mitochondrial function and depression as well as depressive signs and symptoms. The PRISMA guidelines were employed for conducting this review and a specific set of selection criterion were formulated by a team of reviewers for selection of relevant papers. **Results:** The synthesized results from the 21 selected papers highlighted the potential of these interventions to target diverse aspects of depression. Hyperbaric oxygen therapy and psychotherapy demonstrated significant reductions in depression and anxiety scores, with hyperbaric oxygen therapy particularly effective in improving nerve function and daily living activities. Whole-body cryotherapy displayed substantial improvements in depressive symptoms and quality of life. Frequent sauna bathing exhibited a lower risk of depressive symptoms in males. Dietary patterns, including Paleolithic and Mediterranean diets, showcased potential protective effects against depression, anxiety, and stress. The ketogenic diet revealed promise in ameliorating depression and psychosis symptoms alongside positive metabolic changes. Fasting interventions, though challenging, were associated with lower anxiety and depression levels without increased fatigue. Bright white light therapy enhanced remission rates and reduced depression scores in bipolar depression. Probiotic supplementation exhibited potential in reducing depression scores and improving metabolic markers, although further investigation is warranted. **Conclusion:** The diverse array of interventions explored in this study underlines the multifaceted nature of depression treatment. While these findings offer hope for more personalized and effective approaches, it is imperative to consider the variability in study designs, sample sizes, and methodologies among the selected papers. The mechanisms underlying the observed effects remain partially understood, emphasizing the need for continued mechanistic research. This study sets the stage for future investigations and clinical practices, showcasing the potential of various interventions in mitigating the challenges posed by depression and paving the way for more effective treatment strategies.

Keywords: depression; mental health; interventions; hyperbaric oxygen therapy; cryotherapy; dietary patterns; fasting; light therapy; probiotics; exercise; metabolic markers

INTRODUCTION

With the ability to alter physiological responses to changing environmental conditions, mitochondrial entities have ushered in major adaptive and evolutionary benefits for human populations [1]. As a crucial link between environmental factors and biological stress responses, mitochondria have drawn attention for their receptivity to short-term physiological stressors, which can have significant effects on the overall health and functionality of mitochondria [2]. It is intriguing that experimental protocols involving acute physiological stressors have shown promising results in disease prevention and therapeutic approaches, particularly those that carefully combine various

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hormetic and evolutionary interventions [3–5]. These interventions are relevant in terms of both individual and public health due to their cost-effectiveness.

In the area of cellular dynamics, mitochondria show noteworthy mobility. This feature has been seen in neurons in vivo and in a wide range of cell lines in vitro [6]. This mobility plays a crucial part in maintaining cellular activity by enabling effective calcium buffering and ATP provisioning at specific demand areas [6]. Additionally, it plays a crucial role in cellular differentiation and division, ensuring normal genetic inheritance, and enhancing the effectiveness of embryological development, neurodevelopment, and immune responses [7]. The production of cytosolic reactive oxygen species (ROS), calcium balance, and adenosine monophosphate protein kinase (AMPK) signalling are only a few examples of the variables that are necessary for the survival and functional integrity of mitochondria [8].

The complex network of cytoskeletal components and cellular membranes is used to tightly connect and adeptly transport mitochondria across the cellular milieu [9]. A variety of anchoring proteins help this transport mechanism along; one in particular, syntaphilin, a specialised anchoring protein found in nerve cells, is important for maintaining mitochondrial density and survival [6–8]. Within most cell types, the distribution of mitochondrial density is more evident close to the endoplasmic reticulum (ER) and in perinuclear areas. In synaptic regions, neurons in particular show increased mitochondrial density, ensuring the energy support and effectiveness of neural signal transmission [5]. ROS, which are the main cause of the cumulative oxidative stress placed on mitochondria, have a substantial impact on the lifetime of neurons. Syntaphilin appears in this context as a precaution, in charge of the removal of damaged mitochondria. In order to prevent axonal degeneration, it is essential to effectively remove these damaged entities [10].

Recent years have seen a substantial increase in interest in the complex relationship between neurological illnesses and mitochondrial malfunction, which presents a prospective target for therapeutic approaches [11–15]. As essential organelles in charge of cellular energy production, regulation, and signalling, mitochondria are crucial for maintaining neuronal function and general brain health. Neurodegenerative diseases like Parkinson's disease and Alzheimer's disease as well as neuropsychiatric conditions like schizophrenia and bipolar disorder have all been linked to dysregulation of mitochondrial activity [12]. New treatment approaches that target mitochondrial malfunction have evolved as our understanding of mitochondrial biology deepens [13]. These treatments cover a wide range of strategies, such as drugs that alter mitochondrial dynamics, promote mitochondrial biogenesis, or lessen oxidative stress [11–13]. The effectiveness and safety of these mitochondrial-based therapies must be thoroughly evaluated given the complexity and diversity of neurological illnesses [15].

Bar-Yosef et al [16] employed an observational approach to explore the feasibility of employing mitochondrial function profiles for personalized drug prediction in schizophrenia (SZ) and bipolar disorder (BD) patients. Their assessments involving mental and global state evaluations, alongside analyses of mitochondrial respiration parameters and function-related proteins, revealed drug-specific effects on mitochondria in healthy controls and untreated patients. The intriguing correlation between in-vitro and short-term in-vivo treatment effects in responders underscored the potential predictive utility of mitochondrial assessments. Furthermore, their finding that long-term treatment normalized mitochondria-related parameters suggests the promise of tailored interventions for patients with psychosis. Berk et al [17] conducted a randomized controlled trial (RCT) to assess the efficacy of N-acetylcysteine (NAC) and nutraceutical treatments in bipolar depression. Their comprehensive evaluation of clinical and functioning variables highlighted the sustained benefits of combined treatment even beyond the intervention period. The superiority of the combined treatment group in terms of various assessment scores, along with the observed gastrointestinal symptoms in the NAC group, underlined the potential of tailored interventions and demonstrated the importance of considering multifaceted outcomes. Castora et al [18] pursued a prospective approach to unravel the effects of mitochondrial gene expression changes on mitochondrial function in Alzheimer's disease (AD) brains. Through RT2-PCR arrays and intricate analyses involving gene expression, pathway analysis, and mathematical modeling, they identified a set of significant genes associated

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with various aspects of mitochondrial function and AD pathology. The study's holistic perspective deepened our understanding of the genetic basis of mitochondrial dysfunction in AD and paved the way for targeted therapeutic interventions. Da Silva et al [19] adopted an observational methodology to investigate mitochondrial complex function and lactate/pyruvate levels in individuals at clinical high risk for psychosis (CHR) compared to healthy controls. Their assessments of mitochondrial function and associations with prodromal symptoms, microglial activation, and glutathione levels shed light on potential markers and pathways underlying early stages of psychosis. The nuanced findings highlighted the complexity of mitochondrial involvement in CHR and its relevance to disease progression. Deng et al [20], through an animal-based study, unraveled the interactions between pink1/parkin and mitochondrial fusion/fission machinery in Drosophila. Their meticulous assessments of mitochondrial morphology, fusion, and fission revealed a regulatory role of the pink1/parkin pathway in maintaining mitochondrial integrity. The identification of distinct mitochondrial phenotypes in mutants and the exacerbation of the pink1-null phenotype by a heterozygous drp1 mutation added depth to our understanding of mitochondrial dynamics in neurodegenerative conditions. Kikuchi et al [21] employed observational measurements of 8-OHdG/8-OHG levels in serum and cerebrospinal fluid (CSF) to explore oxidative cellular damage markers in Parkinson's disease (PD) and multiple system atrophy (MSA) patients. Their assessments revealed systemic DNA/RNA oxidation in neurodegenerative diseases, with a gender-specific oxidative stress difference in PD. The study underscored the commonality of oxidative stress across neurodegenerative conditions and hinted at the potential implications of gender in disease progression. Manczak et al [22] delved into animal-based assessments to investigate the protective effects of reduced Drp1 expression against amyloid beta (Aβ)-induced mitochondrial and synaptic toxicities in Alzheimer's disease (AD) progression. Through molecular analyses and assays, they unveiled the potential of Drp1 reduction to mitigate Aβ-related toxicities and improve mitochondrial function. Their findings provided mechanistic insights into the interplay between mitochondrial dynamics and AD pathology, offering prospects for novel therapeutic strategies. Wen et al [23] conducted animal-based research to evaluate the effects of chronic unpredictable stress (CUS), exercise, and fluoxetine on mitochondrial function and serotonin levels in a rat model of depression. Their comprehensive assessments ranging from behavioral evaluations to analyses of mitochondrial function and neurotransmitter levels illuminated the potential of exercise and pharmacological interventions to modulate mitochondrial health and neuronal function. The study shed light on the intricate relationship between stress, mitochondrial function, and depression, offering potential avenues for interventions to counteract the detrimental effects of stress on the brain.

An essential part of the intricately orchestrated process of biomass synthesis is played by aerobic glycolytic reactions that appear in non-immune cells [24]. This complex phenomenon shows dualistic implications. Localised aerobic glycolysis, which acts as an anabolic conduit to promote cellular repair, development, and division, is one way that it helps the body resist oxidative stress [25–27]. The Warburg effect, which is the long-term manifestation of aerobic glycolysis, can cause cell swelling, metabolic disturbances, compromised ATP levels, and, depending on the cell type, either apoptosis or necrosis, or even potentially cancerous transformations [8,28].

This systematic review seeks to provide a comprehensive evaluation of the existing literature on mitochondrial-based interventions for clinical depression. By synthesizing evidence from diverse studies, we aim to elucidate the potential benefits, underlying mechanisms, and limitations of these interventions. This review also aims to clarify the possible advantages, methods of action, and restrictions of various mitochondrial therapies by methodically analysing a wide range of data spanning both human trials and animal models.

MATERIALS AND METHODS

Review protocol

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) procedure [29] was followed in this systematic review, assuring a thorough and open approach to literature selection and synthesis. The goal of the review was to thoroughly examine the present level of

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knowledge on treatments that target mitochondrial function when applied to depression. The rigorous planning and execution of the procedure ensured methodological rigour, openness, and methodical analysis, ultimately bringing significant new knowledge to the field of neurological research, the schematic of which have been elucidated in Figure 1.

PECO protocol

This investigation was further guided by a well-defined PECO (Population, Exposure, Comparator, Outcome) protocol to formulate a focused research question and systematically select relevant studies for inclusion. The Population (P) in this context included individuals diagnosed with clinical depression, encompassing diverse demographic characteristics. The Exposure (E) pertained to various mitochondrial-based interventions, encompassing interventions such as hyperbaric oxygen therapy, whole-body cryotherapy, evolutionary-based diets (e.g., paleo diet, ketogenic diet), intermittent fasting, circadian-based interventions (e.g., light therapy, melatonin), fermented drinks, fermented foods, intermittent hypercapnia, intermittent hypoxia, and intermittent exercise, each of which was assessed for their potential impact on clinical depression. The Comparator (C) component encompassed control conditions, placebo interventions, or alternative treatments. Finally, the Outcome (O) focused on changes in depression-related outcomes, which could include standardized measures of depression severity, anxiety, mood, psychological well-being, quality of life, and functional improvement. The PECO protocol facilitated the systematic retrieval of studies that met these specific criteria, enabling a rigorous assessment of the efficacy of various mitochondrial-based interventions in managing clinical depression.

Database search protocol

To ensure the thorough retrieval of pertinent research, the reviewers adopted an extensive database search technique across eight scientific databases. To increase the search's sensitivity and precision, the search method used both MeSH (Medical Subject Headings) keywords and Boolean operators. As represented in Table 1, to combine search phrases and concepts successfully, the Boolean operators "AND" and "OR" were wisely used. The goal of the search approach was to locate papers that investigated the connection between mitochondrial therapies and depression and depressive signs and symptoms. To establish uniform and targeted terminology across the datasets, MeSH keywords were used.

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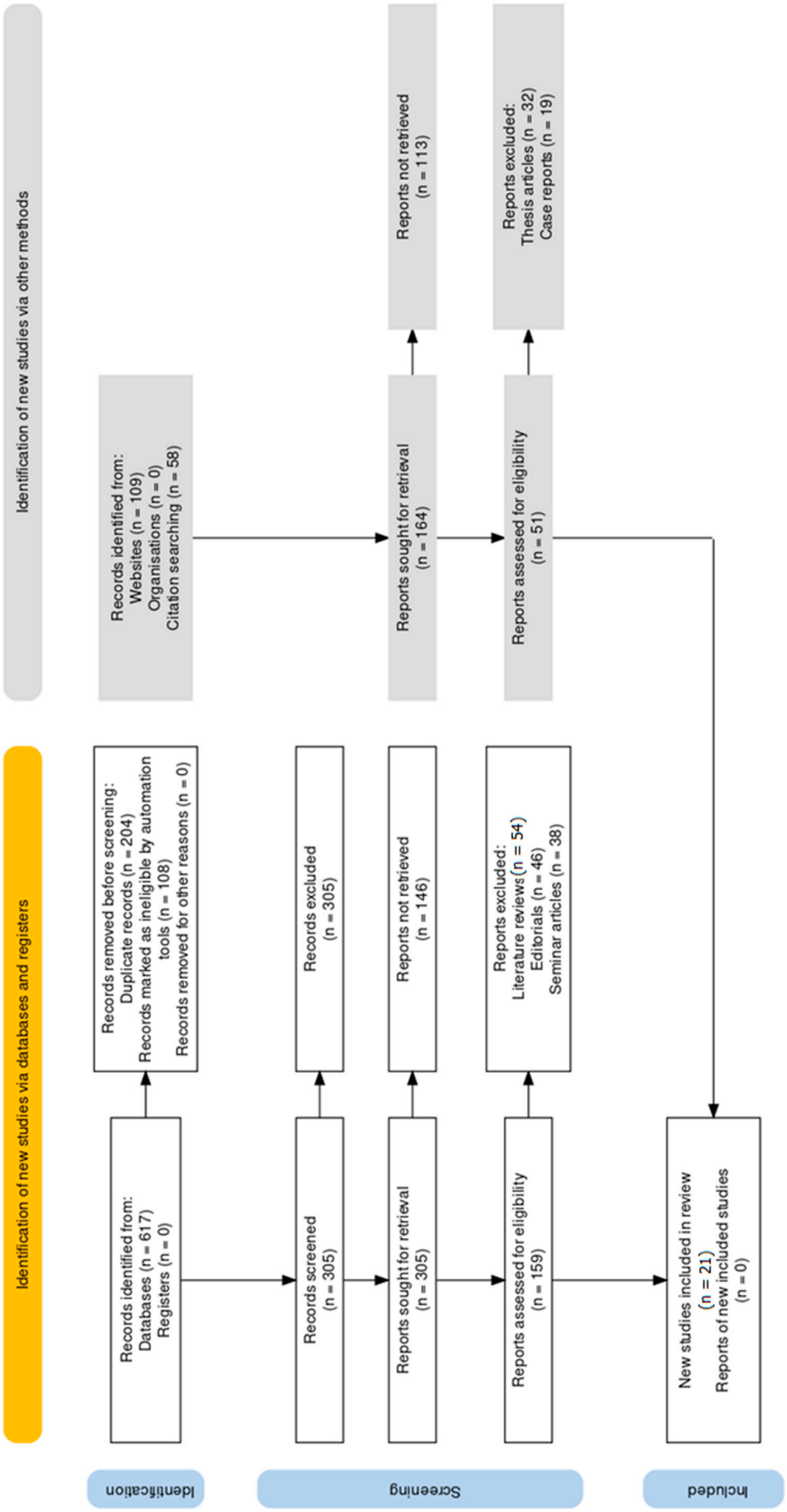

Figure 1. Flowchart representation of the study selection schematics for this review.

Table 1. Search strategy across the different databases.

Database	Intermittent Cold Exposure	Intermittent Heat Exposure	Evolutionary Based Foods	Intermittent Fasting	Circadian-Based Interventions	Fermented Drinks	Fermented Foods	Intermittent Hypercapnia	Intermittent Hypoxia	Intermittent Exercise
PubMed	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")
ScienceDirect	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")
IEEE Xplore	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR	("sauna" OR "infrared sauna") AND ("depression"	("paleo diet" OR "paleolithic diet" OR "ketogenic	("intermittent fasting" OR "caloric restriction" OR	("bluelight therapy" OR "melatonin" OR "bright light	("probiotic drinks" OR "kefir" OR "kombucha"	("fermented foods" OR "miso" OR "natto" OR	("breath holding" OR "hypercapnia") AND	("ihht" OR "altitude training" OR "breath	("hiit" OR "high intensity interval training" OR

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	"cryochamber") AND ("depression" OR "clinical depression")	OR "clinical depression")	diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	"fasting") AND ("depression" OR "clinical depression")	therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	"Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("depression" OR "clinical depression")	holding") AND ("depression" OR "clinical depression")	"tabata" OR "interval training") AND ("depression" OR "clinical depression")
PsycINFO	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")
Web of Science	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression"	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")

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							OR "clinical depression")			
Embase	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")
CINAHL	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")
Scopus	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression"	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy"	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR	("breath holding" OR "hypercapnia") AND ("depression"	("ihht" OR "altitude training" OR "breath holding") AND	("hiit" OR "high intensity interval training" OR "tabata" OR "interval

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	("depression" OR "clinical depression")		diet") AND ("depression" OR "clinical depression")	OR "clinical depression")	OR "blue light blocker") AND ("depression" OR "clinical depression")	AND ("depression" OR "clinical depression")	"strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	OR "clinical depression")	("depression" OR "clinical depression")	training") AND ("depression" OR "clinical depression")
Google Scholar	("ice bath" OR "cold plunge" OR "whole body cryotherapy" OR "cryochamber") AND ("depression" OR "clinical depression")	("sauna" OR "infrared sauna") AND ("depression" OR "clinical depression")	("paleo diet" OR "paleolithic diet" OR "ketogenic diet" OR "carnivore diet") AND ("depression" OR "clinical depression")	("intermittent fasting" OR "caloric restriction" OR "fasting") AND ("depression" OR "clinical depression")	("bluelight therapy" OR "melatonin" OR "bright light therapy" OR "light therapy" OR "blue light blocker") AND ("depression" OR "clinical depression")	("probiotic drinks" OR "kefir" OR "kombucha" OR "ayran" OR "buttermilk") AND ("depression" OR "clinical depression")	("fermented foods" OR "miso" OR "natto" OR "Tempeh" OR "skyr" OR "strained yoghurt" OR "greek yoghurt") AND ("depression" OR "clinical depression")	("breath holding" OR "hypercapnia") AND ("depression" OR "clinical depression")	("ihht" OR "altitude training" OR "breath holding") AND ("depression" OR "clinical depression")	("hiit" OR "high intensity interval training" OR "tabata" OR "interval training") AND ("depression" OR "clinical depression")

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Inclusion and exclusion criterion

Inclusion Criteria:

1. **Study Type:** Peer-reviewed, original research studies, including randomized controlled trials (RCTs), clinical trials, observational studies, and cohort studies, were included. These studies should provide empirical data on the effects of mitochondrial-based interventions on clinical depression.
2. **Participants:** Studies involving human participants of any age and gender, diagnosed with clinical depression according to recognized diagnostic criteria (e.g., DSM-5, ICD-10), were considered.
3. **Intervention Categories:** Studies investigating interventions falling within the following categories were included:
    - Intermittent cold exposure
    - Intermittent heat exposure
    - Evolutionary-based foods
    - Intermittent fasting
    - Circadian-based interventions
    - Fermented drinks
    - Fermented foods
    - Intermittent hypercapnia
    - Intermittent hypoxia
    - Intermittent exercise
4. **Outcome Measures:** Studies that reported relevant clinical outcome measures for depression, such as scores on standardized depression rating scales (e.g., Hamilton Depression Rating Scale, Beck Depression Inventory) or clinical diagnosis of depression by a qualified healthcare provider.

Exclusion Criteria:

1. **Publication Type:** Review articles, meta-analyses, conference abstracts, editorials, letters, commentaries, and non-peer-reviewed sources were excluded.
2. **Studies without relevant data:** Studies that do not provide specific data or information related to the efficacy of mitochondrial-based interventions in the management of clinical depression will be excluded.
3. **Studies with irrelevant interventions:** Studies investigating interventions not falling within the specified categories were excluded to maintain the review's focus on mitochondrial-based interventions.
4. **Studies without targeted outcomes:** Studies that did not include clinical depression as an outcome measure will be excluded, as they did not align with the review's objective.

Data extraction form

The data extraction protocol for this systematic review encompassed the systematic retrieval of critical study details from selected articles. This included the meticulous recording of study identification, participant demographics, intervention particulars, outcome measures, reported findings, statistical methodologies employed, and study conclusions. Furthermore, a quality assessment, utilizing established assessment tools, was conducted to gauge the methodological rigor of the included studies. To ensure consistency and reliability in the data extraction process, an interrater reliability test was implemented. In this test, two independent reviewers extracted data from a subset of studies, and the Cohen's Kappa coefficient was employed to quantify the level of agreement. The aim was to achieve substantial agreement (above 0.60), thereby enhancing the precision and credibility of the data collected and ultimately bolstering the validity of the review's outcomes.

Bias assessment protocol

The Newcastle-Ottawa Scale (NOS) [30] was used in the bias assessment protocol for this systematic review as shown in Figure 2.

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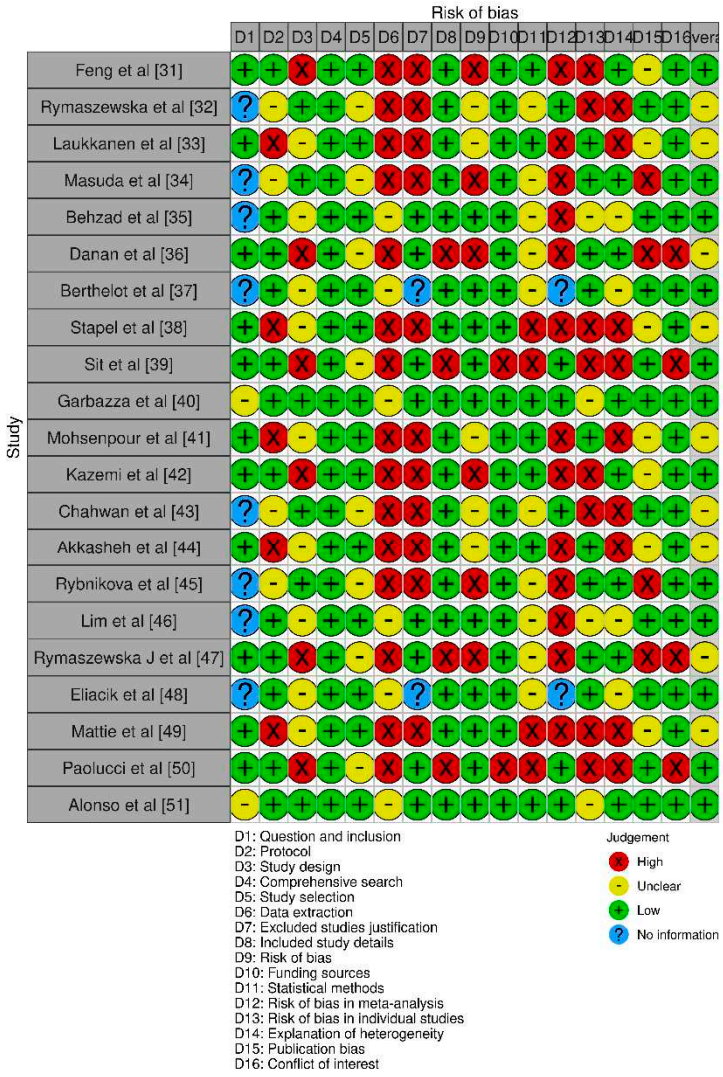

Figure 2. Bias assessment across the studies included in this review.

RESULTS

A thorough search across databases and registrations was used to find the first potential research, and it produced a total of 617 records. The pool for further consideration was simultaneously reduced by 204 duplicate records being eliminated and 108 records being reported as ineligible by automated techniques. Additionally, 58 items were recovered using citation searching, and 109 additional entries were found online. Following the initial identification phase, the screening procedure got under way, during which 305 records were carefully examined. 159 reports were evaluated for eligibility, and 305 data were eliminated based on preset standards. Alternative techniques were used in addition to database and register searches to find pertinent studies. Numerous sources, including websites, citation searches, and organisational sources were used in a thorough search for reports, which helped to identify all of the studies. Ultimately, 21 papers [31–51] were included for thorough assessment as a result of the meticulous screening procedure.

A thorough summary of numerous studies [31–51] looking into the impact of various therapies on psychological and physiological markers associated with depression and related illnesses is provided in Table 2, whereas Table 3 summarizes the key findings from the collection of studies [31–51] investigating various interventions and their effects on parameters associated with depression and psychological well-being. These studies employed diverse assessments to evaluate the impact of

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these interventions, ultimately shedding light on potential avenues for managing and improving mental health.

An RCT was undertaken by Feng et al. [31] to examine the effects of hyperbaric oxygen (HBO) therapy on psychological issues like sadness and anxiety. The Hamilton Depression (HAMD) scale was used to measure depression. This RCT's comprehensive evaluation of HBO therapy's effects on psychological well-being gave us important new understandings about its therapeutic potential. In order to evaluate the effectiveness of Whole-Body Cryotherapy (WBC) on mood, quality of life, and biochemical parameters in people experiencing depressive episodes, Rymaszewska et al [32] undertook a prospective RCT. To assess depression, they used the Beck Depression Inventory-II (BDI-II). With the help of controlled experiments, this study's methodology was able to shed light on the potential benefits of using intermittent, brief exposure to extremely low temperatures to treat depression. A prospective cohort study approach was used by Laukkanen et al [33] to examine the relationship between the frequency of sauna use and the risk of depressive symptoms. Their attention to a particular aspect of lifestyle, sauna use, offers insightful information about possible preventative strategies against depression. To further understand the effects of repeated thermal therapy on individuals with mild depression, Masuda et al [34] conducted an RCT. They used a variety of ratings to gauge factors like hunger and relaxation. They were able to evaluate the effect of thermal therapy on subjective symptoms related to depression because to this study's design. Behzad et al. [35] carried out a cross-sectional study to look into the relationship between Mediterranean and Palaeolithic diets and psychological illnesses in adult women. They evaluated their methods based on diet scores. They were able to investigate the link between nutrition and psychological well-being because to this study's approach. In order to evaluate the effects of a ketogenic diet on persons with severe, persistent mental illness, Danan et al [36] conducted a retrospective analysis. They gauged depression using the Hamilton Depression Rating Scale. Despite being retrospective, this study sheds light on how dietary modifications could affect mental health. In order to ascertain the efficacy of fasting therapies on stress, anxiety, and depression, Berthelot et al [37] carried out a meta-analysis. The levels of stress, anxiety, and depression were assessed using their approach. They made insightful conclusions on how fasting affects mental health by combining the results of several studies. In order to evaluate the effects of fasting on metabolic markers, stress hormones, and mood in depressed inpatients, Stapel et al [38] used a prospective experimental design. They measured stress systems and metabolic factors. A thorough analysis of the physiological and psychological effects of fasting in a therapeutic context was made possible by this study design. An RCT was undertaken by Sit et al. [39] to ascertain the bipolar depression remission rates, depression symptom levels, mood polarity switch rates, and sleep quality. They evaluated their methods by evaluating both sleep quality and depressive symptoms. They offered solid proof of the effectiveness of strong white light therapy through stringent control and randomization. In order to determine the effectiveness and safety of Bright Light Therapy (BLT) for postnatal depression (PND), Garbazza et al [40] undertook a single-blind RCT. Using the EPDS score, they evaluated the severity of depression. This RCT's controlled study of BLT as a viable PND intervention was made possible. An RCT was undertaken by Mohsenpour et al. [41] to look at how milk kefir drinks affected people with Non-Alcoholic Fatty Liver Disease (NAFLD) who were depressed. The BDI-II-Persian depression assessment was the main topic of their technique evaluation. They were able to investigate the effects of dietary treatments on depression in a particular patient population because to this RCT design. In order to examine the impact of probiotic and prebiotic supplements on depression scores and metabolic parameters in individuals with Major Depressive Disorder (MDD), Kazemi et al [42] conducted a double-blind RCT. They used the BDI to evaluate depression ratings. They investigated the possible advantages of probiotics in treating depression symptoms in MDD through this rigorous experimental methodology. In order to ascertain the impact of probiotic supplements on depressive symptoms in patients with mild to severe depression, Chahwan et al [43] conducted an RCT where the assessments of their methods included indicators of vulnerability and symptoms. They were able to research the potential psychological advantages of probiotic supplementation because to this clinical trial methodology. In order to ascertain the effects of probiotic intake on depressive symptoms and metabolic status in individuals

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with Major Depressive Disorder (MDD), Akkasheh et al [44] undertook a randomised, double-blind RCT. They evaluated both metabolic state and symptoms as part of their methodology. This study's approach made it possible to thoroughly examine how probiotics affect MDD patients' metabolic and mental health. In an experimental investigation, Rybnikova et al. [45] investigated the inhibitory effects of hypoxia preconditioning on the emergence of depressed states in rat models. As part of their technique, they evaluated depressive behavioural reactions. The use of animals in this study allowed for controlled testing to investigate any potential antidepressant benefits of hypoxia preconditioning. To ascertain the impact of hyperbaric oxygen (HBO) therapy on TBI-induced depressive-like behaviour and neuroinflammation, Lim et al [46] carried out an experimental investigation utilising a rat model. They evaluated neuroinflammation and behaviour. The design of this animal study shed light on the possible therapeutic effects of HBO therapy on depression-like behaviour brought on by TBI. A clinical experiment was carried out by Rymaszewska J et al [47] to evaluate the effectiveness of WBC as an additional treatment for anxiety and depressive disorders. They used WBC and psychopharmacotherapy as part of their methodology. The evaluation of WBC as an alternative strategy to conventional therapies for mood and anxiety disorders was made possible by the clinical trial design. In order to determine variations in antenatal stressful life events, parenting style, family functioning, depression, and anxiety in mothers of children with breath-holding episodes (BHS), Eliacik et al. [48] conducted a case-control trial. Their methodology evaluated prenatal activities and family dynamics. The goal of this study's design was to investigate the psychosocial aspects of raising children with BHS. In an observational study, Mattie et al [49] compared mothers of children with breath-holding spells (BHS) and depressive symptoms (DS) against mothers of control children to determine how stressed out the mothers were. They evaluated coping strategies and parental stress. Insights regarding the particular difficulties faced by moms of children with BHS and DS were gained through this observational design. Paolucci et al.'s experimental investigation [50] examined how high-intensity interval training (HIIT) affected pro-inflammatory cytokines, depression, anxiety, and perceived stress. They evaluated pro-inflammatory cytokines and mental wellness. This study's methodology made it possible to examine exercise as a potential treatment for mental illness and give insight on the ideal level of exercise intensity. An experimental investigation was undertaken by Alonso et al [51] to determine the effects of an 8-week HIIT exercise on body composition and depression symptoms while confined at home. They evaluated depressed symptoms and body composition. The purpose of this study was to investigate the potential advantages of HIIT as an accessible intervention for enhancing physical and mental health during confinement.

Table 2. Selected papers and their demographic characteristics.

Study	Aims	Study Design	Methodology Assessed	Type of Mitochondrial Intervention Assessed
Feng et al [31]	To investigate the effects of HBO on psychological problems and nerve function, especially on depression and anxiety in patients.	RCT	Hamilton Depression (HAMD) scale,	Hyperbaric oxygen (HBO) therapy
Rymaszewska et al [32]	To assess the efficacy of repetitive short exposure to extremely low temperatures on mood, quality of life, and biochemical measures in people diagnosed with depressive episodes undergoing pharmacological treatment.	Prospective RCT	Beck Depression Inventory-II (BDI-II),	Whole-body cryotherapy (WBC)
Laukkanen et al [33]	To assess the association between frequency of sauna bathing and the risk of depressive symptoms in a population-based study.	Prospective cohort study	Sauna bathing frequency	Sauna bathing
Masuda et al [34]	To clarify the effects of repeated thermal therapy in mildly depressed patients with appetite loss and subjective complaints.	RCT	Scores (hunger, relaxation, etc.)	Thermal therapy (far-infrared ray dry sauna)
Behzad et al [35]	To investigate the association of Paleolithic and Mediterranean diets with psychological disorders in a sample of adult women.	Cross-sectional study	Diet scores (Paleolithic, Mediterranean)	Dietary patterns (Paleolithic, Mediterranean)
Danan et al [36]	To assess the effects of a ketogenic diet on adults with severe, persistent mental illness whose symptoms were poorly controlled despite intensive psychiatric management.	Retrospective analysis	Hamilton Depression Rating Scale,	Ketogenic diet (maximum 20g carb/day)
Berthelot et al [37]	To determine the effectiveness of fasting interventions on stress, anxiety, depression, and their association with fatigue/energy.	Meta-analysis of 11 studies	Stress, Anxiety, Depression levels	Fasting interventions
Stapel et al [38]	To assess the impact of fasting on metabolic parameters, stress hormones, and mood in depressed inpatients.	Prospective study	Metabolic parameters, Stress systems	72-hour fasting
Sit et al [39]	To determine remission rate, depression symptom level, mood polarity switch rate, and explore sleep quality in bipolar depression.	Randomized controlled trial (RCT)	Depression symptoms, Sleep quality	Bright white light therapy
Garbazza et al [40]	To investigate the efficacy and safety of Bright Light Therapy (BLT) for postnatal depression (PND) during the perinatal period.	Single-blind RCT	Depression levels (EPDS)	Bright Light Therapy (BLT)
Mohsenpour et al [41]	To investigate the effect of milk kefir drinks on depression status in individuals with Non-Alcoholic Fatty Liver Disease (NAFLD).	Randomized controlled trial (RCT)	Depression status (BDI-II-Persian)	Milk kefir drinks

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Kazemi et al [42]	To compare the effect of probiotic and prebiotic supplementation on depression scores and metabolic parameters in patients with MDD.	Double-blind RCT	Depression score (BDI)	Probiotic (Lactobacillus helveticus and Bifidobacterium longum), Prebiotic (galactooligosaccharide)
Chahwan et al [43]	To determine the effect of probiotic supplements (Winclove's Ecologic® Barrier) on depressive symptoms in participants with mild to severe depression.	Clinical trial (RCT)	Symptoms, vulnerability markers	Probiotic supplements (Winclove's Ecologic® Barrier)
Akkasheh et al [44]	To determine the effects of probiotic intake on symptoms of depression and metabolic status in patients with Major Depressive Disorder (MDD).	Randomized, double-blind RCT	Symptoms, metabolic status	Probiotic supplements
Rybnikova et al [45]	To study the protective effects of hypoxic preconditioning on the development of depressive states in rat models.	Experimental study	Depressive behavioral reactions	Hypoxic preconditioning (Intermittent hypobaric hypoxia)
Lim et al [46]	To determine the effect of hyperbaric oxygen (HBO) therapy on TBI-induced depression-like behavior and neuroinflammation in rats.	Experimental (Rat Model)	Behavior, neuroinflammation	Hyperbaric Oxygen (HBO) Therapy
Rymaszewska J et al [47]	To assess the efficacy of whole-body cryotherapy (WBCT) as an adjunctive treatment for depressive and anxiety disorders.	Clinical Trial (Control vs Study Group)	Psychopharmacotherapy, WBCT	Whole-Body Cryotherapy (WBCT)
Eliacik et al [48]	To identify differences in antenatal stressful life events, parenting style, family functioning, depression, and anxiety of mothers of children with breath-holding spells (BHS).	Case-Control Study	Antenatal events, family functioning	BHS (hypercapnia induction)
Mattie et al [49]	To examine maternal stress in parenting children with breath-holding spells (BHS) and depressive symptoms (DS) compared to control children.	Observational (Comparative)	Parenting Stress, Coping Mechanisms	BHS (hypercapnia induction)
Paolucci et al [50]	To measure changes in depression, anxiety, and perceived stress along with pro-inflammatory cytokines in response to exercise.	Experimental (Exercise Intervention)	Mental Health, Pro-inflammatory Cytokines	High-Intensity Interval Training (HIIT)
Alonso et al [51]	To observe the impact of an 8-week HIIT protocol on body composition and depressive symptoms during home confinement.	Experimental (Exercise Intervention)	Body Composition, Depressive Symptoms	High-Intensity Interval Training (HIIT)

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Table 3. Selected papers and their related assessments pertaining to mitochondrial interventions and their efficacy in treatment/management of depression/depressive signs and symptoms.

Study	Parameters Assessed	Inferences Observed	Results Observed
Feng et al [31]	Depression (HAMD), Anxiety (HAMA), Nerve function (ASIA score), Activities of daily living (FIM score)	HBO and psychotherapy both significantly reduced HAMD scores compared to the control group. HBO group had lower HAMA scores than the control group. HBO improved ASIA and FIM scores more than psychotherapy. HBO is similar to psychotherapy in reducing depression and anxiety but superior in improving nerve function and daily living activities depressive patients.	- HAMD scores significantly lower in HBO and psychotherapy groups vs. control. - HAMA scores significantly lower in HBO group vs. control. - ASIA and FIM scores significantly higher in HBO and psychotherapy groups vs. control.
Rymaszewska et al [32]	Depressive symptoms (BDI-II, HAM-D 17), Quality of life, Mood, Vitality, Sleep quality, Disease acceptance	WBC showed statistically significant improvements in depressive symptoms (HAM-D 17, BDI-II) and quality of life. No significant changes in sexual satisfaction, vitality, or sleep. WBC is a useful addition to pharmacological treatment for depression.	- Statistically significant improvements in HAM-D 17, BDI-II, and quality of life in the WBC group. - No significant changes in sexual satisfaction, vitality, or sleep.
Laukkanen et al [33]	Risk of depressive symptoms	Frequent sauna bathing (4–7 times per week) was inversely associated with the risk of depressive symptoms in a male population.	- Frequent sauna bathing (4–7 times per week) associated with a significantly lower risk of depressive symptoms in males. - The association remained significant after adjusting for various factors.
Masuda et al [34]	Somatic and mental complaints, hunger, relaxation, plasma ghrelin concentrations, daily caloric intake	Repeated thermal therapy improved somatic complaints, hunger, relaxation, and increased plasma ghrelin concentrations and daily caloric intake.	- Somatic complaints, hunger, relaxation scores significantly improved. - Mental complaints slightly improved. - Increased plasma ghrelin concentrations and daily caloric intake in the thermal therapy group.

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Behzad et al [35]	Psychological disorders (depression, anxiety, stress)	Greater adherence to Paleolithic and Mediterranean diets was associated with a decreased risk of psychological disorders such as depression, anxiety, and stress.	- Higher Paleolithic diet tertile associated with lower odds of depression, anxiety, and stress. - Higher Mediterranean diet tertile associated with lower odds of depression, anxiety, and stress.
Danan et al [36]	Depression (Hamilton Depression Rating Scale), Psychosis (Positive and Negative Syndrome Scale), Metabolic health measures	Ketogenic diet was associated with substantial improvements in depression and psychosis symptoms and multiple markers of metabolic health.	- Significant improvements in Hamilton Depression Rating Scale scores. - Significant improvements in Positive and Negative Syndrome Scale scores. - Improvements in metabolic health measures (weight, blood pressure, blood glucose, triglycerides).
Berthelot et al [37]	Anxiety, Depression levels, Body mass index	Fasting interventions were associated with lower anxiety and depression levels and lower body mass index without increased fatigue. These interventions were found to be safe, even in patients with type 2 diabetes.	- Fasting groups had lower anxiety and depression levels. - Lower body mass index without increased fatigue. - Safe for patients with type 2 diabetes.
Stapel et al [38]	Metabolic parameters, Stress systems, Depression symptoms (BDI-2), BDNF levels	Fasting impacted metabolic parameters and stress systems similarly in both groups. In depressed patients, fasting improved cognitive-affective symptoms, especially in those with moderate/severe symptoms.	- Fasting improved cognitive-affective symptoms in depressed patients with moderate/severe symptoms. - No mood polarity switches observed.
Sit et al [39]	Remission rate, Depression scores, Mood polarity switch rate, Sleep quality	Bright white light therapy was associated with a significantly higher remission rate and lower depression scores compared to placebo light therapy in bipolar depression. Sleep quality improved in both groups.	- Bright white light therapy had a higher remission rate and lower depression scores. - No mood polarity switches observed. - Improved sleep quality.

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Garbazza et al [40]	Depression levels (EPDS)	Morning BLT induced significant remission from PND compared to dim red light (DRL) therapy. The effect was maintained across the perinatal period.	- 73% remission rate with BLT vs. 27% with DRL. - Significant reduction in EPDS scores in the BLT group. - No major side effects reported.
Mohsenpour et al [41]	Depression status (BDI-II-Persian)	Diet + Kefir group showed a significant reduction in depression compared to the Diet group. No significant between-group differences.	- Diet + Kefir group had a significant reduction in depression. - No reduction in depression in the Diet group.
Kazemi et al [42]	Depression score (BDI), Kynurenine/Tryptophan ratio, Tryptophan/BCAAs ratio	Probiotic supplementation resulted in a significant decrease in depression score compared to placebo. No significant inter-group differences in metabolic parameters.	- Probiotic group had a significant decrease in depression score. - No significant differences in metabolic parameters among groups.
Chahwan et al [43]	Symptoms, gut microbiota composition	Probiotic group showed a significantly greater reduction in cognitive reactivity. Probiotics did not significantly alter the gut microbiota.	- Improvement in symptoms in all clinical trial participants. - Greater reduction in cognitive reactivity in probiotic group. - No significant gut microbiota changes.
Akkasheh et al [44]	Symptoms, metabolic markers	Probiotic group had significantly decreased Beck Depression Inventory scores. Significant decreases in serum insulin levels, insulin resistance, and hs-CRP concentrations.	- Significant improvement in depression scores in probiotic group. - Improvement in metabolic markers in probiotic group.
Rybnikova et al [45]	Depressive behavioral reactions, hormonal markers	Hypoxic preconditioning prevented the onset of depressive reactions and hormonal changes. Anxiolytic and antidepressant effects were observed.	- Hypoxic preconditioning prevented depressive reactions in rat models. - Anxiolytic and antidepressant effects observed.
Lim et al [46]	Depression-like behavior, motor function, infarction volume, neuronal apoptosis, microglial activation, TNF-α expression	HBO therapy attenuated TBI-induced depression-like behavior and neuroinflammation.	- Improvement in depression-like behavior with HBO therapy. - Reduced neuroinflammation with HBO therapy.

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Rymaszewska J et al [47]	Hamilton's Depression Rating Scale (HDRS), Hamilton's Anxiety Rating Scale (HARS)	WBCT as an adjunctive treatment led to significant reductions in depression and anxiety in the study group.	- Significant reduction in HDRS and HARS scores in the study group after WBCT.
Eliacik et al [48]	Stressful life events, depression traits, state-trait anxiety, parenting style, family functioning	Mothers of children with BHS had higher exposure to stressful events, anxiety, depression, and poor family functioning.	- Significant differences in stressful events, anxiety, depression, and family functioning between groups.
Mattie et al [49]	Overall stress, attachment, child's behavior, sense of competence, self-identity, positive reinforcement, maternal health, depression/isolation, spousal support, child's mood, life stresses	Parenting children with BHS or DS is more stressful, impacting mothers' sense of competence and self-identity.	- Mothers of BHS and DS children perceive more stress and child's behavior issues. - Significant disruption in mothers' sense of competence for BHS group.
Paolucci et al [50]	Depression, anxiety, perceived stress, pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, CRP)	Moderate-intensity exercise decreases depression and TNF-α levels, while high-intensity exercise increases perceived stress and pro-inflammatory cytokines.	- Depression increased in the control group. - MCT and HIT decreased depression. - HIT increased perceived stress, TNF-α, and IL-6.
Alonso et al [51]	Body fat mass (percentage and kg), body fat mass index (BFMI), depressive symptoms	HIIT during home confinement reduces body fat mass and depressive symptoms.	- Significant reductions in body fat mass and BFMI. - Reduction in depressive symptoms with HIIT.

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DISCUSSION

The findings presented in this review hold significant implications for the field of depression management and have the potential to shape future research and clinical practice. Firstly, the diverse range of interventions explored in these studies underscores the complexity of depression and the need for multifaceted approaches to treatment. Traditional pharmacological and psychotherapeutic interventions, while valuable, may not be sufficient for all individuals with depression. Therefore, the identification of novel interventions such as hyperbaric oxygen therapy, cryotherapy, dietary modifications, fasting, and probiotic supplementation opens up new avenues for personalized and holistic depression care. One of the key implications is the role of lifestyle modifications in depression management. Studies investigating interventions like sauna bathing, dietary patterns (Paleolithic and Mediterranean diets), fasting, exercise, and probiotics reveal the profound influence of lifestyle choices on mental health. These findings emphasize the importance of considering a patient's overall well-being, including their diet, physical activity, and exposure to environmental factors, when developing treatment strategies for depression. Furthermore, the positive outcomes of interventions such as hyperbaric oxygen therapy, cryotherapy, and light therapy in alleviating depressive symptoms indicate the potential of non-pharmacological and non-invasive approaches. These interventions offer a relatively safe and well-tolerated alternative for individuals who may be hesitant or unable to undergo traditional treatments. Incorporating these options into clinical practice may enhance the spectrum of available treatments and improve patient outcomes.

The role of the gut-brain axis is another noteworthy implication. Several studies demonstrate the potential of probiotics and dietary interventions in modulating depressive symptoms. This highlights the bidirectional relationship between the gut microbiota and the central nervous system and suggests that targeting gut health may be a viable strategy for managing depression. Future research in this area may unravel the precise mechanisms through which gut microbiota influences mood and provide more tailored probiotic interventions. Additionally, the study of maternal mental health in the context of childhood health conditions, as seen in studies related to BHS and DS, underscores the importance of a family-centered approach in mental health care. Recognizing the increased stress and disrupted sense of competence among mothers in these situations calls for targeted support programs that address the unique needs of families coping with such conditions.

Feng et al. [31] conducted a study involving HBO therapy and psychotherapy, both of which significantly reduced depression scores compared to a control group. Interestingly, HBO therapy exhibited lower anxiety scores and superior improvements in nerve function and daily living activities compared to psychotherapy. This suggests that HBO therapy might be an effective alternative or complementary approach to traditional psychotherapy for depression management. Rymaszewska et al. [32] investigated WBC and found that it significantly improved depressive symptoms and quality of life. While there were no significant changes in sexual satisfaction, vitality, or sleep, the study highlights WBC as a useful addition to pharmacological treatments for depression. This suggests that WBC might serve as an adjunct therapy for individuals with depressive disorders. Laukkanen et al. [33] explored the relationship between frequent sauna bathing and depressive symptoms, particularly in males. Their findings revealed that frequent sauna bathing (4-7 times per week) was inversely associated with the risk of depressive symptoms. Even after adjusting for various factors, this association remained significant, implying that regular sauna use might have a protective effect against depression, at least in men. Masuda et al. [34] examined the effects of repeated thermal therapy on various parameters, including somatic and mental complaints, hunger, relaxation, plasma ghrelin concentrations, and daily caloric intake. The results showed significant improvements in somatic complaints, hunger, relaxation, and increased plasma ghrelin concentrations and daily caloric intake. These findings suggest that thermal therapy could be a novel approach to improving both physical and mental well-being. Behzad et al. [35] investigated the relationship between dietary patterns (Paleolithic and Mediterranean diets) and psychological disorders such as depression, anxiety, and stress. Their study revealed that greater adherence to these diets was associated with a decreased risk of psychological disorders. This implies that dietary

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modifications can play a significant role in managing and preventing depression and related conditions. Danan et al. [36] explored the effects of a ketogenic diet on individuals with severe, persistent mental illness. The results showed substantial improvements in depression and psychosis symptoms, as well as various metabolic health markers. This suggests that dietary interventions like the ketogenic diet may have a profound impact on mental health outcomes. Berthelot et al. [37] conducted a meta-analysis of fasting interventions and found that they were associated with lower anxiety and depression levels and lower body mass index without increased fatigue. Furthermore, fasting interventions were considered safe, even for patients with type 2 diabetes. This underscores the potential of fasting as an intervention for improving mental health and overall well-being. Stapel et al. [38] investigated the impact of fasting on metabolic parameters, stress systems, and depression symptoms in depressed inpatients. The results revealed that fasting improved cognitive-affective symptoms, particularly in individuals with moderate to severe depression. This suggests that fasting could be a viable complementary approach for managing depression in clinical settings. Sit et al. [39] studied the effects of bright white light therapy in bipolar depression and found that it led to a significantly higher remission rate and lower depression scores compared to placebo light therapy. This intervention also resulted in improved sleep quality, highlighting its potential as a treatment option for bipolar depression. Garbazza et al. [40] examined the efficacy of bright light therapy (BLT) for postnatal depression (PND) and reported a significant remission rate in the BLT group compared to dim red light therapy (DRL). This effect was maintained throughout the perinatal period, suggesting BLT as a promising intervention for PND. Mohsenpour et al. [41] investigated the effect of milk kefir drinks on depression in individuals with Non-Alcoholic Fatty Liver Disease (NAFLD). The results showed a significant reduction in depression in the group that consumed diet and kefir drinks. This indicates that dietary modifications involving kefir may have a positive impact on mood in individuals with NAFLD. Kazemi et al. [42] studied the effects of probiotic and prebiotic supplementation on depression scores and metabolic parameters in patients with Major Depressive Disorder (MDD). Probiotic supplementation resulted in a significant decrease in depression scores, emphasizing the potential role of gut health in influencing mood. Chahwan et al. [43] investigated probiotic supplements and their impact on depressive symptoms. The study revealed a significantly greater reduction in cognitive reactivity in the probiotic group. While there were no significant changes in gut microbiota, the study suggests that probiotics may have a direct effect on mood. Akkasheh et al. [44] explored the effects of probiotic intake on symptoms of depression and metabolic status in patients with Major Depressive Disorder (MDD). The results showed a significant improvement in depression scores and metabolic markers in the probiotic group, further highlighting the potential of probiotics as a complementary approach for managing depression. Rybnikova et al. [45] investigated the protective effects of hypoxic preconditioning on the development of depressive states in rat models. The study demonstrated that hypoxic preconditioning prevented depressive reactions and hormonal changes, suggesting a potential role in mitigating depressive symptoms. Lim et al. [46] examined the effects of HBO therapy on depression-like behavior and neuroinflammation in rats with traumatic brain injury (TBI). The study showed that HBO therapy attenuated depression-like behavior and reduced neuroinflammation, indicating its potential as a therapeutic approach for TBI-induced depression. Rymaszewska J et al. [47] assessed the effectiveness of WBC as an adjunctive treatment for depressive and anxiety disorders. The results revealed significant reductions in depression and anxiety scores in the study group after WBC, suggesting its potential as a complementary intervention for mental health disorders. Eliacik et al. [48] conducted a case-control study to identify differences in antenatal stressful life events, parenting style, family functioning, anxiety, and depression between mothers of children with BHS and healthy controls. The study found significant differences in stressful events, anxiety, depression, and family functioning between the two groups, shedding light on the psychosocial factors associated with BHS. Mattie et al. [49] examined the stress levels and psychological well-being of mothers of children with BHS and mothers of children with depressive symptoms (DS). The study revealed that mothers of children with BHS or DS experienced more stress and disruption in their sense of competence and self-identity, emphasizing the importance of providing support to these mothers. Paolucci et al. [50] investigated

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the effects of different exercise intensities on depression, anxiety, perceived stress, and pro-inflammatory cytokines in adults. The study found that moderate-intensity exercise decreased depression and TNF-α levels, while high-intensity exercise increased perceived stress and pro-inflammatory cytokines. These results highlight the potential of exercise as a non-pharmacological approach to managing depression, with the intensity of exercise playing a crucial role. Alonso et al. [51] examined the impact of HIIT during home confinement on body fat mass and depressive symptoms. The study demonstrated significant reductions in body fat mass and depressive symptoms, underscoring the potential of HIIT as an effective intervention for improving both physical and mental health.

Due to factors like inflammation, the abundance of energy derived from high-calorie dietary practises, sedentary behaviours, and extended periods of inactivity, the modern lifestyle significantly promotes a metabolic transition from oxidative phosphorylation to the prevalent adoption of aerobic glycolysis [52]. According to multiple articles in this regard [53–57], this confluence results in chronic hyperglycemia and an excessive input of fatty acids. According to a conjectural perspective, aerobic glycolysis is a critical pathway mediating the aetiology of the majority, if not all, chronic diseases. This includes a wide range of illnesses like cardiovascular diseases [58], neurodegenerative conditions like AD [18], and a variety of cancer phenotypes and their associated hallmarks.

Although the literature in this regard is substantial, some of the papers that have investigated different types of mitochondrial interventions have exhibited certain limitations which have to be considered while investigating their outcomes. The observational study by Bar-Yosef et al. [16] is prone to potential confounding factors that could affect the reported correlations between mitochondrial function profiles and medication responses, even while it pioneers personalised treatment techniques. Although the relatively brief follow-up time may leave out long-term treatment outcomes and probable relapse patterns, Berk et al.'s randomised controlled trial [17] offers useful information on the sustained effects of therapies. Although it advances our knowledge of mitochondrial gene expression in psychosis-related ailments, Castora et al.'s prospective analysis [18] mostly relies on observational data, which makes it difficult to draw causal conclusions. The study conducted by Da Silva et al. [19] to evaluate mitochondrial function in people who are clinically at high risk for psychosis uses a cross-sectional design, which may miss dynamic changes over time. Longitudinal assessments are necessary to fully understand how mitochondrial alterations progress in relation to symptomatology. Model organisms are used in the animal-based research by Deng et al [20] and Manczak et al [22] to examine mitochondrial dynamics and interventions. However, due to interspecies variables that may affect the applicability of results, careful thought must be given to extrapolating these models' findings to human situations. In addition, Wen et al.'s work [23] focuses on animal models rather than people, raising concerns about the direct application of these findings to people with depressive illnesses. This study sheds information on the impact of stress and therapies on mitochondrial function and neurotransmitter levels in depression. The complexity of human neurological diseases, which cannot be accurately modelled in animal models, potential biases in sample recruitment, variation in technique, and experimental circumstances are additional limitations shared by all of these studies. The importance of future research projects that address these limitations through larger and more diverse study populations, long-term follow-up, and translational approaches bridging the gap between animal models and human conditions is emphasised by these considerations, which also emphasise the need for cautious interpretation.

Long-term aerobic glycolysis can impair the action of enzymes essential to conventional aerobic processes, causing a persistent Warburg effect. Through the activation of the polyol pathway, this metabolic disturbance causes the buildup of intracellular fatty acids, nucleotides, and amino acids as well as the production of sorbitol and the subsequent influx of sorbitol-associated water [56–58]. Underlying the formation of retinopathy, nephropathy, and neuropathy, as well as echoing across the spectrum of aforementioned chronic illnesses, are these accumulative phenomena across the canvas of cellular biomass, promoted by aerobic glycolysis and the contemporaneous polyol pathway [9,15,52].

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The publications covered in this review also offer insightful information on the various methods by which mitochondrial interventions affect the outcomes of mental health, including oxygen-based therapies, dietary habits, gut microbiome manipulation, and physical activity. Feng et al. [31] investigated the effects of hyperbaric oxygen (HBO) therapy, in which the increased oxygen content brought on by exposure to high pressures may have improved mitochondrial function, decreased oxidative stress, and benefited neuronal function and mood regulation. Rymaszewska et al [32] looked into Whole-Body Cryotherapy (WBC), which involved exposing people to extremely low temperatures in the hopes of inducing mitochondrial changes that would lessen inflammation, elevate mood, and enhance quality of life. Additionally, it might trigger endorphin release, which would add to the analgesic and mood-lifting benefits.

Sauna use was investigated by Laukkanen et al. [33], who found that it could boost mitochondrial function by enhancing circulation, lowering oxidative stress, and increasing vascular health. Together, these elements support improved mental health and less depressed symptoms. Masuda et al [34] looked at the effects of thermal therapy in saunas, which probably enhanced mitochondrial function by promoting relaxation, lowering stress levels, and boosting blood flow. Far-infrared photons may permeate tissues and have a good effect on mood and relaxation. Behzad et al.'s investigation of dietary practises [35] focused on the impact of nutrients and antioxidants on mitochondrial activity. Such diets enhanced mitochondrial health, possibly reducing the incidence of anxiety and sadness.

The Ketogenic diet, which directs metabolism towards ketone utilisation, was studied by Danan et al. This alteration may impact neurotransmitter levels, improve mitochondrial performance, and decrease inflammation, all of which may have an impact on mood control. The effects of fasting on mitochondrial function, oxidative stress, and other cellular stress responses, including autophagy and hormesis, were studied by Berthelot et al. [37]. Lower inflammation and improved metabolic indicators may have helped people feel less anxious and depressed. Extended fasting was investigated by Stapel et colleagues [38], which may have stimulated autophagy and maintained control over mitochondrial quality. It is possible that improved mitochondrial activity and decreased oxidative stress are responsible for the observed improvement in cognitive-affective symptoms in depressed patients.

Bright white light therapy, which alters circadian cycles and mood by influencing the suprachiasmatic nucleus, was studied by Sit et al. Regulated neurotransmitter and mitochondrial activities may be the cause of improved mood and sleep in bipolar depression patients. Bright Light Therapy (BLT), which affects circadian rhythms and melatonin synthesis, was examined by Garbazza et al. [40]. Postnatal depression may have been lessened in part by mitochondrial energy generation and oxidative stress pathways.

The impact of probiotics in milk kefir on gut microbiota was investigated by Mohsenpour et al. [41], which indirectly affected mitochondrial function through metabolic and immunological pathways. Reduced depression was likely influenced by improved gut health. The gut-brain axis and mitochondrial function may be affected by probiotics' effects on the composition of the gut microbiota and metabolic pathways, according to research by Kazemi et al. [42]. These pathways may be related to lower depression scores. Probiotic supplements, which may alter gut microbiota and potentially affect systemic inflammation and neurotransmitter synthesis, were studied by Chahwan et al. [43]. increased mitochondrial function and increased gut-brain connection may be related to decreased cognitive reactivity.

Probiotic supplements have been studied by Akkasheh et al. [44] and have been shown to improve gut health, lower systemic inflammation, and positively impact mitochondrial function. A healthy gut microbiome may be related to the decline in depression ratings. Hypoxic preconditioning, which may set off adaptive reactions that guard against depressive states, was studied by Rybnikova et al. [45]. These reactions most likely entail elevated mitochondrial activities connected to cellular survival and energy synthesis. HBO therapy was studied by Lim et al [46], who found that it reduced the neuroinflammation and depressive-like behaviour that a TBI causes. This resulted in an improvement in mood and may have been caused by improved oxygen availability,

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decreased oxidative stress, and support for mitochondrial function. In their investigation of the effects of WBCT, Rymaszewska J et al [47] found that it may lessen inflammation, possibly via improving mitochondrial function and endorphin release. The precise mechanisms causing the decline in anxiety and depression require further study.

Eliacik et al. [48] investigated the production of hypercapnia during breath-holding episodes, which may result in stress reactions that affect mitochondrial function. Further research is needed to determine the precise mitochondrial pathways responsible for the observed variations in anxiety and depression. According to Mattie et al.'s [49] investigation of hypercapnia induction during breath-holding episodes, stress responses may have an impact on mitochondrial function and psychological health. These mechanisms may be related to the alteration of mothers' perceptions of their own competence. High-Intensity Interval Training (HIIT), which affects mood via a variety of processes, including endorphin release and neurotransmitter modulation, was researched by Paolucci et al. [50]. Additionally, it might affect mitochondrial activity, which would lessen sadness and perceived stress. In their study of the effects of HIIT while at home, Alonso et al. [51] found that it decreased body fat mass and depressed symptoms. Improved energy metabolism, mitochondrial function, and general physical and mental wellness may all be factors in these results.

It is important to recognise a number of limitations related to the techniques and designs used in the investigations, despite the fact that the studies provided in this review collectively provide insightful information about the complex link between mitochondrial interventions and depression. Firstly, the heterogeneity in study designs and methodologies across the selected papers poses a significant challenge. While this diversity allows for a comprehensive exploration of interventions, it also makes it challenging to directly compare results and draw generalized conclusions. Some studies employ RCTs, while others adopt observational or experimental designs, leading to differences in the strength of evidence. This variability in research approaches highlights the need for standardized methodologies in future studies to enable more robust comparisons and meta-analyses. Secondly, the majority of studies rely on self-report measures to assess depressive symptoms and related parameters. While self-report instruments are commonly used in depression research due to their practicality, they are subject to various biases, including social desirability and recall bias. This limitation can impact the accuracy of the reported results and calls for the incorporation of more objective measures, such as neuroimaging or biomarkers, in future investigations. Furthermore, the duration of interventions and follow-up periods in these studies varies widely. Some interventions are short-term, spanning only a few weeks, while others extend over several months. This temporal heterogeneity makes it challenging to ascertain the long-term sustainability and durability of the observed effects. Future research should consider longer-term follow-up assessments to better understand the persistence of treatment outcomes. Another limitation is the potential for publication bias, wherein studies with significant or positive findings are more likely to be published than those with null or negative results. This bias can skew the overall impression of intervention effectiveness. Addressing this limitation requires greater transparency in reporting and the inclusion of unpublished studies in systematic reviews and meta-analyses. Additionally, many of the included studies are exploratory or preliminary in nature, often involving small sample sizes. Small sample sizes can limit the generalizability of findings and increase the risk of type II errors, where true effects are not detected due to insufficient statistical power. Future research should prioritize larger and more diverse participant pools to enhance the robustness of results.

CONCLUSION

In a nutshell, the outcomes of the thorough analysis undertaken in this review shed light on the wide range of depression management therapies and provide insightful information about their potential efficacy. The combined findings demonstrate the complexity of depressive illnesses and emphasise the need for a diverse approach to their treatment. The research included in this study suggest that a variety of interventions, including pharmaceutical therapies and lifestyle changes, have showed promise in reducing depressed symptoms and enhancing general mental health. These treatments focus on a range of depressive symptoms, such as mood, anxiety, physical symptoms, and

even metabolic problems. Although these results offer a positive outlook for the treatment of depression, it is important to recognise that the study designs, sample sizes, and methodology used in the chosen publications varied widely, necessitating caution when extrapolating these findings. Further mechanistic research is essential since many times the mechanisms behind the observed effects are still not fully understood.

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